BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
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ROMAINE GILLILAND
Director

LAURIE SQUARTSOFF
Administrator

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

REVISED AGENDA

Date of Posting: **xxxxx**

Date of Meeting: **Thursday, January 22, 2015 at 5:30 PM**

Name of Organization: **The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR).**

Place of Meeting: **Silver Legacy**
Silver/Gold Room
407 N Virginia St
Reno, Nevada 89501

AGENDA

1. **Call to Order and Roll Call**

2. **Public Comment on Any Matter on the Agenda**

3. **Administrative**

   a. **For Possible Action:** Review and Approve Meeting Minutes from July 24, 2014.

   b. Status Update by DHCFP
      i. Public Comment
      ii. Medicaid's overview of the upcoming legislative session
      iii. Introduction of new member, Dr. Michael Owens.

4. **Presentation and Discussion of Nevada's Prescription Monitoring Program**

   a. Jenine M. Davis, Pre-Criminal Intervention Officer, Controlled Substance Abuse Prevention Task Force

5. **Clinical Presentations**

a. **For Possible Action:** Discussion and proposed adoption of updated clinical prior authorization criteria for sofosbuvir (Sovaldi®).
   i. Public comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by the Board and review of utilization data.
   iv. Proposed adoption of updated prior authorization criteria.

b. **For Possible Action:** Discussion and proposed adoption of prior authorization criteria for Ledipasvir-Sofosubuvir (Harvoni®)

   i. Public Comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by the Board and review of utilization data.
   iv. Proposed adoption of updated prior authorization criteria

c. **For Possible Action:** Discussion and proposed adoption of updated clinical prior authorization criteria for simeprevir (Olysio®).

   i. Public comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by Board and review of utilization data.
   iv. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and proposed adoption of updated prior authorization criteria for Oxycodone w/acetaminophen tab CR (Xartemis XR®)

   i. Public Comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by the Board and review of utilization data.
   iv. Proposed adoption of updated prior authorization criteria.

e. **For Possible Action:** Discussion and proposed adoption of updated prior authorization criteria for apixaban (Eliquis®)

   i. Public Comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by the Board and review of utilization data.
   iv. Proposed adoption of updated prior authorization criteria.

f. **For Possible Action:** Discussion and proposed adoption of updated clinical prior authorization criteria for the immunomodulator class of medication.

   i. Public comment on proposed clinical prior authorization criteria.
   ii. Presentation of utilization and clinical information.
   iii. Discussion by Board and review of utilization data.

iv. Proposed adoption of updated prior authorization criteria.

g. **For Possible Action:** Discussion and proposed adoption of updated clinical prior authorization criteria for transdermal fentanyl.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

h. **For Possible Action:** Discussion and proposed adoption of updated clinical prior authorization criteria for palivizumab (Synagis®).

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

6. DUR Board Requested Reports

a. Report on Top 10 Black Box warning medications:

i. Public comment on Black Box warnings.
ii. Discussion by the Board and review of utilization data.

b. Report on controlled substance utilization and trends.

i. Public comment on controlled substance utilization and trends.
ii. Discussion by the Board and review of utilization data.

c. Report on psychotropic drug use in children.

i. Public comment on psychotropic drug use in children.
ii. Discussion by the Board and review of utilization data.

d. Report on buprenorphine and buprenorphine/naloxone use.

i. Public comment on buprenorphine and buprenorphine/naloxone use.
ii. Discussion by the Board and review of utilization data.

e. Report on Nevada Medicaid Lock-in Program

i. Public comment on Lock-in Program.
ii. Discussion by the Board and review of utilization data.

f. Report on Asthma treatment utilization.

i. Public comment on asthma treatment utilization.
ii. Discussion by the Board and review of utilization data.

g. Report on Tussionex Utilization.

i. Public comment on Tussionex Utilization.
ii. Discussion by the Board and review of utilization data.

7. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q2 2014, Q3 2014, and Q4 2014 (by Payment and by Claims).
ii. Top 50 Drugs of Q2 2014, Q3 2014, and Q4 2014 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR)

i. Review of Q2 2014, Q3 2014, and Q4 2014.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR)

i. Public comment on Retro DUR.
ii. Status of previous quarter.
iii. Status of current quarter.
iv. Review and discussion of responses.

8. Closing Discussion

a. Public comments on any subject.

b. Date and location of the next meeting.

i. Discussion of the time of the next meeting.

c. Adjournment.

Nevada Medicaid is unaware of any financial impact to other entities or local government due to this public hearing, other than as stated above.

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and

announced at this meeting by the chairperson. All public comment may be limited to 5 minutes.

This notice and agenda have been posted at www.dhcfp.nv.gov and http://notice.nv.gov

Notice of this meeting and draft copies of the changes will be available on or after the date of this notice at the DHCFP Web site www.dhcfp.nv.gov, Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a draft copy of the changes will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the Rita Mackie at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701, at least 3 days before the public hearing.

All persons that have requested in writing to receive the Public Hearings agenda have been duly notified by mail or e-mail.

Note: We are pleased to make reasonable accommodations for members of the public who are physically challenged and wish to attend the meeting. If special arrangements for the meeting are necessary, please notify the Division of Health Care Financing and Policy, in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Rita Mackie at (775) 684-3681, as soon as possible, or e-mail at rmackie@dhcfp.nv.gov

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Nevada Medicaid
Drug Use Review (DUR) Board
Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) Drug Use Review (DUR) Board conducted a public meeting on July 24, 2014 beginning at 5:30 pm at the following location:

Best Western Airport Plaza Hotel
1981 Terminal Way
Reno, NV 89502-3215

Board Members Present:
Paul Oesterman, Pharm.D., Chairman; Dave England, Pharm.D.; James Marx, M.D; Larry Nussbaum, MD

Board Member Absent:
Jeff Zollinger, DO; Chris Shea, Pharm.D.

Others Present:
DHCFP:
Coleen Lawrence, Chief, Program Services; Mary Griffith, RN, Pharmacy Services Specialist; Darrell Faircloth, Senior Deputy Attorney General;

HPES:
Beth Slamowitz, Pharm.D.

Catamaran:
Carl Jeffery, Pharm.D. Account Manager

Others:
Lori Howarth, Bayer; Scott Larson, BMC; Lisa Borland, Vertex; Cathy Gross, Vertex; Joe Hubbard, CNUCOR; Sandy Sierawski, Pfizer

1. Call to Order and Roll Call

Meeting called to order at 5:32PM.

Roll Call:

Carl Jeffery - Catamaran
Jim Marx - Las Vegas Pain Management Physician
Larry Nussbaum - Reno School of Medicine
David England - Las Vegas Pharmacist
Paul Oesterman - Pharmacist Reno Chair
Darrell Faircloth – Senior Deputy Attorney General
Beth Slamowitz – HP
Mary Griffith – Nevada Medicaid
Coleen Lawrence – Nevada Medicaid

2. Public Comment

Sandy Sierawsky – Pharmacist in Nevada – Pfizer/Medical Division:
Requested board review prior authorization criteria for the oral anticoagulants Pradaxa, Xarelto, and Eliquis. Eliquis has been approved by the FDA for an additional indication, so we would like the criteria used so that it could potentially be incorporated in that criteria.

PO: Because it's not an agenda item, we will add it for the agenda for next time, that way it will be actionable.

3. Administrative

Review and approve April 24, 2014 meeting minutes.

JM: Motion to approve minutes.
DE: Seconded.
Discussion: None.
Board votes unanimous, "Aye."
Minutes approved.

4. Status Update by DHCFP

Mary Griffith – RN, Pharmacy Services Specialist:
Provided the following updates: OPR, (Ordering Prescribing Referring) physicians, we've been talking about that for several months now and we actually have the implementation date. There are web announcements in the back. It's going to be effective/ soft edit/ a portion of it goes into effect August 18th, 2014. That means that if there is a drug that is prescribed by someone who is not a Medicaid provider, there will be a message that comes up that says "This prescription is prescribed by someone who is not enrolled in Medicaid". Next time that fill comes in, if it's after October 1st, it's going to deny. October 15th is the hard edit. So for

October 1st too, it's going to be effective for everybody, not just pharmacy, so if you have any physicians that you go and visit, they will be effected by this also.

Board: When is that effective?
Mary: October 15th. That is when the hard edit hits. The soft edit starts next month.
Coleen: It's common obviously, already, in the pharmacy world, this is on the record, and Medicare has already implemented it. It's implemented in other states and has been implemented in other states for years. I think pharmacy is going to be a natural transition. It's expected in the pharmacy world. I expect that we're going to see unknown impact. It's going to be in other areas in healthcare where there's what I call the triad. And the triad would be physician, or a prescriber; a supplier; and then another provider, so a direct service provider. A good example would be a home health provider, or a DME company. That's where it's going to get a little trickier because the ordering and the direct servicing is going to be a little bit different. As a physician, it's going to be an education pattern that we're going to have to get out there with.
Mary: The hope is that when the pharmacist sees that new message that they inform the recipient. "Hey your doctor is not a Medicaid provider. Next time, if you need a refill on this, it's going to get denied." so that the recipient can go to their own doctor and get them on our enrollment.
PO: Is there a bypass mechanism for somebody who is taking call or covering for a Medicaid provider who is himself not a provider?
Coleen: The only way that I would say in that kind of a scenario, is interns, such as in the emergency room, hospitalists and interns are not applicable to this rule. They fall under the hospital benefit themselves, so that's the only caveat, if you want to say taking call for somebody, that's the only exception to this rule.
LN: So trainees, like residents?
Coleen: Residents are not applicable, interns…
LN: Even if they're in a clinic, not in a hospital?
Coleen: If they fall under the resident role, and I mean the Medicare Resident role, those are the only ones. You're required to have your NPI and follow those rules, you must fall under the OPR.
Mary: Also, there is going to be a mechanism for 30 days after the hard edit for the pharmacist to be able to override, if they come across someone that doesn't have that provider enrollment. They will be able to override that, but that's only going to happen for the first 30 days and then it's going to be turned off.
Coleen: That's only for Pharmacy.
DE: And that's until 11/15, they can override if they need to?
Mary: Right.
The Governor has created a controlled substance task force. Very high level, different political people that are involved in it. Our administrator Laurie Squartsoff is involved in it also. I'm not sure how often they meet, but it's definitely something that we're following because it's gone to the Governor's level on this. We're still involved with the substance abuse task force for the Board of Pharmacy. They haven't had a meeting recently, I don't think, but we're definitely involved with that in encouraging physicians to enroll in the PMP program.
JM: There actually is movement afoot through the Pharmacy Board to be registered at the time of medical licensing (and possibly DOs), or will be required to do that as a part of their relicensure. There will be virtually 100% enrollment. That doesn't mean 100% participation.

Mary: Next month we have someone from the Board of Pharmacy that is familiar with the PMP program to come talk to us [about the changes being made] in October.
Coleen: We're continuously recruiting for positions, whether it's on this board, or the P&T, because we have an open position that will be on the P&T for a psychiatrist. Our goal is to expand the participation on this board by statute of ten members. If there are any nominations, please send them to our office and we'll work with our director for this board, and we'll work with the Governor's office for the P&T. For this board, we're looking for Best Practice and Standards of Care for clinical criteria and utilization and the P&T is strictly for the Preferred Drug List.
PO: Any updates in terms of Healthcare Reform?
Coleen: Last month they hosted the National Association of Medicaid Directors conference in Tahoe. We had feedback from all the different states about what was going on with Healthcare Reform. I will state that Nevada ranked as one of the only states that did a full Medicaid expansion duplicating the current Medicaid benefit. So we're still really proud of that decision by our Director and our Governor to fully replicate our current Medicaid benefit plan as a single Medicaid program. What we have learned from all the other states, if they chose to expand Medicaid, that was step one. Step two was really narrowing their benefit plan. Although there have been hurdles of what's happened on the Medicaid side, I will definitely say that it's been very seamless as to what has happened with our Medicaid expansion. Our eligibility population has grown tremendously. They're projecting somewhere in the area of 500,000 by the end of the year for Medicaid expansion. I can get you the exact numbers, but they are posted on our DHS website, but those are the numbers I keep hearing. On a positive note, at our lowest point of Medicaid expansion, we had up to 60,000+ applications in the queue for our backlog of eligibility. I was at a meeting on Tuesday, and the Division of Welfare and Supportive Services said that they have approximately 6,000 applications in the queue which is by far the best they have ever had in their history. So this administration and DWSS's administration have definitely put all of their resources forward in doing improvements on their welfare process to really streamline what's going on in there. Whoever touches the application is the one who finishes the application. It's very positive on the eligibility side. We're hearing that there are literally determinations that day on eligibility now, so it's very positive.
Very big push for us, on the Medicaid side, to work with our providers to encourage providers to actually accept Medicaid patients. What we're trying to do is figure out what are the barriers. We wake up every day saying "We're not that system who wants to deny patients, or deny care. And we don't want to deny payment." So what we're doing is going out there and in meetings like this, I was in a meeting for the last two days where the federal government is trying to figure out why people are not taking Medicaid. So what we ask for is any feedback as to what are barriers of why people are not taking Medicaid. Our administrator has really put the focus on us to figure out, whether it's prior authorizations, myths…that's our biggest focus right now.
JM: Is there any type of formula for how patients are distributed to managed care verses indemnity? How is that working out?
Coleen: For managed care verses fee for service?
JM: Right.
Coleen: I'll have to get you what the actual numbers are. I do believe that the majority of them are going into the Managed care system because of the dynamics of the state. They're going into urban Washoe, or urban Las Vegas, and well the last numbers I saw, that's what

they were. I would have to get you those specific numbers, but that's what the projections were because Fee for Service would be the (rural). They are falling into the newly eligible calculation which is going into managed care. They are not coming into Fee for Service.
JM: In Managed care, there are panels. Is the problem recruiting into those panels?
Coleen: What we are finding is that it doesn't matter whether you are cash patient, if you are Managed care, fee for service, Medicare. We have a stress on our entire healthcare system right now. Honestly, our own employee system is having a hard time finding doctors right now. Everyone has a long wait list right now. It's not just Medicaid, but my issue is to be concerned with anything we can do to reduce any type of barriers that are out there. So one of our largest focuses right now is to make sure that managed care and fee for service are as streamlined as possible, so Beth and Carl took on a very large project and they are trying to make sure that, for example, our PDLs looked similar, so when a physician looks at it, it looks somewhat seamless. So we're looking at even those types of minute little things to make sure that we are streamlined. But yes. They are going primarily into managed care.

5. Presentations:

a. Annual DUR Report Presentation – Carl Jeffery - Catamaran

(Carl hands out packet to board members) This is a late addition that we've added here, so I apologize for not getting it to you guys sooner for you to review it. This is due September 30, 2014 to CMS Since this is the last meeting before that date, we scrambled to get this put together. Standard answers, very similar to what it was last year. I think the numbers that we'll call out that are different that I think are improving are like the generic trend. So if you look, starting on page 7, see the number of generic claims. It's on the very bottom and then it splits and carries over to page 8. Our generic dispense rate is 80.5%. And this is 2013. We're pushing 82% now and this continues to climb as more generics are available. But still it only makes up 22% of our total expenditure, so that's a huge difference. As more specialty products and biologics hit on the market, the brand names are really pushing the prices up.
PO: Carl, for that 80% is that for those products that have a generic available, or all dispensed?
Carl: That's all dispensed generics. Our rate of dispense when there's a generic available is over 99 percent. There's not too many and think most of those are on the preferred list.
We have a little bit more work to do for cost savings and cost avoidance. These are numbers we've shared before with the DUR board. We're just going to roll those into an annual report instead of the quarterly.
CJ: On the early refill, what is the rationalization for utilizing 80% for one class of drug and 90% for another?
Coleen: The DUR board actually made that recommendation back in 2007 or 2008. There was one tolerance level. At the very beginning when the controlled substance focus started. We started that. That's when the recommendation happened because that's what a lot of states do. They tighten it up on that side.
Carl: CMS is doing a better job about getting these every year they update these reports and ask for different information, for example this year they are asking for e-prescribing trends. They've asked for these cost savings numbers for retro-DUR before and they are doing a better job of rolling these in and getting them back out to the public. We should be seeing standardization across the board.

PO: We need to approve this report for submission, so I'll ask for a motion to approve it.
LN: Motion to Approve.
PO: We have a motion, do we have a second?
DE: Second.
PO: We have a motion and a second to approve the Preliminary Annual DUR Report for CMS. Any additional discussion?
Voted: Unanimously to Approve.

b. Discussion of proposed adoption of updated clinical prior authorization criteria for the medications used for acne – Carl Jeffery – Catamaran

Public Comment: None

Carl: The first page in there is chapter 1200 as it is now only one criteria is that they have to be under 21. So our proposed criteria is to add some criteria to those 22 and over, because we do receive periodic requests and I think there are adults with acne that can lead to infection and scarring, so we want to make sure we have the option available to treat these, so our proposal is that we add the criteria here that would 22 or over with a diagnosis of moderate to severe acne grade 2 or higher. I included a graph if you want to look at the utilization. Almost all of these are going to be patients that are 21 and under. But still the high ones are the Clindamycin, but they are appropriate levels after working through the topicals and then our oral tretinoin are very few. They are following the appropriate guidelines.
PO: There was some consideration for possibly utilizing the oral tretinoin products for just grade 3 or grade 4. Do you know if any of the other programs do anything like that?
Carl: It's across the board. Some other Medicaid programs don't cover these at all because they see them as strictly cosmetic, other ones are pretty open to adults. The criteria that is proposed here is by the clinical call center who does handle other Medicaid programs. This is pretty standard to what they are accustomed to seeing. They've got such a strict REM's set up for the oral tretinoins anymore, we're just adding more hoops to jump through to get those medications.
CL: You already have an overarching criteria that drugs can't be used for cosmetic reasons the call center will be looking at this in addition to that, correct?
PO: In essence we are looking at allowing those patients who fit the criteria of twenty two and over and with grade 2 or higher to include them in being eligible.
JM: Is there any P&T guidance? The thing that really jumps out, other than that tretinoin compound is the benzoyl peroxide – Clindamycin combinations being 100 times more expensive than the individual components. Is there any sort of step type therapy?
Carl: We do have a couple of classes, topical retinoid and combination agents. We've got Retin-A micro, Tazorac, and Ziana as preferred.
JM: Not as much concerned about the Retin-A as the clindamycin.
Carl: We've got the topical benzoyl peroxide antibiotic and combination products out there too.
JM: Those are like dirt cheap and until they combine them and then all of the sudden…
Carl: We've got the BenzaClin as one of our preferred agents.
CL: If you wanted to make a clinical step, you guys could do that, because they are just doing it for an entire class.
JM: The Clindamycin phosphate, for 921 Claims is $41,000, but for the BenzaClin, for 250, it's twice that.

Carl: What you're not seeing is the rebates coming back in. By having a preferred list, that's the whole point of it.
CL: The history of it is this. In many states, the reason the criteria is set under 21 is because it is looked at as cosmetic. Then states had to allow it for children because of the EPSDT rule. Then it was kind of pushed on throughout the years to where adults can have it. Now we've been pushed on and said "What do you do?" Some states allow it and some states stick with saying it's cosmetic for adults. If you treat the acne early…you get pushed on enough and say "What do you want to do?" There are still those cases on the edge. So I think we have a protection in the regulations so it can't be cosmetic, I won't get in trouble on the regulatory side. If we can put something in there that says medically that over 21…
PO: Is there going to be any kind of issue with the grading, the four grades of acne?
Carl: Moderate to Severe means grade two or higher. We can be more aggressive to start. It's always easier to be more aggressive then back off, then we can try to ramp up if we find out that utilization is going crazy. I think by the time they get moderate to severe grade acne, it's to the point of fulminating cystic acne where it's going to cause health issues.
DE: That's where grade two starts anyway.
Carl: I believe so.
PO: Cystic – I think that's three. Would it be possible for grades 1 and 2 to have certain medications available, then three and four, other medications are available? Set it up that way as opposed to anything's available?
Carl: There are clinical guidelines from the American Academy of Pediatrics that defines mild to moderate to severe and also there are some dermatology guidelines. The American Academy of Dermatology also has some recommendations.
DE: Could we possibly make an amendment to section B to make that grade 3 or higher as opposed to grade 2?
Carl: Certainly.
DE: I would think that by the time the patient reached 22, they would have already been on some sort of therapy and persisting after that age, it would be more severe therefore it would justify going to that. Whether they have come to and began a Medicaid program or had been in a Medicaid program, there would have been some treatment prior to that.
What we've got is a revision to the proposed prior authorization criteria with the new addition being the recipient is 22 years of age or older, and has a diagnosis of grade 3 or higher. Prior authorization would be good for one year. Can I get a motion for these proposed criteria?
PO: Can I get a motion for these revised proposed criteria, with the addition being the recipient is 22 or older and a diagnosis of grade 3 or higher of acne. The prior authorization would be good for one year?
DE: So moved.
JM: Second.
PO: We have a motion and a second. Any further discussion? None. All those in favor of the revised proposed prior authorization criteria
Voted: Unanimously to Approve. Motion carries.

c. Clinical review – Xolair – Carl Jeffery – Catamaran

Public Comment: None

Carl Jeffery – Catamaran - Proposed addition for treatment of the urticaria as a new indication for this product. No changes to the actual treatment of asthma, just the addition of the urticaria. I did look into other treatments with H2 blockers for treatment of urticaria. It's really not indicated for that, but they've done some studies and a lot of studies are really old and not well controlled. They weren't blinded or anything. A lot of them were done with hydroxyzine. They think it had more to do with the cimetidine boosting the effects of the hydroxyzine, than the cimetidine having an effect itself. It's really not that much of an impact. But still the criteria is to have the H1s first, oral antihistamines first then go on to the two.
DE: This would still be a relatively limited access anyway. Even using Xolair, even for the asthma.
Carl: We average in the low 20's the number of people who are on this.
PO: Do you recall what the rationalization was for the prior authorization being 3 months? Would it make it easier on the call center if it was one year?
Carl: Yes. It would mean fewer calls.
DE: What I don't recall of the top of my head is where it says chronic idiopathic urticaria I don't remember the underlying passage of what is causing it. It doesn't make sense. By the virtue of saying chronic idiopathic, it would make sense to say the one year approval time as opposed to three months if it's going to be an ongoing process. But I can't recall what would stimulate this, if there was any seasonal variability with it.
Carl: I'm not familiar enough with it either.
DE: I like the criteria though.
CL: The first part of it wasn't for someone who was chronic.
DE: The first part was for persistent asthma that can flare up, but at the same time with chronic idiopathic urticaria…I've dispensed it for patients with asthma, but never for a patient with chronic idiopathic urticaria (CIU), so I'm not that familiar with that utilization of it. If I remember correctly, even when we were using the Xolair, the patient had to meet all of the criteria too. Plus it is limited as to who can prescribe it. Up here we see that it has to be prescribed by the pulmonologist, allergist, and immunologist. We're leaving it pretty open down here in the CIU. Would we want to add the allergist, immunologist section and/or rheumatologist down there as opposed to leaving it for anyone to order because the criteria for Xolair is quite extensive? It has a black box warning. Would we want to add dermatologist, allergist, and immunologist down in the criteria part B in the 'iii' section, moved down one level? Put who can prescribe it in there like we've included up above. In addition we have that the recipient's current weight must be recorded. I think that should be added to the CIU indication also because it's weight based.
Carl: Dosage is also dependent on pretreatment IGE results.
PO: So we've revised the proposed prior authorization criteria, we're not touching the indication for severe persistent asthma, What we're looking at doing is adding the diagnosis of chronic idiopathic urticaria with the proposed criteria of the present here and adding that the prescriber must be either a pulmonologist, dermatologist, or a rheumatologist and recipient's current weight must be recorded. Also extend the prior authorization period to one year. For both.
Carl: For the chronic urticaria, it's not weight based dosing. It's just 150 or 300 mg dosing once every 4 weeks.

PO: How do they determine whether it's for 150 or 300? [Drug information] says dosage of Xolair in CIU patients is not dependent on serum IGE level, or body weight. It just says 150 or 300, but doesn't give any criteria. Not going to add the weight.
Carl: Just to be clear, the motion is to add the specialist, dermatologist, pulmonologist, rheumatologist, the CIU indication, and to increase the prior authorization to 12 months.
DE: I'll move we accept this
JM: Second
PO: Motion and second. No further discussion, Advised Proposed prior authorization criteria for the use of Xolair for both the severe persistent asthma and chronic idiopathic urticaria, with 12 month approvals with prior authorization.
Board: Voted unanimously – Aye
PO: Motion carries.

d.Clinical review – Ivacaftor

Public Comment: Lisa Borland – Medical Affairs with Vertex Pharmaceuticals – Addressing the committee in reference to Ivacaftor. It's known commercially as Kalydeco. First and only available therapy that targets the underlying causes of cystic fibrosis. The underlying cause in a defect in what is called the CF Terra protein. CF terra protein primarily functions as a chloride ion channel. This is really important in regulating fluid and electrolytes across various epithelial tissues – the lung, the pancreas, and the digestive system. Estimated 30,000 persons with cystic fibrosis in the United States. According to the 2012 Cystic Fibrosis Foundation patient registry, there are an estimated 186 patients in the state of Nevada. Kalydeco is indicated for a very specific subset of the CF population. It was originally approved in January of 2012 for persons 6 years of age and older with a mutation known as G551D. That mutation is present in less than 4% of the overall CF population. In February of this year, the label was expanded to include 8 additional mutations. These 8 additional mutations account for less than 1% of the overall CF population. That indication was added for 6 and older for those 8 additional mutations. Should also add that it is not effective for those who have 2 copies of the 508 Dal mutation. That's the most common CF causing mutation. The efficacy of Kalydeco in persons with the G551D mutation was supported by two phase 3 clinical trials – one in persons 12 years of age and older, the other in patients 6-11. In both those studies there was a statistically significant improvement in lung function as measured by percent predicted FEV-1. That was assessed at 24 weeks. The treatment effect was 10.6 in the adolescent population and 12.5% in the pediatric population. Those levels of lung improvement were sustained through 48 weeks of therapy. Those were seen regardless of age, sex, level of disease severity, or geographic location. Patients treated with Kalydeco also saw improvements in weight. In both the adolescent and adult population there was a decrease in risk of pulmonary exacerbations, as well as improvement in patient's respiratory symptoms. The study evaluating and supporting the efficacy for the 8 additional mutations, for which Kalydeco recently gained approval. In the smaller study, because those mutations are very rare, 39 patients, it was an 8 week cross over study. Those patients responded very similarly as the G551D population. So an improvement in percent predicted FEV-1, 10.7%, we didn't see the reduction in risk of pulmonary exacerbations, because the study was only 8 weeks and was too short, but an improvement in MMI and patient reported respiratory symptoms. The safety profile is really based on the three original registration

studies. The discontinuation rate due to adverse events; in the Kalydeco treated patient, it was 2%, that's compared to 5% in the placebo treated patients. The serious adverse events that occurred more commonly with Kalydeco than with placebo, whether or not they were determined to be drug related by the investigator, were increased liver enzymes, abdominal pain, and hypoglycemia. The small study - safety profile was very similar to what was seen in the G551 population.
DE: This basically improves quality of life, but about longevity?
Lisa Borland: The therapy has been on the market for two years, so there isn't enough information to prove its effect on survival. We do have modeling data that suggests that, based on the improvement in just FEV-1.
DE: With the patient being required to be 6 years of age or older, were tests not done on anyone younger than that? Or are there possible studies to be done on younger patients?
Lisa Borland: The dose is the same in those 6-11 as in those 12 and older. The pill is about the size of a large multi vitamin. The pediatric patients just can't take those. The pediatric patients have not been evaluated yet and it would require a different formulation. As of now, though it's outside of the labeled indication, a pediatric study has been conducted in 2-5 year olds with a different formulation.
DE: It's probably a "Do not crush" then.
Lisa Borland: I don't know that the formulation has been released publically, but it is not a large multi vitamin. It's a pediatric formulation.
DE: In the studies do you also see a decrease in hospitalizations?
Lisa Borland: In the phase 3 studies, particularly in the adolescent and the adult population, we didn't see very many pulmonary exacerbations in the pediatric patients, in general. Lung function doesn't start to decline until adolescence. Pediatric patients have healthier lungs. What we saw with hospitalization was a tertiary endpoint in the adolescent and adult population. I didn't see a significantly decreased rate of hospitalizations themselves, but in the duration of the hospitalizations and duration of IV antibiotics, and the duration of those pulmonary exacerbations, when they occurred, and how they were treated, but not the numbers or the even rate.
DE: With this onboard, were there any issues with the patients, if there were a hospitalization, or even outpatient, were they still able to use the inhaled antibiotics, or did it always require, if they had exacerbation, hospitalization where they had to have IV antibiotics as opposed to inhaled or oral.
Lisa Borland: There's no standard definition of pulmonary exacerbation. The way that they were evaluated or defined in clinical trials was 4 of 12 sinopulmonary symptoms and either a change in antibiotics, or an addition of an antibiotic. It wasn't necessarily related to IV antibiotics.
PO: So what we have in front of us is the proposed criteria, amended from what we did have to include the new mutations, as well as the inclusion of the 6 years of age or older criteria. Motion to accept and seconded. No further discussion
DE: Motion to accept
LN: Second
Board: Voted Unanimously - Aye
PO: Motion carries.

e. Clinical review – Updated prior authorization criteria for those medications used to treat ADD/ADHD

PO: We have the previous criteria that was last reviewed in January of 2008. No proposed changes. Just time to take a look at the criteria for review. Call for anyone in the public domain that wishes to speak.

Sandy Sierawsky – Pharmacist in Nevada – Pfizer/Medical Division:
This was addressed in the April meeting, but one of the things that the state wanted to see changed was the removal of the DSM terminology. That's what was discussed. The other issue I wanted to resurface is that it's pretty restrictive criteria for those who are not psychiatrists. If you look at the data that IMS provides, prescriptions for long acting stimulants make up about 60% of treatment for ADHD. Out of that 28% is prescribed by psychiatrists. 72% is prescribed by pediatricians, primary care physicians, etc. Nationally, psychiatrists aren't prescribing the bulk of these medications. The American Academy of Pediatrics require pediatricians to diagnose and treat ADHD. They provide guidelines for them to follow to identify causes, symptoms, vulnerabilities, etc. Nationally, pediatricians provide about 66% of all office visits for children in Medicaid. I feel that the criteria is too restrictive to allow for those healthcare providers to provide treatment.
LN: Is this still being done like this? Where, when I'm writing a prescription, I'm still having to get a prior authorization even when putting down a diagnosis?
Coleen: Top prescribers in Nevada are psychiatrists, not pediatricians.
Sandy Sierawsky: Right because it's too difficult for the pediatricians to write the prescription because the criteria doesn't allow it. They probably just pass on the patients to a psychiatrist.
Coleen: We've also talked about the overall behavioral health of the children. We still have a very high utilization of these medications in Nevada, if you look at the data.
DE: The point of the criteria is to have a psychiatrist in the mix, so that the patient can be evaluated for need. This prevents a child being put on the medication just because there was a complaint from a teacher.
Board discussion: Reviewed Prior Authorization form. How Nevada differs from other states in this matter is the requirement of follow up care. Patients must be seen during a certain timetable. How do we assure that people get appropriate treatment?
Board discussion: Use of the DSM 4 – Updating policies. If the ICD-9 language can be taken out of the policy, (where it's not applicable to the actual policy) it will be removed. If it is pertinent with ICD-9 and it needs to be updated with ICD-10, we cannot make that change because ICD-9 and ICD-10 cannot be run at the same time and it can't be changed to ICD-10 until next October.
Board: Board acknowledges the fact that they have reviewed the updated prior authorization criteria for those medications used to treat ADD/ADHD, but no changes will be made.
Board: No action being taken.

f. Clinical review – Prior authorization criteria for transdermal fentanyl system

Call for public representation: None

Board discussion: Last review by the DUR Board was July 30th, 2009. No proposed changes.

Discussion of criteria of using multiple long acting pain medications and limits set up by the criteria. Suggestion of eliminating item 1C from criteria. Need a better way to handle multiple drug prescriptions for pain, so that abuse can be stopped and doctors can actually prescribe what the patients need.

Carl to bring this discussion back to the next meeting for review. Mentioning morphine equivalent dosing that is ok to move to transdermal fentanyl. Criteria stating the prescriber has checked the PMP.
No action being taken to modify the criteria at this time.

g. DUR Board Requested Reports

1. **Top 10 Black Box Warning Medications** – Being deferred until next meeting. Open to audience discussion.
2. **Controlled Substance Utilization on Trials Report** – Carl Jeffery – Same report as was presented during last meeting. Hydrocodone and Acetaminophen are the highest prescribed medications. 500 mg Acetaminophen is no longer available after January, so it's not on the report. Pretty significant spike in drug utilization, but there has been an increase in Medicaid membership as a whole. Promethazine with Codeine has really dropped off.
    - Carl to bring criteria next meeting to discuss Lock-in program. Consider amending criteria.
3. **Psychotropic medication use in Children** – Report filters diagnosis by age. Appears that the adolescent population is spiking. Count of diagnosis by specialty. The program that pulls the reports doesn't duplicate the numbers. The primary diagnosis is captured. If the child is on an additional medication for another diagnosis, that diagnosis is not captured on the report. The population of children on psychotropic medications is very high.
4. **Pro-DUR edit on late refill correlation to ER visits –** still pending.
5. **Buprenorphine and Buprenorphine-naloxone use –** 2 reports and the Board is asked to return the color coded copies when finished in insure no potential HIPAA violations. Looking at continuity of care with these products. Reports show that the patients are very compliant in taking the medications, or at least getting them filled. Possible criteria for initial fill to limit the quantity for the first 30 days with the requirement of ongoing 30 day fills after the initial fill. Main concern is paying a dispensing fee each time. There are other states that limit the dispensing fee to once a month. Will evaluate how it is done in other states.

h. DUR Board Standard Report

Carl presented drugs by diagnosis. Top 10 prescribed. Everything looks consistent. Hepatitis agents have moved up while Hemophilia has dropped off since the first quarter. Abilify is one of the top medications. Significant change in amount+ spent can be attributed to a few new members that require a very large dose of medication at a time. Abilify to go generic in 2015. Oxycontin should be going generic soon. Generics have been approved. Purdue has a competing product with Zohydro coming out.

Request: Albuterol or asthma medicines as a whole – breakdown of how patients are using the drug and how effective it is for treatment.
Request: Tussionex report
Retro DUR Report: Looking at A-typical antipsychotics in pediatric patients. If they are on 2 or more a-typicals outside of their approved age. Study is not finished. Hoping for feedback by next meeting.

Possibility of going paperless discussed.

6. Date and Location of next meeting

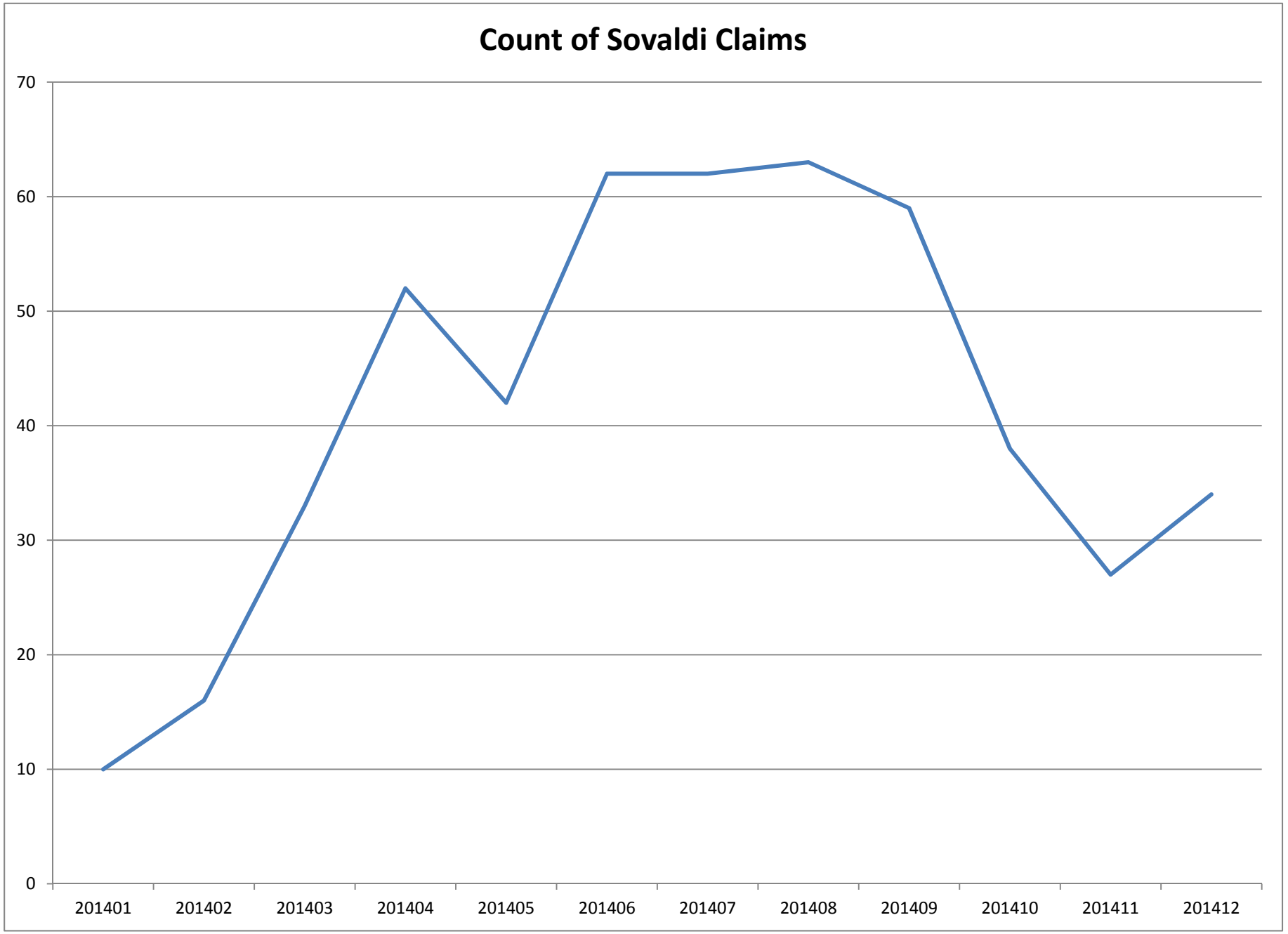
October 23, 2014, at the Best Western in Reno.

7. Adjournment

Meeting Adjourned at 7:53PM

Sovaldi Utilization - 2014

YearMonth Filled	Drug Label Name		Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201401	SOVALDI	TAB 400MG	10	10	280	280	$ 228,525.28
201402	SOVALDI	TAB 400MG	16	16	448	448	$ 428,475.00
201403	SOVALDI	TAB 400MG	33	30	924	924	$ 856,953.60
201404	SOVALDI	TAB 400MG	52	45	1,456.00	1,456	$ 1,428,245.20
201405	SOVALDI	TAB 400MG	42	41	1,176.00	1,176	$ 1,171,158.76
201406	SOVALDI	TAB 400MG	62	55	1,736.00	1,736	$ 1,628,888.36
201407	SOVALDI	TAB 400MG	62	53	1,736.00	1,736	$ 1,629,221.40
201408	SOVALDI	TAB 400MG	63	56	1,764.00	1,764	$ 1,544,886.16
201409	SOVALDI	TAB 400MG	59	55	1,652.00	1,652	$ 1,429,951.20
201410	SOVALDI	TAB 400MG	38	38	1,064.00	1,064	$ 1,000,449.72
201411	SOVALDI	TAB 400MG	27	27	756	756	$ 714,462.36
201412	SOVALDI	TAB 400MG	34	28	952	952	$ 942,976.84


Count of Sovaldi Claims
70
60
50
40
30
20
10
0
201401
201402
201403
201404
201405
201406
201407
201408
201409
201410
201411
201412

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA
Sovaldi (Sofosbuvir)

No Changes Proposed at this time.

VV. Sovaldi® (sofosbuvir)

Therapeutic Class: Anti-Hepatitis Agents-Polymerase Inhibitor Agents
Last Review by the DUR Board: April 24, 2014

Sovaldi® (sofosbuvir) is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations:

   Approval for Sovaldi® (sofosbuvir) for mono-infected or HCV/HIV-1 co-infected recipients will be given if the following criteria are met and documented:

   a. The recipient has a diagnosis of chronic hepatitis C Genotype 1 infection; and the recipient will be treated in combination with peginterferon alfa and ribavirin or, if the recipient is ineligible to receive peginterferon alfa, in combination with ribavirin; or

   b. The recipient has a diagnosis of Chronic Hepatitis C Genotype 2 or 3 Infection; and the recipient will be treated in combination with ribavirin; or

   c. The recipient has a diagnosis of Chronic Hepatitis C Genotype 4 Infection; and the recipient will be treated in combination with peginterferon alfa and ribavirin; or

   d. The recipient has a diagnosis of Chronic Hepatitis C Genotype 1, 2, 3, or 4 infection; and the recipient has a diagnosis of hepatocellular carcinoma and is awaiting a liver transplant; and the recipient will be treated in combination with ribavirin.

2. Prior Authorization Guidelines:

   a. Prior Authorization approval will be for 12 weeks for ALL of the following:

      1. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection and combination therapy with peginterferon alfa and ribavirin.

      2. Recipients with a diagnosis of Chronic Hepatitis C Genotype 2 infection and combination therapy with ribavirin.

   b. Prior Authorization approval will be for 24 weeks for all of the following:

      1. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection and combination therapy with ribavirin.

2. Recipient with a diagnosis of Chronic Hepatitis C Genotype 3 infection and combination therapy with ribavirin.

c. Prior Authorization approval will be for up to 48 weeks or until liver transplantation for recipients with a diagnosis of hepatocellular carcinoma and is awaiting a liver transplant combination therapy with ribavirin.

d. Prior Authorizations will be renewed in 12 week intervals based on genotype.

e. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Hepatitis C Polymerase Inhibitors

Therapeutic Class

- **Overview/Summary:** Sovaldi® (sofosbuvir) and Harvoni® (ledipasvir/sofosbuvir) are once-daily nucleotide analog inhibitors of hepatitis C virus (HCV) nonstructural protein 5B (sofosbuvir) and 5A (ledipasvir) ribonucleic acid (RNA) polymerase, which is essential for viral replication of HCV.[1,2] The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus-1 co-infection.[1] Ledipasvir/sofosbuvir has been proven safe and effective only in genotype 1 infection.[1,2]

- Several treatment guidelines were recently updated to include recommendations on the use of sofosbuvir in the treatment of HCV infection.[3-6] The consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) prefer sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infection. Telaprevir- and boceprevir-containing regimens are considered inferior to the preferred and alternative regimens and are no longer recommended for the treatment of HCV genotype 1 infection.[3]

Table 1. Current Medications Available in Therapeutic Class[1]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with ribavirin alone (without peginterferon alfa) in patients who are ineligible to receive an interferon-based regimen; treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	Tablet: 400 mg	-
Ledipasvir/ sofosbuvir	Treatment of chronic HCV genotype 1 infection in adults	Tablet: 90/400 mg	-

HCV=hepatitis C virus, HIV=human immunodeficiency virus

Evidence-based Medicine

- The Food and Drug Administration (FDA) approval of the polymerase inhibitor sofosbuvir was based on the results of six clinical trials consisting of 1,947 patients who were treatment-naive or had not responded to previous treatment with peginterferon alfa and ribavirin (treatment-experienced), including patients with hepatitis C virus (HCV) and human immunodeficiency virus co-infection. In addition, sofosbuvir was effective in patients who were not eligible for an interferon-based treatment regimen and in patients with hepatocellular carcinoma awaiting liver transplantation, addressing unmet medical needs in these populations.[1,7-9]

- The addition of sofosbuvir to standard therapy (i.e., ribavirin or peginterferon alfa and ribavirin) resulted in significantly higher sustained virologic response rates compared to standard therapy alone in adults with chronic HCV genotype 1, 2, 3 and 4 infections.[1,6-8]
- The FDA approval of Harvoni® (ledipasvir/sofosbuvir) was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection with compensated liver disease. All three phase III trials evaluated efficacy of ledipasvir 90 mg/sofosbuvir 400 mg fixed-dose tablet administered once daily with or without ribavirin. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels. Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL (lower limit of quantification) at 12 weeks after the end of treatment.[2,10-12]
- Ledipasvir/sofosbuvir had a sustained virologic response at 12 weeks in >95% of the patients across the three trials. This included patients that were treatment-naïve and –experienced and patients who both had and did not have cirrhosis.[2,10-12]
- Treatment with Ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).[11]
- The most commonly reported adverse events in clinical studies of sofosbuvir and ribavirin were fatigue and headache. In patients treated with sofosbuvir, ribavirin and peginterferon alfa, the most commonly reported adverse events included fatigue, headache, nausea, insomnia, and anemia. Adverse effects for Ledipasvir/sofosbuvir are similar to sofosbuvir alone.[1,2,7-12]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[3-6]
    - The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 through 6 is the use of sofosbuvir-based combination therapy.
        - Simeprevir, peginterferon alfa, and ribavirin triple therapy regimen is generally recommended as an alternative, rather than a preferred regimen.
        - The use of sofosbuvir plus simeprevir (with or without ribavirin) off-label regimen is recommended in genotype 1 HCV infected patients who are either peginterferon alfa ineligible, prior null or partial responders to peginterferon alfa and ribavirin dual therapy, or liver transplant recipients.
        - In the treatment of HCV genotype 1 infection, telaprevir- and boceprevir-containing regimens are considered inferior to the preferred and alternative regimens and are either no longer recommended or are reserved for patients who are not candidates for the preferred and alternative regimens.
        - No one peginterferon alfa or ribavirin product is preferred or recommended over another.
- Other Key Facts:
    - Sofosbuvir is available as a 400 mg tablet and is dosed 400 mg once daily.[1]
    - Ledipasvir/sofosbuvir is available as a 90/400 mg tablet and is also dosed once dialy.[2]
    - The standard drug regimen for chronic hepatitis C requires 24 to 48 weeks of treatment, with self-injections of peginterferon alfa which is associated with a number of side effects including nausea, mood swings and severe flu-like symptoms. Sofosbuvir combination therapy shortens the treatment duration to only 12 week in genotype 1, 2 and 4 HCV infections and offers an interferon-free regimen in genotype 2 and 3 HCV infections.[1,3]
    - Sofosbuvir is a substrate of P-glycoprotein (P-gp). Thus, coadministration of potent P-gp inducers such as rifampin and St. John's wort should be avoided. Nevertheless, there are fewer drug interactions with sofosbuvir compared to the HCV protease inhibitors.[1,2,15-17]
    - Compared to combination therapy with HCV protease inhibitors for the treatment of genotype 1 HCV infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).[1,13-15]

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Therapeutic Class Review
Hepatitis C Polymerase Inhibitors

Overview/Summary

The hepatitis C polymerase inhibitors include sofosbuvir (Sovaldi®) alone and the combination product ledipasvir/sofosbuvir (Harvoni®) which are used for the treatment of chronic hepatitis C infection.[1,2] The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.[3,4] There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.[4,5] The goal of hepatitis C treatment is HCV eradication in order to prevent complications and death. Genotyping is helpful in the clinical management of patients with hepatitis C for determining the choice of therapy. Assessment of liver disease severity is also recommended for predicting prognosis and determining the timing of therapy.[6,7] Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Sustained virologic response (SVR), defined as the absence of HCV ribonucleic acid (RNA) 24 weeks following discontinuation of treatment, has historically been the most important primary endpoint in clinical trials. Recently, SVR 12 (undetectable HCV RNA 12 weeks after the end of therapy) has also been accepted as a primary endpoint for regulatory approval in the US due to concordance with SVR 24.[6] Prior to the availability of direct-acting antiviral agents, combination of peginterferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.[4-12] The other direct-acting antiviral agents include the nonstructural protein 3 protease inhibitors boceprevir, telaprevir and simeprevir.[13-15] Several other direct-acting antiviral agents are in the final stages of development that aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as to shorten treatment duration.[6] The consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) give preference to sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infections. The choice of treatment regimen is primarily determined by HCV genotype, response to prior treatment (in any), the stage of liver disease, HCV viral load as well as patient's ability to tolerate and be adherent treatment.[1,2,7] For genotype 1 infection, telaprevir- and boceprevir-containing regimens are considered to be markedly inferior to the preferred and alternative regimens due to higher rates of serious adverse events, longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and dietary requirements.[7] Treatment guidelines do not give preference to one specific peginterferon alfa or ribavirin product over another.[4-12]

Sofosbuvir (Sovaldi®) is a nucleotide analog inhibitor of HCV nonstructural protein 5B RNA polymerase, which prevents viral replication of the HCV. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV)-1 co-infection. Prescribing information does not restrict sofosbuvir use to either treatment-naïve or experienced patients.[1] The combination product, Harvoni®, adds ledipasvir to sofosbuvir. Ledipasvir is similar to sofosbuvir; however, it inhibits HCV nonstructural protein 5A.[2] Specific Food and Drug Administration-approved indications are outlined in Table 2. Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).[1,2,13-15]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Sofosbuvir (Sovaldi®)	Hepatitis C virus NS5B polymerase inhibitor	-
Ledipasvir/sofosbuvir (Harvoni®)	Hepatitis C virus HCV NS5A inhibitor/ NS5B polymerase inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[1,2,16]

Indication	Sofosbuvir	Ledipasvir/ sofosbuvir
Treatment of chronic HCV genotype 1 infection in adults		✔
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen	✔	
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin	✔	
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin	✔	
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	✔	

HCV=hepatitis C virus, HIV=human immunodeficiency virus

Pharmacokinetics

Table 3. Pharmacokinetics[1,2,16]

Generic Name	Bioavailability (%)	Protein Binding (%)	Renal Excretion (%)	Metabolism	Serum Half-Life (hours)
Sofosbuvir	Not reported	61to 65	80	hydrolysis and phosphorylation (active metabolite: GS-461203)	0.5
Ledipasvir/ sofosbuvir	Not reported	>99.8/ 61 to 65	<1/80	oxidation/hydrolysis and phosphorylation	47

Clinical Trials

The Food and Drug Administration approval of sofosbuvir was based on the results of five Phase 3 trials (N=1,724) in hepatitis C virus (HCV) mono-infected patients with HCV genotypes 1 to 6 and one Phase 3 trial (N=223) HCV/human immunodeficiency virus (HIV)-1 co-infected subjects with HCV genotype 1, 2 or 3 infection. Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peginterferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV ribonucleic acid (RNA) levels. Sustained virologic response (SVR), the primary endpoint, was defined as HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment.[1]

NEUTRINO (N=327) was an open-label, single-arm Phase 3 trial that evaluated a 12-week regimen of sofosbuvir plus peginterferon alfa and ribavirin in treatment-naïve patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). In this study, 90% of patients treated with sofosbuvir combination therapy achieved a SVR12 as compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. Rates of SVR12 did not differ greatly according to the HCV genotype. The rate of SVR was 92% among patients without cirrhosis and 80% among those with cirrhosis. A SVR occurred in 98% of patients with the CC genotype of IL28B (a marker for improved immune response to HCV), as compared to 87% of patients with the non-CC IL28B genotype.[17]

While sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71% according to the prescribing information. This is based on the observed response rate in NEUTRINO subjects with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).[1]

FISSION (N=499) was a randomized, open-label noninferiority Phase 3 trial that compared treatment with sofosbuvir plus ribavirin for 12 weeks to peginterferon alfa plus ribavirin for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3. A SVR12 was achieved in 67% of patients in both groups. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 3 (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR compared to 38% of those receiving peginterferon alfa plus ribavirin.[17]

No resistance-associated mutations were detected among patients in either NEUTRINO or FISSION trials who received sofosbuvir and had a relapse after virological suppression; the precise reason for relapse is unknown.[17]

POSITRON (N=278) was a randomized, double-blinded Phase 3 trial that compared 12 weeks of treatment with sofosbuvir and ribavirin to placebo in patients with HCV genotype 2 or 3 who were interferon intolerant, ineligible or unwilling. A SVR was achieved in 78% of patients treated with sofosbuvir and ribavirin compared to 0% of those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir and ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 2 (61 vs 93%). Among patients with HCV genotype 3 receiving sofosbuvir and ribavirin, 21% of patients with cirrhosis achieved a SVR compared to 68% without cirrhosis. Among patients with HCV genotype 2 receiving sofosbuvir and ribavirin, 94% of patients with cirrhosis achieved a SVR compared to 92% without cirrhosis.[18]

FUSION (N=201) was a randomized, double-blinded Phase 3 trial that evaluated 12 or 16 weeks of treatment with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Treatment with sofosbuvir and ribavirin resulted in higher rates of SVR in the 12-week (50%) and 16-week groups (73%) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher SVR rate than patients receiving 12 weeks of treatment (difference, -23%; P<0.001). SVR in patients with HCV genotype 2 who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% confidence interval [CI], -24 to 9); however, the difference was not statistically significant. SVR rates in patients with HCV genotype 3 who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the SVR was 31% (60% with HCV genotype 2 and 19% with HCV genotype 3) compared to 61% among patients without cirrhosis (96% with HCV genotype 2 and 37% with HCV genotype 3). Among patients with cirrhosis who received 16 weeks of treatment, the SVR was 66% (78% with HCV genotype 2 and 61% with HCV genotype 2) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 and 63% with HCV genotype 3).[18]

VALENCE (N=419) was a placebo-controlled Phase 3 study that initially evaluated 12 weeks of treatment with sofosbuvir and ribavirin or placebo in treatment-naïve and treatment-experienced patients with HCV genotype 2 and 3. The treatment duration was subsequently extended to 24 weeks for patients with genotype 3 (N=250). In the sofosbuvir groups, SVR was achieved by 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. SVR rates were >90% in treatment-naïve patients, regardless or HCV genotype or liver fibrosis. Among treatment-experienced patients with cirrhosis, the SVR was lower in patients with genotype 3 compared to genotype 2 (61.7 vs 77.8%).[19]

PHOTON-1 (N=223) is an unpublished open-label Phase 3 trial evaluating 12- or 24 weeks of treatment with sofosbuvir and ribavirin in treatment-naïve patients with genotype 1 and treatment-naïve and treatment-experienced patients with genotype 2 or 3 HCV who were all co-infected with HIV.[1] In this trial, 95% of patients

were receiving antiretroviral therapy for their HIV infection. The most common HIV treatment regimens included emtricitabine/tenofovir administered with efavirenz, atazanavir/ritonavir, darunavir/ritonavir or raltegravir.[20] In this trial, SVR was achieved by 76% (87/114) of treatment-naïve patients with HCV genotype 1 receiving 24 weeks of therapy, 88% of treatment-naïve patients with HCV genotype 2 receiving 12 weeks of therapy, and 92% of treatment-experienced patients with HCV genotype 3 receiving 24 weeks of therapy. HIV rebound occurred in two patients (0.9%) on antiretroviral therapy.[1]

An unpublished open-label Phase 2 clinical trial evaluated sofosbuvir plus ribavirin in patients with HCV genotypes 1 to 6 and hepatocellular carcinoma prior to undergoing liver transplantation. Patients meeting the MILAN criteria (a single tumor ≤5 cm in diameter or ≤3 tumors each ≤3 cm in diameter and no extra hepatic manifestations of the cancer or evidence of vascular invasion of tumor) were treated for 24 to 48 weeks or until the time of liver transplantation. The post-transplant virologic response (pTVR) rate was 64% in the 36 evaluable patients who have reached the 12 week post-transplant time point. The safety profile of sofosbuvir and ribavirin was similar to that observed in Phase 3 clinical trials.[1]

An unpublished, ongoing, single-arm, open-label interferon-free Phase 2 pilot study is evaluating 24-week regimen of sofosbuvir plus ribavirin in naïve and treatment-experienced patients with recurrent HCV infection (any genotype) after liver transplantation. The interim SVR4 rate was 80.8% (21/26). There were no episodes of acute or chronic rejection. No drug interaction dose adjustments of immunosuppression have been required.[20]

LONESTAR-2 is an unpublished, ongoing open-label Phase 2 study evaluating a 12-week regimen of sofosbuvir 400 mg once daily added to peginterferon alfa (180 µg/week) and weight-based ribavirin twice daily (1,000 or 1,200 mg/day) among 47 treatment-experienced patients with HCV genotype 2 or 3 infection. In this study 55% of patients had cirrhosis. SVR12 occurred in 83% (20/24) of genotype 3 patients achieved and 96% (22/23) of HCV genotype 2 patients.[22]

The COSMOS trial is an unpublished, randomized, open-label, Phase 2a trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 (N=80) included prior null responders with METAVIR scores F0 to F2 and Cohort 2 (N=87) included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[23]

In the Cohort 1, SVR12 was achieved by 96% (26/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving a 12-week simeprevir and sofosbuvir regimen without ribavirin. In the Cohort 2, SVR12 was achieved by 93% (25/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving simeprevir and sofosbuvir regimen without ribavirin. Treatment was found to be generally safe and well tolerated. There was little to no benefit from adding ribavirin in this difficult to treat groups of hepatitis C patients and 12 week treatment provided similar clinical benefit to 24 week treatment.[23-25]

The FDA approval of Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]) was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection with compensated liver disease. All three phase III trials evaluated efficacy of ledipasvir 90 mg/sofosbuvir 400 mg fixed-dose tablet administered once daily with or without ribavirin. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels. Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL (lower limit of quantification) at 12 weeks after the end of treatment.[2]

ION-1 (N=865) was a phase III, randomized, open-label study that evaluated a 12 and 24-weeks of LDV/SOF ± ribavirin in treatment-naïve subjects with HCV genotype 1 infection, including those with cirrhosis (16%). In this study, over 97% of subjects across all four arms achieved SVR12. The SVR rate was not improved by the addition of ribavirin or by extending treatment from 12- to 24 weeks. The SVR rate was similar regardless of key baseline characteristics including HCV subtype (1a or 1b), race, baseline body mass index (BMI),

cirrhosis, gender, baseline HCV RNA level and IL28B status. The SVR rates in the four treatment groups ranged from 94 to 100% among subjects with cirrhosis, although the study was not designed or powered to formally compare the SVR rates among subjects with cirrhosis and those without cirrhosis.[26]

ION-3 (N=865) was a phase III, randomized, open-label study that evaluated eight weeks of LDV/SOF ± ribavirin and 12 weeks of LDV/SOF in treatment-naïve, non-cirrhotic subjects with HCV genotype 1 infection. The SVR rate was 94% with eight weeks of LDV/SOF, 93% with eight weeks of LDV/SOF+ ribavirin, and 95% with 12 weeks of LDV/SOF. Treatment with LDV/SOF for eight weeks was noninferior to both the 8-week LDV/SOF+ ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week LDV/SOF treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).[27]

ION-2 (N=440) was a phase III, randomized, open-label study that evaluated 12 to 24 weeks of LDV/SOF ± ribavirin in genotype 1 subjects with or without cirrhosis who failed prior therapy with an interferon-based regimen, including those containing an HCV protease inhibitor. The SVR rates was 94% in the group that received 12 weeks of LDV/SOF; 96% in the group that received 12 weeks of LDV/SOF + ribavirin; 99% in the group that received 24 weeks of LDV/SOF; and 99% in the group that received 24 weeks of LDV/SOF+ ribavirin.[28]

Treatment with LDV/SOF± ribavirin for 12-weeks resulted in lower SVR rates in cirrhotic subjects (82 to 86%) compared to non-cirrhotic subjects (95 to 100%). In contrast, 24-week treatment with LDV/SOF± ribavirin resulted in comparable SVR rates amongst subjects with cirrhosis (100%) and without cirrhosis (99%). The difference in SVR rates among subjects with cirrhosis receiving 12 and 24 weeks of treatment was statistically significant (P=0.007).[28]

ELECTRON-2 (N=90) was an unpublished, open-label, phase II study evaluating 12-week regimen of LDV/SOF± ribavirin in treatment-naïve and treatment-experienced subjects with genotype 1 and in treatment-naïve genotype 3 subjects. Treatment with LDV/SOF + ribavirin in subjects with genotype 1 and prior SOF failure lead to an SVR12 of 100% (19/19). Treatment with LDV/SOF in subjects with genotype 1 and Child Pugh Class B cirrhosis led to an SVR12 of 65% (13/20). Treatment with LDV/SOF in treatment-naïve subjects with genotype 3 lead to an SVR12 of 64% (16/25) Treatment with LDV/SOF + ribavirin in treatment-naïve subjects with genotype 3 lead to an SVR12 of 100% (26/26).[29] In the Synergy (N=14), treatment with LDV/SOF in subjects with genotype 1 and prior SOF failure lead to an SVR12 of 100% (14/14); of 14 subjects, seven had cirrhosis.[30]

Another unpublished study, ERADICATE (N=50), was an open-label phase II trial evaluating once-daily LDV+SOF for 12 weeks in treatment-naïve subjects with HCV genotype 1 infection (F0 to F3 liver fibrosis) and HIV co-infection. Cohort A included subjects who were not previously treated with HIV antiretrovirals who either had a stable CD4 count and HIV RNA <500 copies/mL or CD4 count >500 cells/mm^3. Cohort B included subjects on HIV antiretrovirals for at least eight weeks, CD4 count >500 cells/mm^3 and HCV RNA <40 copies/mL. Allowable HIV antiretrovirals included tenofovir, emtricitabine, efavirenz, rilpivirine, and raltegravir. In Cohort A, all 10 participants who were followed through 12 weeks post treatment achieved SVR12. In Cohort B, The SVR4 was achieved by all 22 subjects followed through post-treatment week four.[31]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients				
Lavitz et al[17] (NEUTRINO and FISSION) **NEUTRINO:** Sofosbuvir 400 mg once daily for 12 weeks and peginterferon alfa-2a 180 µg once weekly for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks **FISSION:** Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and	**NEUTRINO:** MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection **FISSION:** AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV	**NEUTRINO:** N=327 12 weeks **FISSION:** N=499 24 weeks	**NEUTRINO:** Primary: SVR12* Secondary: Not reported **FISSION:** Primary: SVR12* Secondary: Not reported	**NEUTRINO:** Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported **FISSION:** Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	infection			Secondary: Not reported
Afdhal et al[26] (ION 1) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not previously received treatment for HCV infection	N=865 12 to 24 weeks	Primary: SVR12* Secondary: Not reported	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR rates were 99% (95% CI, 96 to 100) in the group that received 12 weeks of ledipasvir/sofosbuvir; 97% (95% CI, 94 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of ledipasvir/ sofosbuvir with ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks				
Kowdley et al[27] (ION 3) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection without cirrhosis who had not previously received treatment for HCV infection	N=647 8 to 12 weeks	Primary: SVR12* Secondary: Noninferiority of eight weeks of ledipasvir/ sofosbuvir to the other treatment regimens	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR12 rate was 94% (95% CI, 90 to 97) with eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89 to 96) with eight weeks of ledipasvir/sofosbuvir with ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir/sofosbuvir. Secondary: Treatment with ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).
Treatment of Genotype 1: Treatment-Experienced Patients				
Afdhal et al[28] (ION 2) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not had a SVR with either PEG/ribavirin or NS3/4A protease inhibitor	N=440 12 to 24 weeks	Primary: SVR12* Secondary: SVR24*	Primary: In all four treatment groups, the SVR12 rate was higher than the adjusted historical response rate of 25% (P<0.001 for all comparisons). The SVR12 rates was 94% (95% CI, 87 to 97) in the group that received 12 weeks of ledipasvir/sofosbuvir; 96% (95% CI, 91 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	combined with PEG/ribavirin			Among patients with cirrhosis who were assigned to 12 weeks of treatment, the SVR12 rates were 86% for those who received ledipasvir/sofosbuvir and 82% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 95% and 100%. Among patients with cirrhosis who were assigned to 24 weeks of treatment, the SVR12 rates were 100% for those who received ledipasvir/sofosbuvir and 100% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 99% and 99%. The difference between the SVR rates among patients with cirrhosis who received 12 weeks of treatment and the SVR among patients with cirrhosis who received 24 weeks of treatment was statistically significant (P=0.007). Secondary: All patients who had a SVR12 also had a SVR24. No patient had a relapse after post-treatment week 12.
Treatment of Genotype 2 and 3 Chronic Hepatitis: Treatment-Naïve and Experienced Patients				
Jacobson et al[18] (POSITRON and FUSION) **POSITRON:** Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight	**POSITRON:** DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA	**POSITRON:** N=278 12 weeks **FUSION:** N=201 12 to 16 weeks	**POSITRON:** Primary: SVR12* Secondary: Not reported **FUSION:** Primary: SVR12*	**POSITRON:** Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
≥75 kg) for 12 weeks vs placebo **FUSION:** Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy **FUSION:** AC, DB, MC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen		Secondary: Not reported	21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis. Secondary: Not reported **FUSION:** Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection). Secondary: Not reported
Zeuzem et al[19] (VALENCE) Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12* Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported

*SVR12 was defined as HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment.
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, R=randomized, SG=single-group
Miscellaneous abbreviations: HCV=hepatitis C virus, RNA=ribonucleic acid, SVR=sustained virologic response

Special Populations

Table 5. Special Populations[14]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.
Ledipasvir/ sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease
*Ribavirin has a pregnancy category of X. Sofosbuvir must be used in combination with ribavirin or in combination with peginterferon alfa and ribavirin.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1,2]

Adverse Event(s)	Sofosbuvir	Ledipasvir/sofosbuvir
Fatigue	30* to 59†	13 to 18
Headache	24‡ to 36†	11 to 17
Nausea	13* to 34†	6 to 9
Pruritus	11‡ to 27*	-
Insomnia	15‡ to 25†	3 to 6
Anemia	6* to 21†	-
Asthenia	5† to 21*	-
Rash	8‡ to 18†	-
Decreased appetite	6*‡ to 18†	-
Pyrexia	4*‡ to 18†	-
Chills	2*‡ to 17†	-

Adverse Event(s)	Sofosbuvir	Ledipasvir/sofosbuvir
Neutropenia	<1*‡ to 17†	-
Influenza like illness	3‡ to 16†	-
Myalgia	6‡ to 14†	-
Irritability	10*‡ to 13†	-
Diarrhea	9‡ to 12*†	3 to 7

*Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.
†Sofosbuvir plus peginterferon alfa and weight-based ribavirin for 12 weeks treatment regimen.
‡Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.

Contraindications/Precautions

Ledipasvir/sofosbuvir has no listed contraindications.[2] However, when sofosbuvir is used in combination with peginterferon alfa or ribavirin, contraindications to and precautions with those agents are applicable to combination therapies (Black Box Warnings associated with these agents are outlined below).[1]

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Sofosbuvir combination treatment is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant.[1]

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir. Rifampin and St. John's wort should not be used with sofosbuvir and/or ledipasvir.[1,2]

Black Box Warning for Pegasys® (peginterferon alfa-2a) and Peg Intron® (peginterferon alfa-2b)[32,33]

WARNING
Alfa interferon, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)[34-36]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 7. Drug Interactions (Not All Inclusive)[1,2,37]

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Antacids: aluminum and magnesium hydroxide	Coadministration may result in decreased plasma concentrations of ledipasvir. It is recommended to separate antacid and ledipasvir/sofosbuvir administration by four hours.
Ledipasvir	H_2-receptor antagonists: famotidine	H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Ledipasvir	Proton-pump inhibitors: omeprazole	Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.
Ledipasvir	Antiarrhythmics: digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Ledipasvir, Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	St. John's wort (*Hypericum perforatum*)	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Dosage and Administration

Table 8. Dosing and Administration[1,2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Sofosbuvir	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen: Tablet: 400 mg once daily for 12 weeks (with peginterferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen) Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin: Tablet: 400 mg once daily for 12 weeks	Safety and efficacy in children have not been established.	Tablet: 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin: Tablet: 400 mg once daily for 12 weeks (genotype 2) or 24 weeks (genotype 3) Prevention of post-transplant HCV reinfection in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection: Tablet: 400 mg once daily for up to 48 weeks or until liver transplantation, whichever occurs first		
Ledipasvir/ sofosbuvir	Treatment of chronic HCV genotype 1 infection: Tablet: 90/400 mg once daily for 12 weeks (treatment-naïve with or without cirrhosis* or treatment-experienced without cirrhosis) or 90/400 mg once daily for 24 weeks (treatment-experienced with cirrhosis).	Safety and efficacy in children have not been established.	Tablet: 90/400 mg

HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Ledipasvir/sofosbuvir may be considered for 8 weeks of therapy in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[5]	• Current consensus guidelines provide guidance regarding optimal hepatitis C virus (HCV) treatment assuming that the decision to treat has already been made; guidance regarding in whom and when to initiate treatment will be provided in a future consensus guideline update. • It may be advisable to delay treatment for some patients with documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update. • A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended." • Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below. • Interferon ineligible criteria: o Intolerance to interferon alfa. o Autoimmune hepatitis and other autoimmune disorders. o Hypersensitivity to peginterferon alfa or any of its components. o Decompensated hepatic disease. o Major uncontrolled depressive illness. o A baseline neutrophil count below 1,500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL. o A history of preexisting cardiac disease. Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for

Clinical Guideline	Recommendation(s)
	12 weeks. o Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. <u>Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. <u>Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir.

Clinical Guideline	Recommendation(s)

	Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin
	• Recommended treatments:
	  o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative treatments:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	• Treatments that are not recommended:
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o Any regimen with boceprevir or telaprevir.
	
	Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin
	• Recommended treatments:
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	• Alternative treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	  o Sofosbuvir plus ribavirin for 24 weeks.
	  o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present).
	• Treatments that are not recommended:
	  o Boceprevir or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	
	Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir
	• Recommended treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	• Alternative treatments:
	  o Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks.
	  o Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks.
	• Treatments that are not recommended:
	  o Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistant resistance to protease inhibitor treatment.
	
	Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin
	• Recommended treatments:
	  o Sofosbuvir plus ribavirin for 12 weeks;
	  ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-

Clinical Guideline	Recommendation(s)
	by-case basis. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only) • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. o Interferon ineligible: ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments:

Clinical Guideline	Recommendation(s)
	o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: none. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. • Allowable antiretroviral therapy: o For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. o For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. <u>Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. • Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 2</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 3</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 4</u>

Clinical Guideline	Recommendation(s)
	• Recommended treatments (regardless of treatment history): o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of patients with cirrhosis</u> • Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis. • Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). • Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. o Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks. o This regimen should be used only by highly experienced HCV provider. • The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C): o Any interferon-based therapy. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Telaprevir, boceprevir, or simeprevir-based regimens. <u>Treatment of patients who develop recurrent HCV infection post-liver transplant</u> • Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks. • Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without

Clinical Guideline	Recommendation(s)
	peginterferon alfa, for 24 weeks. • Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2014)[7]**	Treatment considerations • The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. • Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. • Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months. • Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. • Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued. • Interferon ineligible or intolerant criteria: o Platelet count <75,000/mm^3. o Decompensated liver cirrhosis (Child Turcotte Pugh class B or C). o Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy. o Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation. o Inability to complete a prior treatment course due to documented interferon-related adverse effects. • Treatment of patients with HCV/HIV co-infection is similar to that of HCV mono-infected patients. Drug-drug interactions must be carefully considered. Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism). Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None.

Clinical Guideline	Recommendation(s)
	Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy. Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen (peginterferon alfa and ribavirin null responders only): o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-naïve patients • Preferred regimen: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-experienced patients • Preferred regimens: o Sofosbuvir plus ribavirin for 12 to 16 weeks. o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o None. Treatment of HCV genotype 3 in treatment-naïve patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients • Preferred regimens:

Clinical Guideline	Recommendation(s)
	o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only). <u>Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma</u> • Preferred regimens: o Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first. • Alternative regimen: o None. <u>Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant</u> • Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks <u>Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung)</u> • Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients. <u>Discontinuing HCV treatment based on lack of virologic response</u> • Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (RNA) assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any timepoint thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increased (i.e., >1 $\log_{10}$ IU/mL from nadir) or if the HCV RNA is ≥25 IU/mL at week 8 of therapy, discontinuation of all treatment should be strongly considered. • Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued. <u>Use in renal insufficiency</u> • Sofosbuvir use is not recommended if creatinine clearance <30 mL/min or end-stage renal disease due to insufficient safety and efficacy data. • No simeprevir dose adjustment is needed if creatinine clearance <30 mL/min. • Peginterferon alfa-2a dosage should be reduced to 135 µg/week once weekly for creatinine clearance <30 mL/min, including hemodialysis. • Peginterferon alfa-2b dosage should be reduced by 25% for creatinine clearance 30 to 50 mL/min and by 50% for creatinine clearance <30 mL/min, including hemodialysis. • Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30-50 mL/min and 200 mg daily for creatinine clearance <30 mL/min, including hemodialysis. <u>Use in hepatic impairment</u> • No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. • No sofosbuvir dosage adjustment in required for patients with any degree of renal impairment. • Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C).

Clinical Guideline	Recommendation(s)
	Mental health and substance-use disorders • Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. Substance or alcohol use • The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. • There are no published data supporting minimal length of abstinence as an inclusion criterion for HCV antiviral treatment. • Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialist.
European Association for the Study of the Liver: **Treatment of Hepatitis (2014)**[4]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. • Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. Indications for treatment • All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis (F3 to F4). • Treatment is justified in patients with moderate fibrosis (F2). • In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized. • Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy. Treatment considerations for HIV/HCV-coinfection • Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection. • The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir. • Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. • No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs. Treatment options for HCV genotype 1 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).

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	o Not recommended for HCV genotype 1a with Q80K polymorphism. o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week 4, 12 or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only). o Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies. o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. o Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available. • Sofosbuvir plus simeprevir for 12 weeks. o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <u>Treatment options for HCV genotype 2 infection</u> • Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced). • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients. <u>Treatment options for HCV genotype 3 infection</u> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks • Sofosbuvir plus ribavirin for 24 weeks o Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <u>Treatment options for HCV genotype 4 infection</u> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week 4, 12 or 24. • Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks. o Daclatasvir should be given for 12 weeks in combination with

Clinical Guideline	Recommendation(s)
	peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. • Sofosbuvir plus ribavirin for 24 weeks. o Should be reserved for interferon alfa intolerant or -ineligible patients. • Sofosbuvir plus simeprevir for 12 weeks. o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced). o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. <u>Treatment options for HCV genotype 5 or 6 infection</u> • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Sofosbuvir plus ribavirin for 24 weeks. o Should be reserved for interferon alfa intolerant or -ineligible patients. <u>Treatment monitoring</u> • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy. • In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. • In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week 4, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. • In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week 4, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy. • In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy. <u>Stopping (futility) rules</u> • Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week 4, 12 or 24. • No futility rules have been defined for other treatment regimens. <u>Virological response-guided triple therapy</u> • With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks.

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	• Patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. • No response-guided therapy is used in other treatment regimens. Measures to improve treatment adherence • HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. Retreatment of non-sustained virological responders • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. Patients with an indication for liver transplantation • In patients awaiting liver transplantation, antiviral therapy is indicated,

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	because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks. • In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group. <u>Post-liver transplantation recurrence</u> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. <u>Hepatitis B virus (HBV) co-infection</u> • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. <u>Hemodialysis patients</u> • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free

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	regimen. • Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. <u>Non-hepatic solid organ transplant recipients</u> • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is important in the absence of safety data in this population. <u>Active drug addicts and patients on stable maintenance substitution</u> • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy. <u>Treatment of acute hepatitis C</u> • Peginterferon alfa monotherapy for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection.

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	• Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.
World Health Organization: **Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection (2014)[8]**	Recommendations for treatment of HCV infection • All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment. • Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin. • Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4). • Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone. • In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost–effective. • Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use into consideration. • Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration. • Absolute contraindications to peginterferon alfa: o Uncontrolled depression, psychosis, or epilepsy. o Uncontrolled autoimmune disease. o Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in HCV/HIV coinfection). o Pregnancy or unwillingness to use contraception. o Breastfeeding women. o Severe concurrent medical disease including severe infections. o Poorly controlled hypertension, cardiac failure, or diabetes. o Solid organ transplant (except liver transplant recipients). o Chronic obstructive pulmonary disease. o Age <2 years old. • Relative contraindications to peginterferon alfa: o Abnormal hematological indices: ▪ Hb <13 g/dL in men or <12 g/dL in women. ▪ Neutrophil count $<1.5x10^9$/L. ▪ Platelet count $<90x10^9$/L. o Serum creatinine >1.5 mg/dL. o Hemoglobinopathies (sickle cell disease or thalassemia). o Significant coronary artery disease. o Untreated thyroid disease. • Treatment for HCV infection is both efficacious and cost-effective in PWID and is therefore recommended. • Specialist care needs to address the additional needs of special populations

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	of patients, including PWID, persons coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis. • The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.
Centers for Disease Control and Prevention: **Hepatitis ABC Fact Sheet (2012)**[9]	Hepatitis C • For acute hepatitis C, antivirals and supportive treatments are used. • Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.

American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[10]	• The treatment of choice is peginterferon plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with peginterferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with peginterferon and 800 mg of ribavirin daily, with the following exceptions:
	  • A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  • Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four.
	  • Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

Sovaldi® (sofosbuvir) and Harvoni® (ledipasvir/sofosbuvir) are once-daily nucleotide analog inhibitors of hepatitis C virus (HCV) nonstructural protein 5B (sofosbuvir) and 5A (ledipasvir) ribonucleic acid (RNA) polymerase, which is essential for viral replication of HCV.[1,2] The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus-1 co-infection.[1] Ledipasvir/sofosbuvir has been proven safe and effective only in genotype 1 infection. These approvals have changed the way in which hepatitis C is treated.

Similar to HCV protease inhibitors, sofosbuvir and ledipasvir/sofosbuvir may be used in both treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers.[1,2,13-15] Sofosbuvir must be administered in combination with ribavirin or peginterferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to polymerase inhibitor combination treatment.[1] Ledipasvir/sofosbuvir combintaiton therapy is a one-tablet, once-a-day therapy.[2] The safety and efficacy of sofosbuvir and ledipasvir/sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitors.[1]

Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir + pegylated interferon + ribavirin and ledipasvir/sofosbuvir combination therapies offer potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).[1,2,13-15]

The 2014 consensus guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) give preference to sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 through 6 infection. The use of telaprevir- and boceprevir-

containing regimens is no longer recommended in the treatment of HCV genotype 1 infection.[5] Treatment guidelines do not give preference to one specific peginterferon alfa or ribavirin product over another.[4-12] To date, no head-to-head trials have been published to directly compare the efficacy of HCV polymerase inhibitor sofosbuvir and HCV protease inhibitors.

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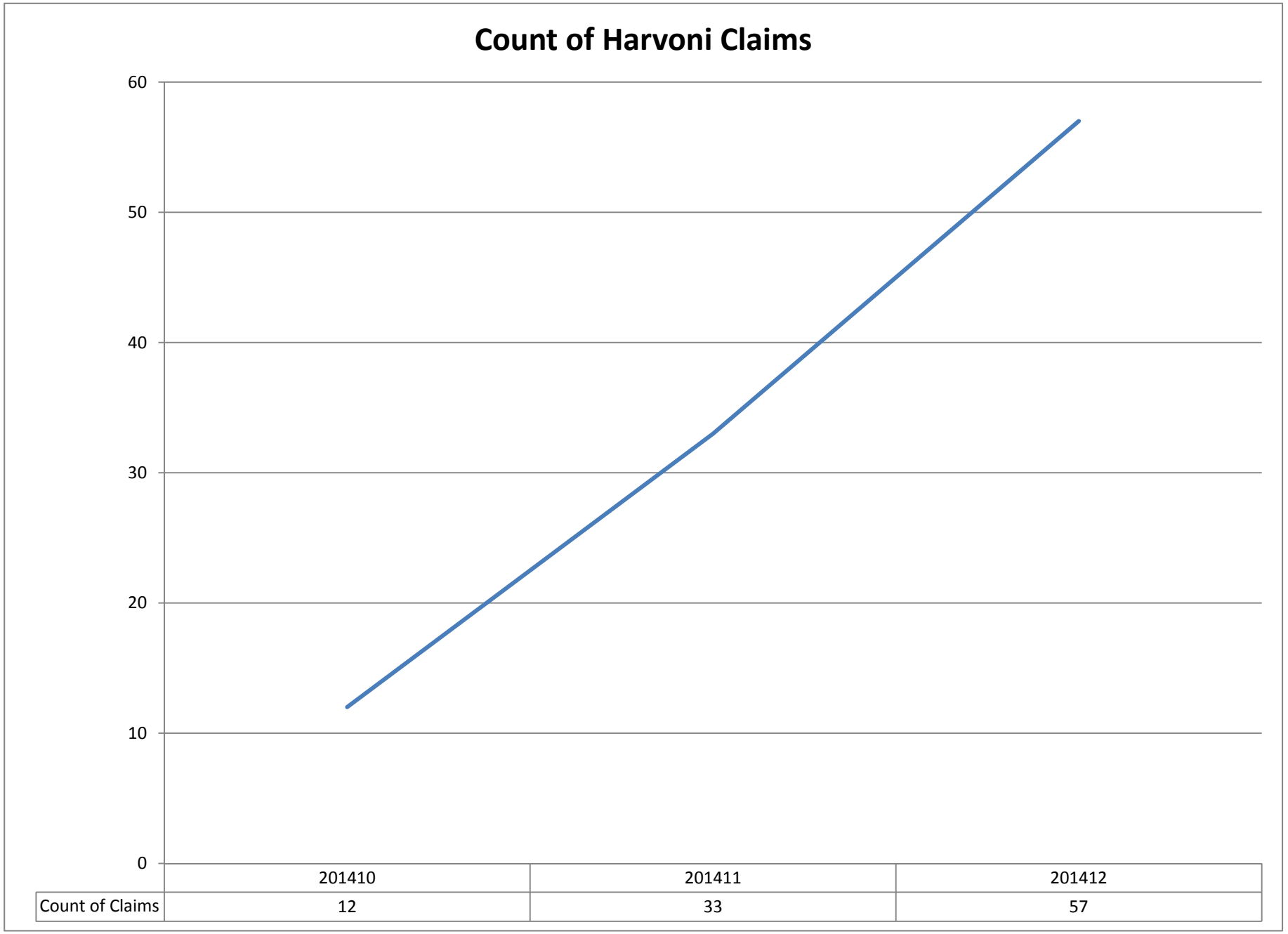
Harvoni Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Amt Paid
201410	HARVONI TAB 90-400MG	12	12	336	336	$ 385,617.12
201411	HARVONI TAB 90-400MG	33	32	924	924	$ 899,791.28
201412	HARVONI TAB 90-400MG	57	49	1,596	1,596	$ 1,671,025.52



	201410	201411	201412
Count of Claims	12	33	57

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

Requests for Harvoni® (ledipasvir/sofosbuvir)

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection.
AND
b. The recipient is 18 years of age or older.
AND
c. The requested dose is 90 mg/400 mg once daily.
AND
d. There is a clinically appropriate reason why the recipient cannot or should not use the preferred alternative.
AND
e. Approval will be granted for 8 weeks of therapy if the recipient is treatment-naïve, does not have cirrhosis and as a pre-treatment (within the last 12 weeks) HCV RNA viral load less than 6 million IU/mL.
OR
f. Approval will be granted for 12 weeks of therapy if **one** the following are met:
    1. The recipient is treatment-naïve, does not have cirrhosis and has a pre-treatment (within the last 12 weeks) HCV RNA viral load greater than or equal to 6 million IU/mL.
    OR
    2. The recipient is treatment-naïve and has cirrhosis.
    OR
    3. The recipient is treatment-experienced (failed treatment with peginterferon alfa + ribavirin ± an HCV protease inhibitor) and does not have cirrhosis (NOTE: patents who have failed a previous course of therapy with Sovaldi® is also acceptable to meet this criterion).

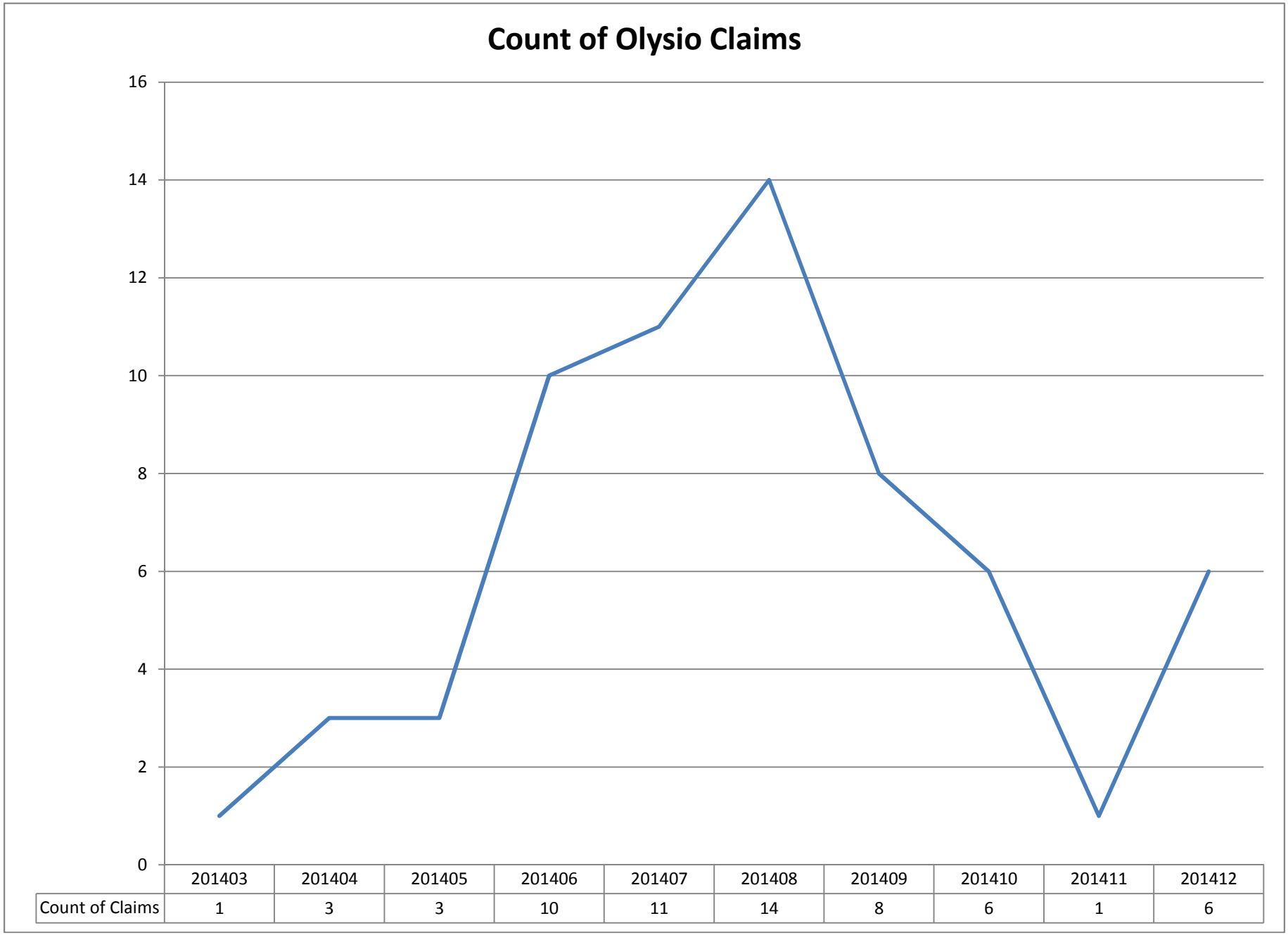
    OR
g. Approval will be granted for 24 weeks of therapy if the recipient is treatment-experienced (failed treatment with peginterferon alfa + ribavirin ± an HCV protease inhibitor) and has cirrhosis (NOTE: patents who have failed a previous course of therapy with Sovaldi® is also acceptable to meet this criterion).

2. PA Guidelines:
Prior Authorization approval may be for 8 weeks, 12 weeks or 24 weeks depending on clinical criteria.

3. Quantity Limitations:
1 tablet/day

Olysio Utilization - 2014

YearMonth Filled	Drug Label Name		Count of Claims	Count of Members	Qty Disp	Days Supply	Amt Paid
201403	OLYSIO	CAP 150MG	1	1	28	28	$ 22,567.16
201404	OLYSIO	CAP 150MG	3	2	84	84	$ 67,701.48
201405	OLYSIO	CAP 150MG	3	3	84	84	$ 67,701.48
201406	OLYSIO	CAP 150MG	10	6	280	280	$ 203,108.04
201407	OLYSIO	CAP 150MG	11	10	308	308	$ 203,377.24
201408	OLYSIO	CAP 150MG	14	11	392	392	$ 204,184.84
201409	OLYSIO	CAP 150MG	8	8	224	224	$ 91,079.84
201410	OLYSIO	CAP 150MG	6	6	168	168	$ 113,105.00
201411	OLYSIO	CAP 150MG	1	1	28	28	$ 22,567.16
201412	OLYSIO	CAP 150MG	6	4	168	168	$ 112,839.40



	201403	201404	201405	201406	201407	201408	201409	201410	201411	201412
Count of Claims	1	3	3	10	11	14	8	6	1	6

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA
Olysio (simeprevir)

No Changes Proposed at this time.

HH. Anti-Hepatitis Agents – Protease Inhibitor Agents

Therapeutic Class: Anti-Hepatitis Agents-Protease Inhibitors
Last Reviewed by the DUR Board: April 24, 2014

Victrelis® (boceprevir), Incivek® (telaprevir), and Olysio® (simeprevir) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations:

Approval will be given if the following criteria are met and documented:

a. Victrelis® (boceprevir)

1. For treatment initiation (treatment weeks 5 through 28), the recipient must have all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with peginterferon alfa and ribavirin for four weeks prior to starting Victrelis® (boceprevir) and will continue peginterferon alfa and ribavirin for the entire duration of treatment with Victrelis® (boceprevir); and

c. The recipient has not received a previous course of therapy with Incivek® (telaprevir), Olysio® (simeprevir) or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug.

2. For treatment continuation for treatment weeks 28 through 36, the recipient must have one of the following:

a. The recipient is treatment-naïve and their HCV-RNA level was detectable at treatment week eight and undetectable at treatment week 24; or

b. The recipient is a previous partial responder or a relapser to peginterferon alfa and ribavirin and their HCV-RNA was undetectable at treatment week eight and treatment week 24.

3. For treatment continuation for treatment weeks 28 through 48, the recipient must have one of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 with compensated cirrhosis and their HCV-RNA was detectable at treatment week 24; or

b. The recipient had a <2-$\log_{10}$ HCV-RNA drop by treatment week 12 on prior treatment with peginterferon alfa and ribavirin and HCV-RNA on triple therapy is undetectable at treatment week 24; or

c. The recipient is treatment-naïve and poorly interferon responsive based on <1-$\log_{10}$ decline in HCV-RNA at treatment week four following lead-in therapy with peginterferon alfa.

b. Incivek® (telaprevir)

1. For treatment initiation (weeks one through eight) the recipient must have all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with concomitant peginterferon alfa plus ribavirin; and

c. The recipient has not received a previous course of therapy with Incivek® (teaprevir), Olysio® (simeprevir) or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug.

2. For treatment continuation for treatment weeks nine through 12:

a. The recipient is treatment-naïve and their HCV-RNA level was <1000 IU/mL at treatment week four.

c. Olysio® (simeprevir)

1. For treatment initiation (treatment weeks one through eight), the recipient must meet all of the following:

a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection; and

b. The recipient will be treated with concomitant peginterferon alfa plus ribavirin; and

c. The recipient has not received a previous course of therapy with Incivek® (telaprevir), Olysio® (simeprevir), or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug; and

d. The recipient has been pre-screened and does not test positive for the 1A NS3 Q80K polymorphism.

2. For treatment continuation for treatment weeks nine through 12, the recipient must have one of the following:

a. The recipient is treatment-naïve, and their HCV-RNA level was <25 IU/mL at treatment week four; or

b. The recipient is a previous prior relapser and their HCV-RNA level was <25 IU/mL at treatment week four; or

c. The recipient is a partial or a null-responder to previous therapy of interferon and ribavirin alone (no other HCV protease inhibitors) and their HCV-RNA was <25 IU/mL at treatment week four.

2. Prior Authorization Guidelines:

a. Victrelis® (boceprevir)

1. Initial prior authorization will be for 24 weeks (through treatment week 28).

2. For recipients meeting criteria for continuation treatment for treatment weeks 28 through 36, a prior authorization may be renewed once for an additional eight weeks.

3. For recipients meeting criteria for continuation treatment for treatment weeks 28 through 44, a prior authorization may be renewed once for an additional 24 weeks.

b. Incivek® (teleprevir) and Olysio® (simeprevir)

1. Initial prior authorization approval will be for eight weeks.

2. For recipients meeting criteria for continuation treatment for treatment weeks nine through 12, a prior authorization approval may be renewed once for an additional four weeks.

c. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Hepatitis C Protease Inhibitors

Therapeutic Class

- **Overview/Summary:** Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis®), simeprevir (Olysio®), and telaprevir (Incivek®). All agents are Food and Drug Administration (FDA) approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with peg interferon alfa and ribavirin. The hepatitis C protease inhibitors can be used in both treatment naïve and experienced patients, and the specific FDA approved indications are outlined in Table 1.[1-3] These direct acting antivirals inhibit the replication of hepatitis C virus (HCV) host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.[1-4] Because these agents must be used in combination with peg interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors. In addition, the incidence of rash is increased when the hepatitis C protease inhibitors are used in combination with peg interferon alfa and ribavirin. In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care. The frequencies of administration of boceprevir, telaprevir, simeprevir are once daily, two times daily, and three times daily, respectively.[1-3] According to the American Association for the Study of Liver Diseases, boceprevir or telaprevir in combination with peg interferon alfa and ribavirin are recommended for the treatment of HCV genotype 1.[5] Treatment guidelines were published prior to the availability of simeprevir and do not address its place in therapy. No one peg interferon or ribavirin product is preferred or recommended over another.[5-10] Furthermore, no one hepatitis C protease inhibitor is preferred over another and current recommendations for their use are in line with FDA approved indications and dosing.[1-10] Clinical trials have demonstrated that when a hepatitis C protease inhibitor is added to the current standard of care, sustained virologic response rates are significantly increased.[11-23]

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Boceprevir (Victrelis®)	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Capsule: 200 mg	-
Simeprevir (Olysio®)	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Capsule: 150 mg	-
Telaprevir (Incivek®)	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers	Tablet: 375 mg	-

Evidence-based Medicine

In clinical trials, the addition of hepatitis C protease inhibitors to standard therapy (i.e., peg interferon alfa and ribavirin) resulted in significantly higher sustained virologic response rates compared to standard

therapy alone in adults with chronic hepatitis C genotype 1 infection. These results were achieved in both treatment-naïve and experienced patients. Additionally, results demonstrated that in select patients who achieve an early virologic response with boceprevir or telaprevir-containing regimen, there is potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] vs 48 weeks [standard therapy]). The treatment duration with simeprevir combination therapy is fixed at either 24 or 48 weeks depending on the response to prior treatment with peg interferon alfa and ribavirin. Use of hepatitis C protease inhibitors was also associated with a greater incidence of adverse events, including rash, compared to the standard therapy alone. In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.[1-3,11-23]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin.[5,6]
        - No one protease inhibitor is preferred or recommended over another.[5-10]
        - No one peg interferon or ribavirin product is preferred or recommended over another.[5-10]
        - Patients with genotype 2 or 3 infection may receive treatment for up to 24 weeks and patients with genotype 1 or 4 infection may receive treatment for up to 48 weeks.[5-10]
        - Treatment guidelines were published prior to the availability of simeprevir and do not address its place in therapy.[5-10]
- Other Key Facts:
    - Boceprevir is available as a 200 mg capsule and is dosed 800 mg three times daily.[1]
        - Boceprevir is initiated after a four week lead-in period of peg interferon alfa and ribavirin alone.[1]
    - Telaprevir is available as a 375 mg tablet and is dosed 1,125 mg twice daily.[2]
        - Telaprevir is initiated with peg interferon alfa and ribavirin.[2]
    - Simeprevir is available as a 150 mg capsule and is dosed 150 mg once daily.[3]
        - Simeprevir is initiated with peg interferon alfa and ribavirin.[3]
    - Prior to initiating therapy with simeprevir, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced drug efficacy; alternative therapy should be considered if this polymorphism is present.[3]
    - When added to standard therapy, both boceprevir and telaprevir are associated with an increase in the incidence of anemia. In addition, telaprevir is associated with an increase incidence in rash, which can be serious in nature.[1,2]
    - Select patients with a satisfactory early virologic response to a regimen containing boceprevir or telaprevir may be candidates for shorter duration of total treatment.[1,2]
        - If a patient has an undetectable HCV ribonucleic acid (RNA) level at treatment weeks eight and 24 with a boceprevir-containing regimen, 28 or 36 weeks of total treatment is effective in achieving a sustained virologic response (SVR).
        - If a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving an SVR.
    - Futility rules, based on HCV RNA levels, apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection.[1-3]
        - Futility should be assessed at treatment weeks 12 and 24 with boceprevir-containing regimens, and at treatment weeks four, 12 and 24 with simeprevir and telaprevir-containing regimens.

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Therapeutic Class Review
Hepatitis C Protease Inhibitors

Overview/Summary

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.[1,2] There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.[2,3] Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment. Treatment goals for the management of chronic hepatitis C include preventing complications and death. Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Of most importance is sustained virologic response (SVR), which is defined as the absence of HCV ribonucleic acid 24 weeks following discontinuation of treatment.[2] Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.[3] Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.[2-6] Newer treatment strategies which aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as to shorten treatment duration are currently being developed and include the newly approved nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as nonstructural protein 5B polymerase inhibitor, sofosbuvir.[8-11] According to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, boceprevir or telaprevir in combination with peg interferon alfa and ribavirin is the recommended treatment for patients with genotype 1 chronic hepatitis C.[3,4] Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents. Overall, treatment guidelines do not give preference to one specific peg interferon or ribavirin product over another.[2-7] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with Food and Drug Administration (FDA)-approved indications and dosing.[2-10]

Included in this review are the hepatitis C protease inhibitors boceprevir (Victrelis®), simeprevir (Olysio®), and telaprevir (Incivek®). All three agents are FDA-approved for the treatment of adults with chronic hepatitis C genotype 1 infection, when used in combination with peg interferon alfa and ribavirin. The agents can be used in treatment-naïve and experienced patients, and the specific FDA-approved indications are outlined in Table 2. These direct acting antivirals inhibit the replication of HCV host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.[8-10] In general, clinical trials demonstrate that the use of protease inhibitors, in combination with peg interferon alfa and ribavirin, yields higher SVR rates, with a potential to decrease the total duration of treatment (24 [telaprevir], 28 [boceprevir] or 36 [boceprevir] compared to 48 weeks [standard of care]) in patients who achieve an early virologic response. The treatment duration with simeprevir in combination with peg interferon alfa and ribavirin is either 24 or 48 weeks depending on the response to prior treatment. In clinical trials, use of protease inhibitors was associated with a greater incidence of rash compared to the standard of care.[2,4,10,13-22] In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.[8-10]

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Boceprevir (Victrelis®)	Hepatitis C protease inhibitor	-
Simeprevir (Olysio®)	Hepatitis C protease inhibitor	-
Telaprevir (Incivek®)	Hepatitis C protease inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[8-10]

Indication	Boceprevir	Simeprevir	Telaprevir
Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	✔	✔	✔

There are additional factors that should be considered before initiating therapy with protease inhibitors. These agents should never be used as monotherapy and should only be used in combination with peg interferon alfa and ribavirin. The efficacies of protease inhibitors have not been evaluated in patients who have previously failed therapy with a treatment regimen that includes hepatitis C virus (HCV) nonstructural protein (NS) 3/4A protease inhibitors.[8-10]

With regard to boceprevir-containing regimens, efficacy in patients documented to be historical null responders (<2 $\log_{10}$ HCV ribonucleic acid decrease by treatment week 12) during prior therapy with peg interferon alfa and ribavirin has been evaluated in the currently ongoing and unpublished study, PROVIDE, though a high proportion of previous null responders did not achieve a sustained virologic response (SVR). Poorly interferon responsive patients treated with a boceprevir-containing regimen have a lower likelihood of achieving a SVR, and a higher rate of detection of resistance-associated substitutions upon treatment failure, compared to patients with a greater response to peg interferon alfa and ribavirin.[8]

With regard to simeprevir-containing regimens, the efficacy in combination with peg interferon alfa and ribavirin is influenced by baseline host and viral factors. The efficacy is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.[10]

With regard to telaprevir-containing regimens, a high proportion of previous null responders, particularly those with cirrhosis, did not achieve a SVR and had telaprevir resistance-associated substitutions emerge on treatment with telaprevir-containing regimens.[9]

Pharmacokinetics

Table 3. Pharmacokinetics[12]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Boceprevir	Not reported	9	None	3.4
Simeprevir	Not reported	<1	None	41
Telaprevir	Not reported	1	R diastereomer*	9 to 11

*30-fold less active compared to telaprevir.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the hepatitis C protease inhibitors are outlined in Table 4. Data from clinical trials support the Food and Drug Administration (FDA)-approved indications and dosing recommendations for these agents. Overall, the addition of hepatitis C protease inhibitors to standard therapy (i.e., peg interferon alfa and ribavirin) is associated with a significant increase in sustained virologic response (SVR) (undetectable hepatitis C virus [HCV] ribonucleic acid [RNA] levels 24 weeks after completion of treatment) rates. The addition of these agents to standard therapy is also associated with a higher incidence

of adverse events, such as rash.[13-22] In contrast to boceprevir or telaprevir combination therapy, simeprevir combination therapy was not associated with additional anemia compared to the standard of care.[10]

Based on the FDA-approved dosing for boceprevir, patients are required to initiate standard therapy for a period of four weeks before initiating treatment with boceprevir.[8] This is based on phase 2 trial data in which it was determined that in order to decrease the rate of viral breakthrough and relapse in patients receiving boceprevir, HCV RNA levels should be lowered as much as possible before initiation of boceprevir.[22]
Poordad et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment-naïve adults with chronic HCV genotype 1 infection (SPRINT-2; N=1,097). Patients were excluded if they were co-infected with human immunodeficiency virus (HIV) or hepatitis B. There were three treatment regimens (control [i.e., standard therapy], response-guided therapy and fixed duration therapy), all of which included a four week lead-in period consisting of only standard therapy. Of note, self-described nonblack and black patients were enrolled into two separate cohorts due to the marked difference in rates of SVR between these two populations (nonblack; N=938, black; N=159). The control regimen consisted of an additional 44 weeks of standard therapy (48 weeks of treatment total). Response-guided therapy consisted of 24 weeks of boceprevir plus standard therapy, at which point if a rapid virologic response (undetectable HCV RNA at treatment week eight through 24) was achieved, treatment was considered complete (28 weeks of treatment total). However, if a rapid virologic response was not achieved, standard therapy alone was continued for an additional 20 weeks (48 weeks of treatment total). Fixed duration therapy consisted of 44 weeks of boceprevir plus standard therapy (48 weeks of treatment total). All patients were followed for a total of 72 weeks, which included either 24, 44 or 48 weeks of follow up, depending on total treatment duration.
For SPRINT-2, the primary efficacy endpoint of SVR was significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) among the nonblack and black cohorts, compared to control. Specifically, within the nonblack cohort, SVR rates were 40 (N=311), 67 (N=316) and 68% (n =311) with control, response-guided therapy and fixed duration therapy (*P*<0.001 vs control for both). Within the black cohort, the corresponding rates were 23 (N=52), 42 (N=52) and 53% (N=55) (*P*=0.04 vs control for response-guided therapy and *P*=0.004 vs control for fixed duration therapy).[13]

Subgroup analyses of SPRINT-2 revealed that regardless of the degree of HCV RNA decrease from baseline after a four week lead-in period with standard therapy (<1 or ≥1 $\log_{10}$ IU/mL), the addition of boceprevir was consistently more likely to result in SVR compared to standard therapy alone. Overall, however, a decrease of <1 $\log_{10}$ IU/mL (poor interferon response) was associated with lower SVR rates and higher rates of boceprevir-resistance-associated variants. In addition, the SVR rates among patients with undetectable HCV RNA levels at treatment week eight were high regardless of treatment regimen; however, patients receiving boceprevir-containing regimens were three times more likely to achieve this early virologic response compared to patients receiving standard therapy alone. With regard to response-guided and fixed duration therapies, SVR rates within the nonblack cohort were similar (67 vs 68%; *P* value not reported), whereas within the black cohort they were higher with fixed duration therapy (42 vs 53%; *P* value not reported). Furthermore, among nonblack patients treated with a boceprevir-containing regimen who had an early virologic response (HCV RNA level undetectable at treatment week eight) (60%), and those who remained undetectable through 24 weeks of treatment (47%), the SVR rate was similar between response-guided (24 weeks of boceprevir) and fixed duration (44 weeks of boceprevir) therapies (97 vs 96%; *P* value not reported). Similar SVR rates between response-guided and fixed duration therapies were also observed among patients who did not have an early response (74% for each). Fatigue, headache and nausea were the most common adverse events reported in all treatment groups, with dysgeusia and anemia occurring more frequently with boceprevir-containing regimens.[13]

Results from SPRINT-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment-naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of anemia. The data also supports the efficacy of response-guided therapy, which consisted of individualized treatment duration based on HCV RNA levels between treatment weeks eight and 24.[13]

Bacon et al evaluated the safety and efficacy of boceprevir, in combination with standard therapy, in treatment-experienced adult patients with chronic HCV genotype 1 infection (RESPOND-2, N=403). In this trial, patients had to have demonstrated previous responsiveness to interferon based therapy (minimum of 12 weeks), but experienced either a nonresponse (decrease in the HCV RNA level ≥2 $\log_{10}$ IU/mL by treatment week 12 of prior therapy, but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR) or relapse (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR). RESPOND-2 and SPRINT-2 were similar in design in that patients co-infected with HIV or hepatitis B were excluded, there were three treatment regimens (control [N=80], response-guided therapy [N=162] and fixed duration therapy [N=161]) and all treatment regimens consisted of a four week lead-in period with standard therapy alone. In contrast, RESPOND-2 did not separate nonblack and black patients and, as mentioned previously, patients were treatment-experienced. Similar to SPRINT-2, the control regimen consisted of standard therapy for an additional 44 weeks (48 weeks of total treatment) and the fixed duration therapy consisted of boceprevir plus standard therapy for 44 weeks (48 weeks of total treatment). Response-guided therapy consisted of boceprevir plus standard therapy for 32 weeks, if at which point HCV RNA levels were undetectable at treatment weeks eight and 12, treatment was considered complete (36 weeks of total treatment). However, if the HCV RNA level was detectable at treatment week eight and undetectable at treatment week 12, standard therapy alone was continued for an additional12 weeks (48 weeks of total treatment). All patients were followed for a total of 72 weeks which included either 24, 36 or 60 weeks of follow up, depending on treatment duration.[17]

For RESPOND-2, the primary efficacy endpoint of SVR was again significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) compared to control. Specifically, SVR rates were 21, 59 and 66% with control, response-guided therapy and fixed duration therapy, respectively (*P*<0.001 vs control for both). Among the two subgroups of treatment-experienced patients, those with a prior relapse (29, 69 and 75% with control, response-guided and fixed duration therapies, respectively) or prior nonresponse (7 vs 40 and 52%, respectively) both had higher SVR rates with boceprevir-containing regimens compared to standard therapy alone. With regards to response-guided and fixed dose therapies, no difference was observed in overall SVR rates (odds ratio, 1.4; 95% confidence interval [CI], 0.9 to 2.2). In addition, of the patients who responded poorly to therapy (HCV RNA level decrease <1 $\log_{10}$ IU/mL at treatment week four), SVR was more likely to be achieved with boceprevir-containing regimens compared to standard therapy alone (0 vs 33 and 34%, respectively; *P* values not reported) and similar results were observed among good responders (HCV RNA level decrease ≥1 $\log_{10}$ IU/mL) (25 vs 73 and 79%, respectively; *P* values not reported). The proportions of patients who achieved an early response (undetectable HCV RNA level at treatment week eight), were 46 and 52% with response-guided and fixed duration therapies, respectively, which was approximately six times higher compared to control (9%). Serious adverse events and anemia were reported more frequently with boceprevir-containing regimens.[17]

Results from RESPOND-2 demonstrated that the addition of boceprevir to standard therapy significantly increased the SVR rate among treatment-experienced adult patients with chronic HCV genotype 1 infection. The data also suggested that boceprevir-containing regimens may be more effective in achieving SVR in patients with a previous relapse (69 to 75%) compared to those who experienced a nonresponse to previous therapy (40 to 52%). Similar to SPRINT-2, achievement of an early virologic response resulted in similar SVR rates with response-guided therapy (32 weeks of boceprevir) and fixed duration therapy (44 weeks of boceprevir), further supporting the notion that patients who respond early to treatment with a boceprevir-containing regimen may be appropriate for a shorter duration of total treatment.[17]

Most trials with boceprevir have evaluated its use in combination with peg interferon alfa 2b, but Flamm et al evaluated the efficacy of boceprevir in combination with peg interferon alfa 2a and ribavirin in patients who were relapsers or nonresponders to prior therapy. Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall SVR rate of 21% in the peg interferon/ribavirin only treatment group compared to an SVR rate of 64% with boceprevir (P<0.001). Rates of SVR among patients with a history prior relapse were 70% with boceprevir and 28% with peg interferon/ribavirin only treatment group, while SVR rates among patients with prior nonresponse were 47% with boceprevir compared to 5% in the peg interferon/ribavirin only treatment group (*P* values not reported).[20]

Most recently**,** boceprevir has been studied in patients documented to be historical null responders (<2 $\log_{10}$ HCV ribonucleic acid decrease by treatment week 12) with prior therapy consisting of peg interferon alfa and ribavirin in a currently ongoing and unpublished study, though preliminary data has been released permitting a labeling update to expand its indication to include the treatment of prior null responders. The PROVIDE is an ongoing, open-label, single-arm study of adult subjects with HCV genotype 1 infection who did not achieve SVR while in the peg interferon alfa/ribavirin control arms of previous Phase 2 and 3 studies. Subjects who were prior null responders received a four week peg interferon alfa/ribavirin lead-in treatment followed by boceprevir 800 mg three times daily and peg interferon alfa/ribavirin for 44 weeks. Overall, 38% (20/52) achieved SVR, and the relapse rate was 14% (3/22) among the null responders.[8]

Based on the FDA-approved dosing of telaprevir, patients can initiate triple therapy (i.e., telaprevir plus standard therapy) at the same time. In contrast to boceprevir, lead-in period with standard therapy is not required before initiation of telaprevir.[9]

Jacobson et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-naïve adult patients with chronic HCV genotype 1 infection (ADVANCE; N=1,088). Patients were excluded if they had decompensated liver disease, liver disease from other causes or hepatocellular carcinoma. There were three treatment regimens (control [N=361] and two response-guided therapies [N=727]). The control regimen consisted of 48 weeks of standard therapy (48 weeks of total treatment). The two response-guided therapies were T12/PR (N=363) and T8/PR (N=364). T12/PR consisted of telaprevir plus standard therapy for 12 weeks, and depending on whether or not an extended rapid virologic response (undetectable HCV RNA at treatment week four that remained undetectable at week 12) was achieved or not, standard therapy was continued for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of total treatment). T8/PR consisted of telaprevir plus standard therapy for eight weeks, followed by standard therapy alone for an additional four weeks. At which point, depending on whether or not an extended rapid virologic response was achieved, standard therapy alone was administered for an additional 12 (24 weeks of treatment total) or 36 weeks (48 weeks of treatment total). All patients were followed for a total of 72 weeks.[14] For ADVANCE, the primary efficacy endpoint of SVR was significantly higher with both response-guided therapies (75 [*P*<0.0001 vs control], 69 [*P*<0.0001 vs control] and 44% with T12/PR, T8PR and control, respectively), with no difference observed between T12/PR and T8/PR (treatment difference, 6%; 95% CI, -12.5 to 0.6). When the results were analyzed according to extended rapid virologic response, fibrosis stage or race, SVR rates were consistently higher with telaprevir-containing regimens; however, comparisons were not always significant compared to control. Data suggests that 12 weeks of telaprevir may be more effective than eight weeks. Specifically, 12 weeks of telaprevir resulted not only in a nonsignificantly higher SVR rate, but also in a lower virologic failure rate (8 vs 13%; *P* value not reported). The difference in the rate of virologic failure was noted to be due to a higher failure rate in patients after telaprevir was discontinued. Beyond week 12, the rates of virologic failure were higher with T8PR compared to T12PR (10 vs 5%, respectively), with more frequent emergence of wild-type and lower-level resistant variants. Adverse events were reported more frequently with telaprevir-containing regimens included pruritis, nausea, rash, anemia and diarrhea.[14,22]

Results from ADVANCE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment-naïve adult patients with chronic HCV genotype 1 infection, with an increased incidence of both rash and anemia. The data also demonstrated that 12 weeks of telaprevir is more efficacious than eight weeks.[14]

Sherman et al also evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-naïve adult patients with chronic HCV genotype 1 infection (ILLUMINATE; N=540). In contrast to the other clinical trials, ILLUMINATE was an open-label, noninferiority trial. In this trial, patients were excluded if they were co-infected with HIV or hepatitis B. All patients received telaprevir plus standard therapy for 12 weeks, followed by standard therapy alone for an additional eight weeks. If at treatment week 20, an extended rapid virologic response was not achieved; standard therapy alone was administered for an additional 28 weeks (48 weeks of total treatment). If at treatment week 20 an extended rapid virologic response was achieved, standard therapy was administered for either an additional four (T12/PR24, 24 weeks of total

treatment) or 28 weeks (T12PR48, 48 weeks of total treatment). Patients were followed for a total of 72 weeks.[15]

In the ILLUMINATE trial, similar proportions of patients achieved the primary efficacy endpoint of SVR with T12PR24 compared to T12PR48 (92 vs 88%; 95% CI, -2 to 11; *P* value not reported). Overall, 332 patients achieved an extended rapid virologic response, of which 162 and 160 were randomly assigned to T12PR24 and T12PR48, respectively. The SVR rate among patients who did not achieve an extended rapid virologic response (N=118) was 64%.[15,22]

Results from ILLUNIMATE support the concept that select patients who achieve an early virologic response with telaprevir-containing regimens may be candidates for a shorter duration of total treatment.[15]

Zeuman et al evaluated the safety and efficacy of telaprevir, in combination with standard therapy, in treatment-experienced adult patients with chronic HCV genotype 1 infection (REALIZE; N=662). Patients in this trial consisted of prior relapsers (undetectable HCV RNA level at the end of prior therapy without subsequent attainment of a SVR), partial responders (decrease in HCV RNA level ≥2 $\log_{10}$ IU/mL by treatment week 12 of prior therapy, but not achieving HCV RNA undetectable status at the end of prior therapy), and null responders (decrease in HCV RNA level <2 $\log_{10}$ IU/mL at treatment week 12 of prior therapy). There were three treatment regimens evaluated in the REALIZE trial (control, lead-in therapy and nonlead-in therapy). The control regimen consisted of standard therapy for 48 weeks (48 weeks of total treatment). The lead-in regimen (Lead-in T12PR48) consisted of standard therapy for four weeks, followed by telaprevir plus standard therapy for an additional 12 weeks, followed by standard therapy alone for an additional 32 weeks (48 weeks total of treatment). The non-lead-in regimen (T12PR48) consisted of telaprevir plus standard therapy for 12 weeks, followed by standard therapy alone for an additional 36 weeks (48 weeks of total treatment). All patients were followed for a total of 72 weeks.[18]

In the REALIZE trial, the primary efficacy endpoint of SVR was significantly higher with both telaprevir-containing regimens (66 [*P*<0.001 vs control], 64 [*P*<0.001 vs control] and 17% with lead-in T12PR48, T12PR48 and control), with no difference observed between lead-in T12PR48 and T12PR48 (*P* value not reported). Among the various subpopulations of treatment-experienced patients, SVR rates were consistently significantly higher with telaprevir-containing regimens (*P*<0.0001 for all comparisons). Subgroup analyses according to the stage of liver fibrosis or baseline viral load showed higher SVR rates with telaprevir-containing regimens compared to control. Reported adverse events were consistent with those described in other clinical trials evaluating telaprevir.[18,22]

Results from REALIZE demonstrated that the addition of telaprevir to standard therapy significantly increased the SVR rate among treatment-experienced adult patients with chronic HCV genotype 1 infection. The data also supports the FDA-approved dosing of telaprevir in that no lead-in period is required and patients can initiate triple therapy at the same time.[18]

The efficacy of simeprevir in patients with HCV genotype 1 infection was evaluated in four unpublished studies, including two Phase 3 trials in treatment-naïve patients (QUEST 1 and QUEST 2), one Phase 3 trial in patients who relapsed after prior interferon-based therapy (PROMISE) and one Phase 2b trial in patients who failed prior therapy with peg interferon alfa and ribavirin (including prior relapsers, partial and null responders) (ASPIRE).[10]

Patients in these trials had chronic hepatitis C with compensated liver disease (including cirrhosis) and HCV RNA ≥10,000 IU/mL. In patients who were treatment-naïve and prior relapsers, the overall duration of treatment with peg interferon alfa and ribavirin in the Phase 3 trials was response-guided. In these patients, the planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy criteria were met: HCV RNA <25 IU/mL (detectable or undetectable) at week four and undetectable HCV RNA at week 12. Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner.[10]

The primary end point, SVR, was defined as undetectable HCV RNA 24 weeks after the end of treatment (SVR24) in the Phase 2b trial and was defined as HCV RNA <25 IU/mL (detectable or undetectable) 12 weeks after the end of treatment (SVR12) in the Phase 3 trials.[10]

QUEST 1 (N=394) and QUEST 2 (N=391) were similarly designed, randomized, double-blind, placebo-controlled, two-arm, multicenter, Phase 3 trials evaluating the efficacy of simeprevir in treatment-naïve patients with HCV genotype 1 infection. All patients received simeprevir 150 mg once daily for 12 weeks or placebo, plus peg interferon alfa-2a (QUEST 1 and QUEST 2) or peg interferon alfa-2b (QUEST 2) and ribavirin, followed by 12 or 36 weeks of therapy with peg interferon alfa and ribavirin in accordance with the response-guided therapy criteria. Patients in the control groups received 48 weeks of peg interferon alfa-2a or -2b and ribavirin.[10,23,24]

In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (80 vs 50%). Eighty eight percent of patients in the simeprevir group were eligible to shorten total treatment duration to 24 weeks; in these patients, the SVR12 rate was 88%. SVR12 rates were higher in the simeprevir group compared to control group regardless of the fibrosis stage (84 vs 55% for F0 to F2 and 68 vs 36% for F3 to 4), sex, age, race, body mass index, HCV genotype/subtype, baseline HCV RNA load, and IL28B genotype. In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (58%) compared to those without the Q80K polymorphism (84%). The corresponding SVR12 rates in the control group were 52 and 43%, respectively.[1]

The PROMISE trial (N=393) was a randomized, double-blind, placebo-controlled, two-arm, multicenter, Phase 3 trial in patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy. All patients received simeprevir 150 mg once daily for 12 weeks or placebo, plus peg interferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peg interferon alfa-2a and ribavirin in accordance with the response-guided therapy criteria. Patients in the control group received 48 weeks of peg interferon alfa-2a and ribavirin.[1,25]

A greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (79 vs 37%). Ninety three percent of patients in the simeprevir group were eligible to shorten total treatment duration of 24 weeks; in these patients, the SVR12 rate was 83%. SVR12 rates were higher in the simeprevir group compared to peg interferon alfa-2a and ribavirin group regardless of the fibrosis stage (82 vs 41% for F0 to F2 and 73 vs 24% for F3 to 4), sex, age, race, body mass index, HCV genotype/subtype, baseline HCV RNA load, prior HCV therapy, and IL28B genotype. In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (47%) compared to those without the Q80K polymorphism (78%). The corresponding SVR12 rates in the control group were 30 and 26%, respectively.[1]

The ASPIRE trial (N=264) was a randomized, double-blind, placebo-controlled, seven-arm, Phase IIb trial in patients with HCV genotype 1 infection, who failed prior therapy with peg interferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Patients received 12, 24 or 48 weeks of simeprevir 100 or 150 mg in combination with 48 weeks of peg interferon alfa-2a and ribavirin, or 48 weeks of placebo in combination with 48 weeks of peg interferon alfa-2a and ribavirin.[1,26]

Overall, SVR24 rates were significantly higher in the groups treated with simeprevir 100 mg and 150 mg for 12 weeks compared to control (61 and 80% vs 23%; *P*<0.001). In the pooled results of simeprevir 100 mg and 150 mg given for 12 weeks, the SVR rates were significantly higher with simeprevir compared to placebo, regardless of prior response to peg interferon and ribavirin: prior null response, 45 vs 19%; prior partial response, 67 vs 9%; prior relapse, 83 vs 37%. In prior partial responders, SVR24 rates in the simeprevir treatment group were 47 and 77% in patients with HCV genotype 1a and 1b, respectively, compared to 13% and 7%, respectively, in the control group. In prior null responders, SVR24 rates in the simeprevir treatment group were 41 and 47% in patients with HCV genotype 1a and 1b, respectively, compared to 0 and 33%, respectively, in the control group. SVR24 rates were higher in the simeprevir group compared to control group, regardless of HCV genotype/subtype, fibrosis stage, and IL28B genotype.[1,26]

The COSMOS trial is an ongoing, unpublished randomized, open-label, phase IIa trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 (N=80) included prior null responders with METAVIR scores F0 to F2 and Cohort 2 (N=87) included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4. Only the results of an interim analysis are available at this time.[27]

In the Cohort 1, SVR12 was achieved by 96% (26/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving a 12-week simeprevir and sofosbuvir regimen without ribavirin. In the Cohort 2, SVR4 was achieved by 93% (14/15) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 100% (14/14) of patients receiving simeprevir and sofosbuvir regimen without ribavirin. Treatment was found to be generally safe and well tolerated. There was little to no benefit from adding ribavirin in this difficult to treat groups of hepatitis C patients and 12 week treatment provided similar clinical benefit to 24 week treatment.[27,28]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1 Chronic Hepatitis: Treatment-Naïve Patients				
Poordad et al[13] SPRINT-2 Group 1 (control): Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peg interferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peg interferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks	PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma HCV RNA level ≥10,000 IU/mL	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 (*P*<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (*P*=0.04 vs Group 1) and 53% (*P*=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peg interferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
separately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.				Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.
Jacobson et al[14] ADVANCE Telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peg interferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR) vs telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 8 weeks, followed by an additional 16 or 40 weeks of peg interferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T8PR)	DB, PC, PG, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection with no previous treatment	N=1,088 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients with undetectable HCV RNA at week 72, four, 12 or both four and 12, at the end of treatment and 12 weeks after the last planned dose of treatment; safety	Primary: SVR rates were significantly higher with telaprevir-containing regimens compared to control (75, 69 and 44% with T12PR, T8PR and control (*P*<0.001 for T12PR and T8PR vs control). Secondary: Seventy three, 67 and 44% of patients receiving T12PR, T8PR and control had undetectable HCV RNA 72 weeks after starting treatment (*P*<0.001 for T12PR and T8PR vs control). Sixty eight, 66 and nine percent of patients, respectively, had undetectable HCV RNA at week four (rapid virologic response), and 58, 57 and eight percent of patients, respectively, had undetectable HCV RNA at weeks four and 12 (extended rapid virologic response) (*P* values not reported). Among patients with an extended rapid virologic response assigned to receive a total of 24 weeks of therapy, SVR rates were 89 and 83% with T12PR and T8PR (*P* value not reported). Among patients who had undetectable HCV RNA levels after the last dose of treatment, relapse rates were nine, nine and 28% with T12PR, T8PR and control (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks (control) Patients in the T12PR and T8PR groups who met criteria for an extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peg interferon alfa-2a plus ribavirin (24 total weeks of treatment). Patients who had detectable HCV RNA either at week 4 or 12 received an additional 36 weeks of peg interferon alfa-2a plus ribavirin (48 total week of treatment).				Subgroup analyses demonstrated that SVR rates were higher with telaprevir-containing regimens. Subgroup analyses included HCV genotype subtype (1a and 1b), African Americans, baseline HCV RNA levels (≥800,000 IU) and bridging fibrosis or cirrhosis. The incidence of gastrointestinal disorders, pruritis, rash and anemia was ≥10 percentage points higher with telaprevir-containing regimens. A total of 10, 10 and seven percent of patients receiving T12PR, T8PR and control discontinued all treatment at some time during the trial owing to adverse events (*P* values not reported); with seven, eight and four percent of these patients discontinuing during the telaprevir (or placebo) phase. Anemia and rash were the most frequently reported adverse events that lead to discontinuation. One case of Stevens-Johnson syndrome occurred approximately 11 weeks after the last dose of telaprevir had been administered.
Sherman et al[15] ILLUMINATE Peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day plus telaprevir 750 mg three times a day for 12 weeks (T12PR12), followed by peg interferon alfa-2a plus ribavirin for 12 or 36 weeks. Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) after 20 weeks were randomized to continue peg interferon alfa-2a plus ribavirin for an	MC, NI, OL, RCT Patients 18 to 70 years of age with chronic hepatitis C genotype 1 infection for ≥6 months, no previous treatment and with no hepatitis B or HIV	N=540 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR in T12PR24 compared to T12PR48 Secondary: Not reported	Primary: The absolute difference in SVR rate between T12PR24 vs T12PR48 was four percentage points (92 vs 88%; 95% CI, -2 to 11). The lower limit of this 95% CI (-2%) exclude the NI margin -10.5%. The SVR rate in patients who did not achieve an extended rapid virologic response therefore received a total of 48 weeks of treatment was 64% (76/118). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
additional 4 (24 weeks total treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48). Patients who did not achieve an extended rapid virologic response after 20 weeks received peg interferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).				
Kumada et al[16] (Group A) Telaprevir 750 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peg interferon alfa-2a plus ribavirin vs (Group B) Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 48 weeks	AC, DB, MC, RCT Patients 20 to 65 years of age with chronic HCV genotype 1 infection who had not received prior treatment and had a current HCV RNA ≥5.0 $\log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	N=189 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR, nonresponder rate, proportion of patients with an RVR at week four, safety, and adverse events Secondary: Not reported	Primary: Treatment with telaprevir (Group A) was associated with a statistically significant increase in SVR rate (73.0 vs 49.2%; *P*=0.0020) compared to standard of care (Group B). The nonresponder rate was significantly lower in Group A (triple therapy) compared to Group B (0.8 vs 20.6%; *P*<0.0001). A higher proportion of women achieved an SVR in Group A compared to Group B (70.0 vs 43.3%; *P*=0.0214). In addition, patients ≥50 years of age achieved a significantly higher SVR in Group A compared to Group B (67.1 vs 42.9%; *P*=0.0125). Furthermore, more patients with a high HCV RNA viral load at baseline (≥7 $\log_{10}$ IU/ml) achieved a SVR in Group A compared to Group (69.2 vs 27.8%; *P*=0.0132). A significantly greater proportion of patients achieved a RVR at four weeks in Group A compared to Group B (84.0 vs 4.8%; *P*<0.0001). The most commonly reported adverse events were anemia, pyrexia, leukocytopenia, thrombocytopenia and malaise. Drugs were discontinued due to adverse events in a similar number of patients in Groups A and B (16.7 vs 22.2%, respectively; *P* value not reported). Telaprevir was discontinued in 19.0% of patients in Group A. Anemia occurred in 91.3 and 73.0% of patients in Groups A and B,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively. Combined, Grade 1 and 2 anemia was more common in Group A compared to Group B (38.1 vs 17.5%; *P*=0.0045). Grade 3 anemia occurred in 11.1% in Group A only. During the follow-up, hemoglobin increased both in Groups A and B, and returned to pretreatment levels 12 weeks after the completion of therapy. Skin disorders occurred in a similar proportion of patients in Groups A and B (89.7 vs 84.1%, respectively; *P* value not reported). Most skin disorders were mild and categorized as Grade 1. Combined, skin disorders of Grades 2 to 4 occurred more frequently in Group A than Group B (46.8 vs 23.8%; *P*=0.0026). Serious skin disorders developed in three patients in Group A, but zero patients in Group B. Stevens-Johnson syndrome occurred in one patient after 35 days of treatment and led to the discontinuation of treatment. Secondary: Not reported
Treatment of genotype 1 chronic hepatitis: Treatment-experienced patients				
Bacon et al[17] RESPOND-2 Group 1 (control): Peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peg interferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12	PC, PG, RCT Patients with chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)	N=403 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups 1, 2 and 3, respectively (*P*<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peg interferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; *P* values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (*P* values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (*P* values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 $\log_{10}$ IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; *P*<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; *P*<0.001), low viral load at baseline (OR vs high load, 2.5; *P*=0.02) and absence of cirrhosis (OR vs presence, 2.1; *P*=0.04).
Zeuzem et al[18] REALIZE Telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an	DB, PC, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no	N=662 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Effect of lead-in treatment with peg	Primary: Compared to control, SVR rates were significantly higher with telaprevir-containing regimens in patients who had a previous relapse (83, 88 and 24% with T12PR48, Lead-in T12PR48 and control), for those who did not have a previous virologic response (41, 41 and 9%), including those who had a partial response (59, 54 and 15%) and those who had no response (29, 33 and 5%) (*P*<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
additional 36 weeks of peg interferon alfa-2a plus ribavirin (T12PR48) vs peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 4 weeks, followed by telaprevir 750 mg three times a day plus peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 32 weeks of peg interferon alfa-2a plus ribavirin (Lead-in T12PR48) vs peg interferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 48 weeks (control) Patients could have 1 of 3 previous responses to peg interferon alfa plus ribavirin therapy; no response (reduction <2 log_{10} in HCV RNA after 12 weeks of therapy), partial response (reduction ≥2 log_{10} in HCV RNA after 12 weeks of therapy but with detectable HCV RNA) or relapse (undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter).	SVR to 1 previous course of peg interferon alfa and ribavirin despite receiving at least 80% of the intended dose		interferon alfa-2a plus ribavirin on SVR, proportion of patients who had undetectable HCV RNA at four and eight weeks, relapse, change from baseline in log_{10} HCV RNA, safety	SVR rates were similar with T12PR48 and Lead-in T12PR48 among patients who had a relapse or no response or a partial response to previous therapy (*P* values not reported). Secondary: Overall, SVR rates were 64, 66 and 17% with T12PR48, Lead-in T12PR48 and control. Differences was 47 percentage points between T12PR48 and control (95% CI, 37 to 57; *P*<0.001) and 50 percentage points between Lead-in T12PR48 and control (95% CI, 40 to 60; *P*<0.001). In patients with a previous relapse, the proportion of patients with an undetectable HCV RNA were 70 and 93, three and 89 and three and 10% with T12PR48, Lead-in T12PR48 and control (*P* values not reported). In patients with a previous partial response, the corresponding proportions were 65 and 82, zero and 65 and zero and zero percent (*P* values not reported). Relapse rates were lower with telaprevir-containing regimens among patients who had a previous relapse or no response or a partial response to previous therapy. Changes in log_{10} HCV RNA levels are provided in graphic form only. The most frequently reported adverse events (>25% of patients) with telaprevir were fatigue, pruritus, rash, nausea, influenza-like illness, anemia and diarrhea. Serious adverse events (12 vs 5%) and those leading to treatment discontinuation (13 vs 3%) were more frequent with telaprevir.
Hayashi et al[19] Telaprevir 750 mg three times a day	MC, OL Patients 20 to	N=141 (109 relapsers	Primary; SVR, relapse,	Primary: The SVR rate was 88.1% (96/109) in patients who were prior relapsers to treatment and 34.4% in patients who were previous nonresponders to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus peg interferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peg interferon alfa-2a plus ribavirin	65 years of age with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peg interferon alfa and ribavirin with a current HCV RNA ≥5.0 $\log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	and 32 non-responders) 24 weeks (plus 24 weeks of follow up)	breakthrough, nonresponse, and safety Secondary: Not reported	treatment 34.4% (11/32). The RVR and ETR rates in prior relapsers were 87.2% (95/109) and 94.5% (103/109), respectively (P values not reported). In prior nonresponders, the RVR and ETR rates were 71.9% (23/32) and 59.4% (19/32), respectively. In prior relapsers, the SVR rate in the patients who achieved undetectable HCV RNA at week four was significantly higher compared to patients achieving undetectable HCV RNA after week four of treatment (91.8 vs 66.7%; *P*=0.0487). In the prior nonresponder group, undetectable HCV RNA at week four did not appear to have an effect on SVR rates (39.1 vs 28.6%; *P*=1.0). The SVR rate in previous relapsers was significantly higher in males compared to females (93.9 vs 79.1%; *P*=0.0316), while there was no difference in SVR rate between genders in patients who were previous nonresponders to therapy. The rates of nonresponse, breakthrough and relapse were 0.9% (1/109), 0.9% (1/109) and 7.3% (8/109), respectively, in patients who were prior relapsers. The incidence of nonresponse, breakthrough and relapse in prior nonresponders was 6.3% (2/32), 18.8% (6/32) and 40.6% (13/32), respectively. The incidence of adverse events was similar between the prior relapsers and prior nonresponders. Serious adverse events were reported in 11.9% (13/109) of prior relapsers and 9.4% (3/32) of prior nonresponders. Overall, the most frequently reported adverse events in prior relapsers and prior nonresponders were anemia (88.1 vs 100%, respectively), pyrexia (82.6 vs 93.8%, respectively), decreased white blood cell count (76.1 vs 69.8%, respectively), blood uric acid increase (66.1 vs 78.1%, respectively) and platelet count decrease (67.0 vs 68.6%, respectively). Overall, 17.4% of prior relapsers discontinued treatment due to adverse events compared to 12.5% of prior nonresponders. Anemia was the most frequently reported adverse event leading to discontinuation in both

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment groups. Adverse events related to skin disorders were observed in 82.3% (116/141) of patients. Skin disorders reported in over 10% of the patients were rash 39.0% (55/141), drug eruption in 24.1% (34/141), injection site reaction in 12.8% (18/141) and injection site erythema in 12.8% (18/141) of the patients. Despite ribavirin dose modification, the median hemoglobin levels in prior relapsers and prior nonresponders decreased to 10.6 and 10.4 g/dL at week 12, respectively. No patient discontinued all the study drugs because of a neutrophil decrease. Secondary: Not reported
Flamm et al[20] Peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total vs boceprevir 800 mg three times a day plus peg interferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44 weeks (total treatment duration of 48 weeks) All patients entered a 4 week lead in period in which peg interferon alfa-2a and ribavirin were administered. In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA	PC, PG, RCT Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peg interferon alfa and ribavirin	N=201 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001). Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (*P* values not reported). The rates of SVR among patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peg interferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (*P* values not reported). Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
level at week 12 based on futility rules; these patients then entered the follow up period.				commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%). Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double blind, MC=multicenter, NI=non-inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ETR=end of treatment response, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, RNA=ribonucleic acid, RVR=rapid viral response, SVR=sustained virologic response

Special Populations

Table 5. Special Populations[8-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Boceprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B*	Unknown; use with caution.
Simeprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; safety and efficacy in moderate to severe hepatic impaired have not been established.	C*	Unknown; use with caution.
Telaprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; use is not recommended in moderate to severe impairment.	B*	Unknown; use with caution.

*Ribavirin has a pregnancy category of X. Boceprevir, simeprevir, and telaprevir must be used in combination with ribavirin and peg interferon alfa.

Adverse Drug Events

The adverse events reported in clinical trials for boceprevir (regardless of causality) with a frequency ≥10% of patients receiving boceprevir in combination with peg interferon and ribavirin, and reported at a rate ≥5% than peg interferon and ribavirin alone are outlined in Table 6. In addition, adverse events reported in clinical trials for simeprevir or telaprevir, in combination with peg interferon and ribavirin, with a frequency ≥3% and ≥5% higher, respectively, compared to peg interferon and ribavirin alone are also outlined in Table 6.[8-10]

Table 6. Adverse Drug Events (%)[8-10]

Adverse Event(s)	Boceprevir*	Simeprevir	Telaprevir
Blood and Lymphatic System Disorders			
Anemia	50/45	-	36
Neutropenia	25/14	-	-
Central Nervous System			
Dizziness	19/16	-	-
Insomnia	34/30	-	-
Irritability	22/21	-	-
Gastrointestinal			
Anorectal discomfort	-	-	11
Diarrhea	25/24	-	26
Dry mouth	11/15	-	-
Dysgeusia	35/44	-	10
Hemorrhoids	-	-	12
Nausea	46/43	22	39

Adverse Event(s)	Boceprevir*	Simeprevir	Telaprevir
Vomiting	20/15	-	13
General Disorders and Administration Site Conditions			
Asthenia	15/21	-	-
Chills	34/33	-	-
Fatigue	58/55	-	56
Metabolism and Nutrition Disorders			
Decreased appetite	25/26	-	-
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	19/23	-	-
Myalgia	-	16	-
Respiratory			
Dyspnea, including exertional dyspnea	-	12	-
Dyspnea, exertional	8/11	-	-
Skin and Subcutaneous Tissue Disorders			
Alopecia	27/22	-	-
Dry skin	18/22	-	-
Pruritis	-	22	47
Rash	17/16	28	56

- Event not reported or incidence <1%.
*Reported as: treatment-naïve patients/previous treatment failures (percent/percent).

Contraindications/Precautions

The hepatitis C protease inhibitors are contraindicated in women who are or who may become pregnant and in men whose female partners are pregnant because of the risk for birth defects and fetal death associated with ribavirin.[8-10]

Boceprevir and telaprevir are contraindicated when combined with drugs that are highly dependent on cytochrome P450 (CYP) 3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Boceprevir and telaprevir are also contraindicated when combined with drugs that strongly induce CYP3A, which may lead to a lower exposure and reduced efficacy of hepatitis C protease inhibitors. Medications that are contraindicated with either boceprevir or telaprevir include: alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's Wort, lovastatin, simvastatin, pimozide, sildenafil, tadalafil, triazolam, or orally-administered midazolam. In addition, carbamazepine, phenobarbital, phenytoin, and drospirenone are contraindicated with the use of boceprevir, while atorvastatin is contraindicated with the use of telaprevir.[8,9]

Simeprevir does not induce CYP3A4 and is a substrate and mild inhibitor of intestinal CYP3A, but not hepatic CYP3A4 activity. Co-administration of simeprevir with moderate or strong inducers or inhibitors of CYP3A is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively.[10]

Because the hepatitis C protease inhibitors must be used in combination with peg interferon alfa and ribavirin, the contraindications and warnings associated with those agents are also applicable to the hepatitis C protease inhibitors (Black Box Warnings associated with these agents are outlined below). Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and men must use at least two forms of effective contraception during treatment, and for at least six months after treatment has ended. Systemic hormonal contraceptives may not be as effective in women taking hepatitis C protease inhibitors; therefore, two alternative effective methods of contraception (e.g., intrauterine devices, barrier methods) should be used in women during treatment with these agents.[8-10]

Anemia has been reported in patients receiving peg interferon alfa and ribavirin, and the addition of a either boceprevir or telaprevir is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be monitored prior to and at least every four weeks during treatment with boceprevir or telaprevir.

For the management of anemia, ribavirin dose should be reduced. If ribavirin dose reductions are inadequate, consideration to discontinuing treatment with a boceprevir or telaprevir should be evaluated along with the ribavirin therapy.[8,9] In contrast, no additional anemia has been observed with the addition of simeprevir to peg interferon alfa and ribavirin.[10]

Serious skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens Johnson Syndrome were reported in less than one percent of patients receiving telaprevir in combination with peg interferon alfa and ribavirin compared to none who received peg interferon alfa and ribavirin alone. Presenting signs of DRESS may include rash, fever, facial edema and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. Presenting symptoms of SJS may include fever, target lesions and mucosal erosions or ulcerations (e.g., conjunctivae, lips). If serious skin reactions develop in patients receiving telaprevir, all treatment must be discontinued immediately. In addition, rash developed in 56% of patients who received telaprevir in combination with peg interferon alfa and ribavirin. Patients with mild to moderate rashes should be followed, and if the rash progresses and becomes severe or if systemic symptoms develop, telaprevir must be discontinued; however, peg interferon alfa and ribavirin may be continued.[9]

Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with boceprevir, peg interferon alfa and ribavirin. If such an acute reaction occurs, combination therapy should be discontinued and appropriate medical therapy immediately instituted.[8]

Rash has been reported with simeprevir in combination with peg interferon alfa and ribavirin, including severe rash requiring discontinuation of treatment. Patients with mild to moderate rashes should be followed for possible progression of rash. Treatment should be discontinued if the rash becomes severe. In addition, photosensitivity reactions (e.g., burning, erythema, exudation, blistering, and edema) have been reported with simeprevir in combination with peg interferon alfa and ribavirin, including serious reactions resulting in hospitalization. Measures to limit sun exposure are recommended. Expert consultation is advised if a decision is made to continue therapy in the setting of a photosensitivity reaction.[10]

As mentioned previously, according to the Food and Drug Administration approved package labeling of the hepatitis C protease inhibitors, these agents are not to be used as monotherapy and must be administered with peg interferon alfa and ribavirin.[8-10]

Black Boxed Warning for Incivek® (telaprevir)[9]

WARNING
Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with Incivek® combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive Incivek® combination treatment after a serious skin reaction was identified. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, Incivek®, peg interferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.

Black Box Warning for Pegasys® (peg interferon alfa-2a) and Peg Intron® (peg interferon alfa-2b)[29,30]

WARNING
Alfa interferons, including peg interferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peg interferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)[31-33]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 7. Drug Interactions[34]

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	HMG-CoA Reductase Inhibitors	HMG-CoA Reductase Inhibitors plasma concentrations may be elevated, increasing the pharmacologic effects and risk of myopathy and rhabdomyolysis. Coadministration of boceprevir or telaprevir with either lovastatin or simvastatin is contraindicated. Coadministration of atorvastatin with telaprevir is contraindicated. Atorvastatin dose should not exceed 40 mg daily when coadministered with either boceprevir or simeprevir. Rosuvastatin dose should not exceed 10 mg daily when coadministered with simeprevir.
Hepatitis C protease inhibitors (all)	Human Immunodeficiency Virus Protease Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Human Immunodeficiency Virus Protease Inhibitors. Co-administration of simeprevir with any Human Immunodeficiency Virus Protease Inhibitor, with or without ritonavir, is not recommended. Co-administration of boceprevir or telaprevir with either darunavir/ritonavir or lopinavir/ritonavir is not recommended. Co-administration of boceprevir with atazanavir/ritonavir is not recommended. Co-administration of telaprevir with fosamprenavir/ritonavir is not recommended.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Non-Nucleoside Reverse Transcriptase Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Non-Nucleoside Reverse Transcriptase Inhibitors. Co-administration of boceprevir or simeprevir with efavirenz is not recommended. Telaprevir dosage should be increased to 1,125 mg every eight hours when co-administered with efavirenz. Co-administration of any Hepatitis C protease inhibitor with nevirapine is not recommended. Co-administration of simeprevir with delavirdine or etravirine is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated by boceprevir or telaprevir, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of cardiac arrhythmias.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Boceprevir, telaprevir	α-1 adrenergic blockers	α-1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Benzodiazepines	Plasma concentrations of certain benzodiazepines may be elevated, increasing the pharmacologic effects and risk of severe sedation and prolonged respiratory depression.
Boceprevir, telaprevir	Contraceptives, hormonal	Plasma concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Boceprevir, telaprevir	Cyclosporine	Cyclosporine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Ergot derivatives	Ergot derivative plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir, telaprevir	Phosphodiesterase Type 5 Inhibitors	Phosphodiesterase type 5 inhibitor plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Coadministration with a phosphodiesterase type 5 inhibitor for pulmonary hypertension is contraindicated. Coadminister phosphodiesterase type 5 inhibitors for erectile dysfunction with caution.
Boceprevir, telaprevir	Lomitapide	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity
Boceprevir, telaprevir	Pimozide	Pimozide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of life-threatening cardiac arrhythmias.
Boceprevir, telaprevir	Tacrolimus	Tacrolimus plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including QT prolongation.
Simeprevir	Antifungals	Simeprevir plasma concentrations may be increased by certain antifungals. Co-administration with systemic itraconazole, fluconazole, ketoconazole, posaconazole, and voriconazole is not recommended.
Simeprevir	Clarithromycin, erythromycin, telithromycin	Simeprevir plasma concentrations may be increased. Erythromycin plasma concentration may also be increased. Co-administration with clarithromycin, erythromycin or telithromycin is not recommended.
Simeprevir	Dexamethasone	Simeprevir plasma concentrations may be reduced by systemic dexamethasone. Co-administration with systemic dexamethasone is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Simeprevir	Elvitegravir/cobicistat/ emtricitabine/tenofovir	Simeprevir plasma concentrations may be increased by cobicistat-containing product elvitegravir/cobicistat/emtricitabine /tenofovir. Co-administration with cobicistat-containing product is not recommended. □
Simeprevir	Oxcarbazepine	Simeprevir plasma concentrations may be reduced, leading to loss of virologic response.

Dosage and Administration

All three protease inhibitors are administered with food in combination with peg interferon alfa and ribavirin. Both boceprevir and telaprevir were previously indicated for three times daily administration; the prescribing information for telaprevir was recently updated recommending twice daily dosing based on comparable pharmacokinetics and safety profiles to three times daily dosing. Simeprevir is administered once-daily. [8-10]

In addition, the overall duration of therapy with boceprevir and telaprevir is response-guided based on hepatitis C virus (HCV) ribonucleic acid (RNA) levels at certain treatment weeks. While the overall duration of therapy with simeprevir is not response-guided, the stopping rules which allow for early discontinuation of therapy in patients with inadequate on-treatment virologic response, apply to all three protease inhibitors. In general, patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance substitutions. General dosing recommendations for protease inhibitors are outlined in Table 8, while the recommendations for response-guided therapy and/or stopping rules are outlined in Tables 9, 10 and 11.[8-10]

Boceprevir is added to peg interferon alfa and ribavirin after a four week lead-in period of peg interferon alfa and ribavirin alone (treatment weeks one through four), and is administered for either 24 or 32 weeks depending on the patient's treatment history and HCV RNA levels.[8] Simeprevir and telaprevir are initiated with peg interferon alfa and ribavirin and administered for 12 weeks regardless of treatment history or HCV RNA levels.[9,10]

Table 8. Dosing and Administration[8-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Boceprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Capsule: initial, after four weeks of peg interferon alfa and ribavirin administer 800 mg TID (every seven to nine hours) with food (a meal or light snack)	Safety and efficacy in children have not been established.	Capsule: 200 mg
Simeprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Capsule: 150 mg QD with food for 12 weeks	Safety and efficacy in children have not been established.	Capsule: 150 mg
Telaprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with peg interferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Tablet: 1,125 mg BID (every 10 to 14 hours) with food	Safety and efficacy in children have not been established.	Tablet: 375 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	(containing approximately 20 grams of fat) for 12 weeks		

BID=twice daily, QD=once daily, TID=three times daily

Table 9. Boceprevir Response-guided Treatment in Patients Without Cirrhosis[8]

	Assessment* (HCV RNA Results†)		Recommendation‡
	At Treatment Week Eight	At Treatment Week 24	
Treatment-Naïve Patients	Undetectable	Undetectable	Complete boceprevir, peg interferon alfa and ribavirin at treatment week 28
	Detectable	Undetectable	Continue boceprevir, peg interferon alfa and ribavirin and finish through treatment week 36; then administer peg interferon alfa and ribavirin and finish through treatment week 48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete boceprevir, peg interferon alfa and ribavirin at treatment week 36
	Detectable	Undetectable	Continue boceprevir, peg interferon alfa and ribavirin and finish through treatment week 36; then administer peg interferon alfa and ribavirin and finish through treatment week 48
Previous Null Responders	Detectable or undetectable	Undetectable	Continue all three medications and finish through week 48.

HCV=hepatitis C virus, RNA=ribonucleic acid

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥100 IU/mL at treatment week 12, discontinue boceprevir, peg interferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue boceprevir, peg interferon alfa and ribavirin.

†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.

‡Includes the four week lead in phase of peg interferon and ribavirin therapy.

Consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at treatment week four) with four weeks peg interferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peg interferon alfa and ribavirin in order to maximize rates of sustained virologic response. Patients with cirrhosis should receive four weeks of peg interferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peg interferon alfa and ribavirin.[8]

Table 10. Simeprevir Duration of Treatment[10]

	Recommendations		
	Triple Therapy (Simeprevir, Peg interferon alfa and Ribavirin)*	Dual Therapy (Peg interferon alfa and Ribavirin)*	Total Treatment Duration*
Treatment-Naïve and Prior Relapse Patients Including Those with Cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior Partial and Null Responder Patients Including Those with Cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥25 IU/mL at treatment week four or 12, discontinue simeprevir, peg interferon alfa and ribavirin. If the patient has HCV RNA results ≥25 IU/mL at treatment week 24, then discontinue peg interferon alfa and ribavirin. In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 15 IU/mL.

Table 11. Telaprevir Response-guided Treatment[9]

	Assessment* (HCV RNA Results†)	Recommendations		
		Triple Therapy (Telaprevir, Peg interferon alfa and Ribavirin)	Dual Therapy (Peg interferon alfa and Ribavirin)	Total Treatment Duration
Treatment-Naïve and Prior Relapse Patients	Undetectable at treatment weeks four and 12	First 12 weeks	Additional 12 weeks	24 weeks
	Detectable (≤1,000 IU/mL) at treatment weeks four and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients	All patients	First 12 weeks	Additional 36 weeks	48 weeks

HCV=hepatitis C virus, IU=international units, RNA=ribonucleic acid
*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥1,000 IU/mL at treatment week four or 12, discontinue telaprevir, peg interferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue peg interferon alfa and ribavirin.
†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 10 IU/mL.

Treatment-naïve patients with cirrhosis who have an undetectable HCV RNA level at treatment weeks four and 12 may benefit from an additional 36 weeks of peg interferon alfa and ribavirin (48 weeks total).[9]

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)[4]**	• The optimal therapy for hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peg interferon alfa and weight-based ribavirin. Treatment-naïve patients • The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus peg interferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peg interferon alfa plus ribavirin alone. o Patients without cirrhosis treated with boceprevir, peg interferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peg interferon alfa and ribavirin, followed by 24 weeks of triple therapy). o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peg interferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peg interferon alfa plus ribavirin (without telaprevir). o Patients without cirrhosis treated with telaprevir, peg interferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24.

Clinical Guideline	Recommendation(s)
	• Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peg interferon alfa and ribavirin should receive therapy for a duration of 48 weeks. Treatment-experienced patients • Re-treatment with boceprevir or telaprevir, in combination with peg interferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peg interferon alfa and/or ribavirin. • Retreatment with telaprevir, in combination with peg interferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peg interferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. Adverse events • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors. Use and Interpretation of HCV RNA Results During Triple Therapy • An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. IL28B testing • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peg interferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
Department of Veterans Affairs Hepatitis C	Recommendations in patients being considered for HCV therapy • All patients with chronic HCV infection should be evaluated for HCV antiviral

Clinical Guideline	Recommendation(s)
Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[5]	treatment. • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peg interferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. <u>Recommendations for treatment-naïve patients with genotype 1 infection</u> • Peg interferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for 36 more weeks. • If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peg interferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peg interferon-ribavirin should be continued until week 36, followed by peg interferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-peg interferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peg interferon-ribavirin is required after the four-week lead-in. <u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u> • For patients who previously failed peg interferon-ribavirin, retreatment with boceprevir or ribavirin and peg interferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peg interferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36.

Clinical Guideline	Recommendation(s)
	• If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peg interferon-ribavirin can be continued for an additional 36 weeks. • If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 36 weeks. <u>Recommendations for dose modification</u> • Peg interferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets. • If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued. • A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peg interferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations. • A peg interferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peg interferon alfa dose reductions. <u>Recommendations for treatment monitoring</u> • Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated. • Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit. • Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment. • In patients receiving telaprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level >1,000 IU/mL at week four or 12. o Detectable HCV RNA levels at week 24 or at any time point thereafter. o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). • In patients receiving boceprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur: o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen. o Detectable HCV RNA levels at week 24 or at any time point thereafter.

Clinical Guideline	Recommendation(s)
	o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA). • Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor. Recommendations for groups with special considerations for therapy • Peg interferon alfa monotherapy may be used to treat patients with contraindications to ribavirin. • For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peg interferon-ribavirin may be sufficient. • Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy. • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peg interferon-ribavirin at standard doses for 48 weeks. • Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection • Treatment-naïve patients should be treated with peg interferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. Recommendations in patients with genotype 4 infection • Appropriate candidates with HCV genotype 4 infections should be treated with peg interferon alfa-2a 180 µg per week or peg interferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. Recommendations in patients with decompensated cirrhosis • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. Recommendations in patients following solid organ transplantation • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver transplantation, peg interferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy

Clinical Guideline	Recommendation(s)
	and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. Recommendations in patients with renal disease • Considered modified doses of antiviral therapy with interferon (standard or pegylated). • Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peg interferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peg interferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peg interferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
American Association for the Study of Liver Diseases: **Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)**[2]	• Treatment decisions should be individualized based on severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient's readiness for treatment. • Optimal therapy for chronic HCV infection is peg interferon alfa in combination with ribavirin. • In genotypes 1 and 4, treatment with peg interferon alfa and ribavirin for 48 weeks is recommended. In patients who do not achieve an early virological response (early virologic response; ≥2 log reduction in HCV RNA at 12 weeks), treatment may be discontinued. Patients who do not achieve a

Clinical Guideline	Recommendation(s)
	complete early virologic response (undetectable HCV RNA at 12 weeks) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. Finally, for patients who have delayed virus clearance (HCV RNA test becomes negative between 12 and 24 weeks); consideration should be given to extending therapy to 72 weeks. • In genotypes 2 or 3, treatment with peg interferon alfa and ribavirin for 24 weeks is recommended. Patients who receive treatment for 24 weeks and who have a negative HCV RNA measurement, should be retested for HCV RNA 24 weeks later to evaluate for a SVR. Regardless of genotype, patients with HCV-related cirrhosis who achieve a SVR should be monitored at six to 12 month intervals for hepatocellular carcinoma development. • The same criteria for evaluating which patients should receive treatment can be used to determine which children, age two to 17 years of age, who are infected with HCV should receive treatment. • Children should be treated with the combination of peg interferon alfa 2b, 60 µg/m^2 weekly, and ribavirin 15 mg/kg daily for 48 weeks.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2013)**[3]	<u>Goals and endpoints of HCV therapy</u> • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients. • Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. <u>Indications for treatment</u> • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. <u>First line treatment of chronic hepatitis C genotype 1</u> • Triple therapy with boceprevir or telaprevir added to peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peg interferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peg interferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peg interferon alfa-2a (180 µg/week) and peg interferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peg interferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy

Clinical Guideline	Recommendation(s)
	First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6 • The combination of peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. Treatment monitoring • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. • During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. • During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. • The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed. • Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. • Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable. • Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. • Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. • Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. • For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. • Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. • Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. Treatment dose reductions and stopping rules • The peg interferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Peg interferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. • If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peg interferon alfa dose.

Clinical Guideline	Recommendation(s)
	• If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. <u>Measures to improve treatment success rates</u> • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peg interferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure for dual therapy; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peg interferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. <u>Post treatment follow up of patients who achieve an SVR</u> • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. <u>Retreatment of nonsustained virological responders to peg interferon alfa and ribavirin</u> • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior

Clinical Guideline	Recommendation(s)
	therapy with peg interferon alfa and ribavirin should be considered for retreatment with the triple combination of peg interferon alfa, ribavirin and a protease inhibitor. • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. <u>Treatment of patients with severe liver disease</u> • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peg interferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peg interferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. <u>Treatment of special groups</u> • Indications for HCV treatment in patients with human immunodeficiency virus (HIV) coinfection are identical to those in patients with HCV monoinfection. The same peg interferon alfa regimen should be used in HIV coinfected patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfected with HIV and HCV genotype 1 should be considered for

Clinical Guideline	Recommendation(s)
	telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions. • HIV patients with a diagnosis of acute HCV infection should be treated with peg interferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfected with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. • Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peg interferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless these is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. <u>Follow up of untreated patients and of patients with treatment failure</u> • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. <u>Treatment of acute hepatitis C</u> • Peg interferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.
Centers for Disease Control and Prevention: **Hepatitis ABC Fact Sheet (2012)**[7]	<u>Hepatitis C</u> • For acute hepatitis C, antivirals and supportive treatments are used. • Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.
American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[6]	• The treatment of choice is peg interferon plus ribavirin. • Patients with genotypes 1 and 4 require 48 weeks of therapy with peg interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). • Patients with genotypes 2 and 3 can be treated for only 24 weeks with peg interferon and 800 mg of ribavirin daily, with the following exceptions: • A longer duration of therapy may be considered on an individual

Clinical Guideline	Recommendation(s)
	patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy. • Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four. • Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.

Conclusions

Boceprevir (Victrelis®), simeprevir (Olysio®), and telaprevir (Incivek®) are Food and Drug Administration (FDA)-approved for the treatment of adults with chronic hepatitis C genotype 1 infection with compensated liver disease (including cirrhosis). Hepatitis C protease inhibitors inhibit the replication of hepatitis C virus (HCV) host cells by binding to the nonstructural 3/4A protease of HCV genotype 1a and 1b. All three agents are FDA-approved for use in treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers. Protease inhibitors must be administered in combination with peg interferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to protease inhibitor combination treatment.[8-10]

Boceprevir is added to standard therapy (peg interferon alfa and ribavirin) after a four week lead-in period with standard therapy alone. It is administered three times daily for either 24, 32 or 44 weeks based on a patient's treatment history and HCV ribonucleic acid (RNA) levels.[8] Simeprevir and telaprevir can be initiated with standard therapy and are administered once daily and two times daily, respectively, for 12 weeks, regardless of treatment history or HCV RNA levels.[9,10] Boceprevir and telaprevir are associated with an increased risk of anemia when administered with standard therapy.[8,9] In addition, telaprevir is associated with the development of rash, which can be serious in nature.[9] Prior to initiating therapy with simeprevir, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced efficacy of simeprevir combination therapy. Alternative therapy should be considered for patients with HCV genotype 1a infection with the Q80K polymorphism.[10]

The pivotal clinical trials demonstrate that use of the hepatitis C protease inhibitors, in combination with peg interferon alfa and ribavirin, results in significantly higher sustained virologic response (SVR) rates among adult patients with chronic hepatitis C genotype 1 infection compared to standard therapy alone. In select patients with satisfactory early virologic responses, the total treatment duration may be shortened (i.e., response-guided treatment).[13-15,17,18,23-25] Specifically, clinical trial data demonstrates, and FDA-approved dosing states, that if a patient has an undetectable HCV RNA level at treatment weeks four and 12 with a telaprevir-containing regimen, 24 weeks of total treatment is effective in achieving a SVR.[9,14,15,18] A patient with an undetectable HCV RNA level at treatment weeks eight and 24 with a boceprevir-containing regimen requires 28 or 36 weeks of total treatment depending on their previous treatment history.[9,13,17] The total duration of treatment with simeprevir-containing regimen is either 24 weeks in treatment-naïve and prior relapser patients or 48 weeks in prior partial and null responder patients.[10,23-26] Of note, standard treatment futility rules apply to any triple therapy regimen used for the treatment of chronic hepatitis C genotype 1 infection. Futility should be assessed at treatment weeks four, 12 and 24 with simeprevir and telaprevir-containing regimens, and at treatment weeks 12 and 24 with boceprevir-containing regimens.[8-10]

Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.[3-6] The hepatitis C protease inhibitors are recommended, along with standard therapy, for the treatment of chronic hepatitis C genotype 1 infection.[3,4] To date, no head-to-head trials between the commercially available hepatitis C protease inhibitors have been published to directly compare their efficacy. Treatment guidelines do not give preference to one specific peg interferon alfa or ribavirin product over another.[3-7] Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with FDA-approved indications and dosing.[2-10] Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents.[2-7]

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Xartemix XR Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201407	XARTEMIS XR TAB 7.5-325	1	1	120	30	286.28

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Xartemis® XR (Oxycodone and Acetaminophen) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:

Authorization will be given if the following criteria are met and documented:

a. The recipient is 18 years old or older
b. The ICD-9 code of Acute pain (338.1) is transmitted electronically on the pharmacy claim.
c. The quantity does not exceed 20 tablets per 5 day supply. One 5 day supply is allowed every 6 months.

Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-17] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication[18]. Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[18] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[18] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[19]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[19] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[20]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[20]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[20,21]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[22]

Even though OxyContin® (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[23] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[24] Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[25]

In October 2013, the FDA approved the first sole entity hydrocodone product in an extended-release formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone extended-release) was approved based on an FDA Division Director's rationale that the benefit-risk

balance for Zohydro ER® (hydrocodone extended-release) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[10]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains extended-release morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[16,26] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, Embeda® will be available as soon as possible once the stability issue is resolved.[27] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[28]

On March 11, 2014, the FDA approved a new combination product Xartemis XR® (oxycodone/acetaminophen), which contains oxycodone and acetaminophen. It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[17]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	✔
Hydrocodone (Zohydro®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Capsule, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg	-
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release‡: 8 mg 12 mg 16 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		32 mg	
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Dispersible tablet for oral suspension: 40 mg Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg	✔
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	✔
Oxycodone (OxyContin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¶	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg	✔ #

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		40 mg 60 mg‡ 80 mg‡	
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	✔
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time for patients in whom tolerance to an opioid of comparable potency is established.	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡	-
Oxycodone/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, extended release: 7.5 mg/325 mg	-

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- In one trial, treatment with the buprenorphine transdermal system significantly improved the average pain score over 24 hours at week 12 compared to treatment with buprenorphine 5 µg/hour (P<0.001 for both). In a second trial, treatment with either 10 or 20 µg/hour of buprenorphine transdermal system resulted in a treatment difference favoring buprenorphine (95% confidence interval [CI], -1.02 to -0.14; P=0.01) compared to placebo. Two other trials failed to show efficacy for buprenorphine transdermal system in patients with low back pain and osteoarthritis, respectively against oxycodone/acetaminophen and oxycodone immediate-release. In another trial, treatment with either buprenorphine transdermal system 20 µg/hour or oxycodone immediate-release was compared to treatment with buprenorphine transdermal system 5 µg/hour in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours was greater in the buprenorphine

transdermal system 20 µg/hour and oxycodone immediate-release treatment groups compared to the buprenorphine transdermal system 5 µg/hour group, however the difference was not significant (P values not reported).[1,29]

- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[30-32]
- A trial comparing hydrocodone extended-release capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone extended-release had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly higher amount of treatment responders in the hydrocodone extended-release group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone-extended release group compared to placebo (P<0.0001).[33]
- In one trial, hydromorphone extended-release demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[34] In a noninferiority analysis of a hydromorphone extended-release compared to oxycodone extended-release, two agents provided similar pain relief in the management of osteoarthritic pain.[35]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[36,37]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate extended-release) and MS Contin® (morphine sulfate controlled-release) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[38] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[39]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[27]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[40]
- Oxycodone controlled-release has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[41-43] For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release (P=0.01), and the incidence of nausea and sedation were similar between treatments.[44]
- Oxymorphone extended-release has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain.[45,46] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release from morphine sulfate or oxycodone controlled-release. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[45] In another trial, oxymorphone extended-release demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[47]
- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol extended-release compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[48] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with

tapentadol extended-release and oxycodone controlled-release relative to placebo (P<0.001).[49] Schwartz et al evaluated tapentadol extended-release among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol extended-release group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[50]

- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (*P*<0.0001).[51]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[52]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine.[53,54]
    - Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[54]
    - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain.[53]
    - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.[53,54]
    - In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[53]
    - Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.[53]
    - Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.[53]
    - In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.[53,54]
- Other Key Facts:
    - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
    - Only fentanyl transdermal system is approved in children (age 2 to 17 years).
    - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.

- Only oxymorphone is contraindicated in severe hepatic disease.
- Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
- Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[11,16] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[5-9,12] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,14,15,17] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[10]. Xartemis XR (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[17]
- Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven. Fentanyl may be applied to the chest, back, flank or upper arm while buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1-2]
- Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-17] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[10,11,16] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[11] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[10,11,16] It is recommended to only swallow one Zohydro ER® (hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,13-15]
- Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-17] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

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Therapeutic Class Review
Long-acting Opioids

Overview/Summary

As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-17] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[18] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[18] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[18] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[19]

Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[19] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[20]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[20]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[20,21]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[22]

Even though OxyContin® (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[23] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[24] Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[25]

In October 2013, the FDA approved the first sole entity hydrocodone product in an extended-release formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone extended-release) was approved based on an FDA Division Director's rationale that the benefit-risk balance for Zohydro ER® (hydrocodone extended-release) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[10]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains extended-release morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[16,26] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, Embeda® will be available as soon as possible once the stability issue is resolved.[27] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[28]

On March 11, 2014, the FDA approved a new combination product oxycodone/acetaminophen (Xartemis XR®). It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[17]

Medications

Table 1. Medications Included Within Class Review[1-17]

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine (Butrans®)	Opiate partial agonist	-
Fentanyl (Duragesic®*)	Opioid agonist	✔
Hydrocodone (Zohydro ER®)	Opioid agonist	-
Hydromorphone (Exalgo®*)	Opioid agonist	✔
Methadone (Dolophine®*, Methadose®*)	Opioid agonist	✔
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	Opioid agonist	✔
Oxycodone (OxyContin®*)	Opioid agonist	✔ †
Oxymorphone (Opana®* ER)	Opioid agonist	✔
Tapentadol (Nucynta ER®)	Opioid agonist	-
Combination Products		
Morphine sulfate/naltrexone (Embeda®)	Opioid agonist/opioid antagonist	-
Oxycodone/acetaminophen (Xartemis XR®)	Opioid agonist/analgesic, antipyretic	-

*Generic is available in at least one dosage form or strength.
†Generic availability is sporadic and does not include all strengths.

Indications

Table 2. Food and Drug Administration Approved Indications[1-17]

Generic Name	Indications
Single Entity Agents	
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative

Generic Name	Indications
	treatment options are inadequate.*
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.§
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Combination Products	
Morphine sulfate/ naltrexone	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time for patients in whom tolerance to an opioid of comparable potency is established. ‡
Oxycodone/ acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†Avinza® 90 mg and 120 mg capsules and Kadian® /MS Contin 100 mg and 200 mg capsules/tablets are only for use in patients who are tolerant to opioids.
§OxyContin® 60 mg and 80 mg tablets or a single dose >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.
‡Embeda® 100 mg/4 mg capsules are only for use in patients who are tolerant to opioids.

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program. Regulatory exceptions to the general requirement for certification to provide opioid agonist treatment include the following the situations: during inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07[c], to facilitate the treatment of the primary admitting diagnosis), and during an emergency period of no longer than three days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07[b]).[5-9]

Pharmacokinetics

Table 3. Pharmacokinetics[1-17,29]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Buprenorphine	15	27	Norbuprenorphine	26
Fentanyl	92	75 as metabolites; <7 to 10 as unchanged	None reported	20 to 27
Hydrocodone	Not specified	Not specified (primary route)	Norhydrocodone, hydromorphone	8
Hydromorphone	24	75; 7 as unchanged	Unknown	11
Methadone	36 to 100	Not specified	None reported	7 to 59
Morphine sulfate	<40	90; 2 to 12 unchanged	Morphine-6-glucuronide	1.5 to 15.0
Oxycodone	60 to 87	19 unchanged; 50 conjugated oxycodone; 14 or less conjugated oxymorphone	Noroxycodone, oxymorphone	4.5 to 8.0
Oxymorphone	10	<1 unchanged; approximately 39 major metabolites	None reported	7.25 to 9.43
Tapentadol	32	99; 70 conjugated; 3 unchanged drug	None reported	4 to 5
Combination Products				
Morphine sulfate/ naltrexone	<40 (morphine sulfate); highly variable (naltrexone)	90; 2 to 12 unchanged (morphine sulfate and metabolites); not reported (naltrexone)	Morphine-6-glucuronide (morphine sulfate)/ 6-β-naltrexol (naltrexone)	29
Oxycodone/ acetaminophen	60 to 87/APAP not reported	19 unchanged; 50 conjugated/<9	Noroxycodone, oxymorphone/none	4.5 ± 0.6/ 5.8 ± 2.1

APAP=acetaminophen

Clinical Trials

As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of noncancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain is available. Clinical trials demonstrating the effectiveness and safety of the long-acting opioids are outlined in Table 4. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in adverse event profiles and associated improvements in quality of life or sleep domains.[30-73]

Food and Drug Administration (FDA) approval of buprenorphine transdermal system was based on four unpublished, 12-week double-blind clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. The description of these trials has been obtained from the prescribing information and the manufacturer product dossier. Two of these four trials demonstrated efficacy in patients with chronic low back pain. In one trial (N=1,160), treatment with buprenorphine transdermal system resulted in significant treatment differences in the average pain score over the last 24 hours at week 12 in favor of transdermal buprenorphine 20 µg/hr and oxycodone immediate-release compared to buprenorphine 5 µg/hr (P<0.001 for both). In the second trial (N=1,024), treatment with either 10 or 20 µg/hr of buprenorphine transdermal system resulted in a treatment difference in favor of buprenorphine (95% confidence interval [CI], -1.02 to -0.14; P=0.01) compared to placebo. Two other trials failed to show efficacy for buprenorphine

transdermal system in patients with low back pain and osteoarthritis, respectively. In the first trial (N=134), treatment with either buprenorphine 5, 10, or 20 µg/hr or a combination of oxycodone and acetaminophen was compared to placebo in patients with low back pain. Differences in the mean change from baseline for "pain on average" and "pain right now", the two primary endpoints, between the buprenorphine transdermal system and the placebo groups were significant for the maintenance period (P=0.04 and P=0.045, respectively). However, differences between placebo and oxycodone and acetaminophen combination, the active control, were not significant (P value not reported). When the trial was evaluated using pain scores at week 12 (an analysis preferred by the FDA), the buprenorphine transdermal system treatment group did not yield a significant difference from placebo (P value not reported). In another trial (N=418), treatment with either buprenorphine transdermal system 20 µg/hr or oxycodone immediate-release was compared to buprenorphine transdermal system 5 µg/hr in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours scores from baseline, the primary endpoint, was greater in the buprenorphine transdermal system 20 µg/hr and oxycodone immediate-release treatment groups as compared to the buprenorphine transdermal system 5 µg/hr group, but did not achieve significance (P values not reported). Furthermore, none of the results of the sensitivity analyses were significant, supporting the conclusion that this trial lacked assay sensitivity and is a failed trial.[1,74]

Two smaller, double-blind, crossover trials compared buprenorphine transdermal system to placebo in patients with chronic low back pain. In both trials, patients were randomized to receive buprenorphine transdermal system or placebo for four weeks and crossed over to alternate treatments at the end of week 4 for a total of eight weeks. In the first trial (N=79), the treatment difference between buprenorphine 5 to 20 µg/hour and placebo in the average pain score over the last week at the end of each treatment phase, the primary endpoint, was small but statistically significant when reported using a five-point ordinal scale (P=0.0226). When the same endpoint was reported using a visual analogue scale, there was no statistically significant difference between the two treatment groups (P=0.0919).[31] In the second trial (N=78), the difference in average pain score over the last 24 hours for buprenorphine 10 to 40 µg/hour was significantly lower compared to placebo when reported using both the visual analogue scale and the five-point ordinal scale (P=0.005 and P=0.016, respectively).[31]

In total, 18 clinical pharmacology trials and 15 chronic pain trials have been completed with buprenorphine transdermal system. Overall, there is a consistent pattern of pain reduction or continuing stable pain control in chronic, non-cancer, non-neuropathic pain models, supporting the analgesic efficacy of buprenorphine transdermal system.[74]

Fentanyl transdermal systems have demonstrated efficacy in the treatment of neuropathic pain, moderate to severe chronic pain due to nonmalignant and malignant disease, and moderate to severe osteoarthritis pain in both open-label and placebo-controlled trials.[32-36] The effectiveness of fentanyl in relieving pain also appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[39-41]

Hydrocodone extended-release has demonstrated safety and efficacy in a phase III placebo controlled trial. The trial evaluated the safety and efficacy of hydrocodone extended-release in opioid-experienced adults with moderate to severe chronic low back pain in a 12 week double-blind, multicenter, randomized, placebo-controlled trial. 302 subjects were randomized in a 1:1 fashion to receive either hydrocodone extended-release or placebo after a conversion/titration phase of up to six weeks in length to establish each subject's appropriate dose of hydrocodone extended-release. The primary endpoint evaluated was the change in mean pain intensity score from baseline to end of treatment, which was based on the 11-point numerical rating scale that was recorded daily in an electronic diary. The numerical rating scale scores ranged from zero to ten, with zero equal to "no pain" and ten equal to the "worst pain imaginable." The secondary endpoints measured were "treatment responders," defined by the percentage of subjects with at least a 30% average improvement in pain intensity scores from baseline to end of treatment and subject satisfaction with their pain medication, measured by the mean increase in Subject Global Assessment of Medication scores from baseline to end of treatment. The Subject Global Assessment of Medication is conducted by asking subjects, "How satisfied are you with your pain medicine?" The answers accepted are "not at all," "a little bit," "moderately," "very much" and "completely". The answers

are given a score of 1 to 5, respectively, and a higher Subject Global Assessment of Medication indicated greater satisfaction with subjects' treatments. Mean change from baseline to end of treatment in pain intensity score ± standard deviation (SD) was significantly lower for hydrocodone extended-release vs placebo (0.48 ± 1.56 vs to 0.96 ± 1.55, respectively; P=0.008). There was a significantly higher amount of treatment responders in the hydrocodone extended-release group compared to the placebo group (68% vs 31%, respectively; P<0.001) at the end of treatment, and Subject Global Assessment of Medication scores increased from baseline significantly in the hydrocodone-extended release group compared to placebo (0.8 ± 1.3 vs 0.0 ± 1.4, respectively; P<0.0001).[42]

The available published clinical trial information demonstrating the efficacy and safety of hydromorphone extended-release is currently limited. In a placebo-controlled trial, the medication demonstrated superior efficacy in the treatment of lower back pain with regards to reducing pain intensity (P<0.001) and pain scores (P<0.01). In addition, treatment was well tolerated.[45] In a 2007 noninferiority analysis of a hydromorphone extended-release formulation available only in Europe compared to oxycodone extended-release, it was demonstrated that the two agents provided similar pain relief in the management of osteoarthritic pain.[44]

Methadone has demonstrated "superior" efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[48,49]

A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate extended-release) and MS Contin® (morphine sulfate controlled-release) significantly reduced pain from baseline (P≤0.05 for both). In addition, both treatments reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each of the treatments statistically improved certain sleep parameters compared to placebo, and when compared head-to-head; Avinza®, administered in the morning, significantly improved overall quality of sleep compared to MS Contin® (P value not reported).[48] In another cross-over trial, morphine sulfate (MS Contin®) was compared to treatment with fentanyl transdermal systems. In this trial, more patients preferred treatment with fentanyl (P<0.001), and reported on average, lower pain intensity scores than during the morphine sulfate phase (P<0.001).[52]

Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[27] Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[55]

Oxycodone controlled-release has demonstrated "superior" efficacy over placebo for the treatment of neuropathic pain and chronic refractory neck pain.[56-58] For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release (P=0.01), and the incidence of nausea and sedation were similar between treatments.[59]

Oxymorphone extended-release has established safety and efficacy in the management of cancer pain.[61,62] Specifically, the agent produced comparable mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain. Patients were initially stabilized on morphine sulfate or oxycodone controlled-release and then switched to treatment with oxymorphone extended-release. The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release. No significant changes were observed in mean visual analog pain scores, quality of life domains, or quality of sleep for any of the treatment groups.[62] In another placebo-controlled trial, oxymorphone extended-release demonstrated "superior" efficacy for the treatment of osteoarthritis pain.[63]

The efficacy and safety of tapentadol extended-release was evaluated in three placebo-controlled and active controlled comparator trials along with one 52-week long-term safety trial. Afilalo et al conducted a

12-week randomized, double-blind, multicenter, active- and placebo-controlled trial among adults (N=1,030) with osteoarthritis of the knee who were assigned to receive tapentadol extended-release or oxycodone controlled-release (titrated to response) or placebo. Significant pain relief was achieved with tapentadol extended-release vs placebo, with a least squares mean (LSM) difference of - 0.7 (95% confidence interval [CI], -1.04 to -0.33) at week 12 of the maintenance period compared to placebo. Comparatively, the average pain intensity rating at endpoint compared to baseline with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (LSM difference vs placebo: -0.3), but was not significantly lower at week 12 of the maintenance period (LSM of -0.3; P values not reported). The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week 12 of the maintenance period was not significantly different between tapentadol extended-release and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Tapentadol extended-release resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period vs placebo (32.0 vs 24.3%; P=0.027) compared to treatment with oxycodone controlled-release which resulted in a reduction vs placebo of 17.3 vs 24.3% (P=0.023).[65] Buynak et al evaluated the efficacy of tapentadol extended-release compared to placebo in a prospective, double-blind, placebo controlled, active comparator trial with oxycodone controlled-release in adults (N=981) with moderate to severe lower back pain. Throughout the 12 week maintenance period, average pain intensity scores (primary endpoint) improved in both the tapentadol extended-release and oxycodone controlled-release groups relative to placebo. The mean change in pain intensity from baseline to week 12 was -2.9 for tapentadol extended-release and -2.1 for placebo, resulting in a LSM difference vs placebo of -0.8 (P<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for the tapentadol extended-release group and -2.1 for the placebo group, corresponding to a LSM difference vs placebo of -0.7 (P< 0.001).[66] Schwartz et al evaluated the efficacy of tapentadol extended-release in a 12 week, randomized, double-blind, placebo-controlled, maintenance trial among adults (N=395) with at least a six month history of painful diabetic peripheral neuropathy. The LSM change in average pain intensity from the start of double-blind treatment to week 12 (primary endpoint) was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol extended-release group, indicating no change in pain intensity, corresponding to a LSM difference of -1.3 (95% CI, -1.70 to -0.92; P<0.001). The mean changes in average pain intensity scores from baseline to week 12 among those receiving tapentadol extended-release were similar regardless of gender, age (<65 years or >65 years), and history of previous opioid use. At least a 30% improvement in pain intensity was observed in 53.6% of tapentadol extended-release -treated patients and 42.2% of placebo-treated patients (P=0.017) at week 12; and ≥50% improvement in pain intensity was observed in 37.8% of tapentadol extended-release-treated patients and 27.6% of placebo-treated patients.[63] Wild et al evaluated the long-term safety of tapentadol extended-release in a randomized, active-controlled, open-label, trial compared to oxycodone controlled-release among adults with chronic knee or hip osteoarthritis or low back pain. The proportion of patients who completed treatment in the tapentadol extended-release and oxycodone controlled-release groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1 vs 36.8%). Overall, 85.7% of patients in the tapentadol extended-release group and 90.6% of patients in the oxycodone controlled-release group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), vomiting (7.0 vs 13.5%), and pruritis (5.4 vs 10.3%) were lower in the tapentadol extended-release group than in the oxycodone controlled-release group, respectively. There were no clinically-relevant, treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol extended-release group and 36.8% of patients in the oxycodone controlled-release group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol extended-release group than in the oxycodone controlled-release group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol extended-release and oxycodone controlled-release groups (5.5 vs 4.0%, respectively).[68]

The efficacy of the combination product oxycodone/acetaminophen efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded

that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/acetaminophen and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/acetaminophen was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in pain intensity after two hours was 63.1% for oxycodone/acetaminophen compared to 27.2% for placebo (*P*<0.0001).[72]

Methadone is the only long-acting narcotic that is FDA-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[73]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moderate to Severe Pain				
Gordon et al[30] Buprenorphine transdermal system 5, 10 or 20 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Codeine/ acetaminophen 30/300 mg one or	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	N=79 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last week on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 mm (no pain) to 100 mm (excruciating pain) Secondary: PDI, Pain and Sleep Questionnaire, level of activity, SF-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Primary: In the ITT analysis, the average pain score reported by patients using the five-point scale at the last week of each treatment phase was 1.8±0.6 for buprenorphine and 2.0±0.7 for placebo (P=0.0226). When the pain score was reported using the VAS, the score was 40.2±20.2 for buprenorphine and 44.4±20.2 for placebo (P=0.0919). Secondary: In the per-protocol analysis, when buprenorphine was compared to placebo at the last week of each treatment phase, there were no treatment differences with regard to improvement in any of the subscales or the total score of the PDI (results not reported; P=0.4860), the Pain and Sleep Questionnaire (172.4±122.8 vs 178.2±112.6; P value not reported), the level of activity (43.8±23.0 vs 43.9±23.7; P=0.9355) or the SF-36 (results not reported; P value not reported). There was no difference between the two treatment groups in patient- and investigator-rated treatment effectiveness at the end of each treatment phase. The patient-rated scores were 1.3±1.1 and 0.9±1.0 for buprenorphine and placebo, respectively (P=0.1782), while the investigator-rated scores were 1.2±1.0 and 0.9±1.0, respectively (P=0.1221). Forty-three percent of patients preferred the buprenorphine treatment phase, 38% of patients preferred the placebo phase and 19% of patients had no preference (P=0.6473). Similarly, 43% of investigators preferred buprenorphine for their patients, 36% of investigators preferred placebo and 21% of investigators had no preference (P=0.5371). More patients reported drowsiness with buprenorphine compared to placebo (P=0.0066). More patients reported at least one adverse event during treatment with buprenorphine compared to placebo (P=0.0143). The most commonly reported adverse events include nausea, somnolence and application site reactions. ES Phase: Forty-two of 51 patients (82%) who completed the DB phase continued to receive OL buprenorphine treatment. The average PI score over the past 24 hours measured by VAS were significantly lower at the end of the ES phase compared to the DB phase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
two tablets every 4 to 6 hours as needed was allowed.				(13.2±20.2 vs 39.5±19.1; P=0.0001). There were no differences between the ES and DB phases in the average pain score over the last week and all other study endpoints, with the exception of the standardized physical component of the SF-36, which was significantly lower in the ES phase compared to the DB phase (P=0.0226).
Gordon et al[31] Buprenorphine transdermal system 10 to 40 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before randomization and antidepressants or anticonvulsants at a stable dose for 8 weeks before randomization were permitted. Supplemental analgesic medication was	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with moderate to severe chronic low back pain for >3 months, requiring one or more tablet of opioid analgesics daily	N=78 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last 24 hours on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 (no pain) to 100 mm (excruciating pain) Secondary: Pain and Sleep Questionnaire, PDI, SF-36, treatment effectiveness on a four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	Primary: In the ITT analysis, buprenorphine was associated with a lower average pain score over the last 24 hours compared to placebo. When reported using VAS, the pain score was 44.6±21.4 for buprenorphine and 52.4±24.0 for placebo (P=0.005). The score reported using the five-point scale was 2.0±0.7 and 2.2±0.8 for buprenorphine and placebo, respectively (P=0.016). Secondary: The overall score of the Pain and Sleep Questionnaire was significantly lower for buprenorphine compared to placebo (117.6±125.5 vs 232.9±131.9; P=0.027). No significant differences were noted between the two treatment groups with regard to the PDI and SF-36 (P value not reported for all endpoints). The treatment effectiveness of buprenorphine was rated significantly higher than placebo by patients (1.8±1.1 vs 1.0±1.1; P=0.016) and investigators (1.8±1.1 vs 1.0±1.1; P=0.013). Sixty-six percent of patients preferred the buprenorphine treatment phase, 24% of patients preferred the placebo phase and 10% of patients had no preference (P=0.001). Similarly, 60% of investigators preferred the buprenorphine treatment phase for their patients, 28% of investigators preferred the placebo phase and 12% of investigators had no preference (P=0.008). Significantly more patients in the buprenorphine group reported adverse events compared to patients in the placebo group (65.0 vs 64.7%; P=0.003). The most commonly reported adverse events with buprenorphine were nausea, dizziness, pruritus, vomiting and somnolence. ES Phase: Forty of 49 patients (81.6%) who completed the ES phase continued to receive OL buprenorphine treatment. The improvements in daily PI, PDI and SF-36 were maintained

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
permitted throughout the study. Acetaminophen 325 mg one or two tablets every 4 to 6 hours as needed was allowed.				throughout the ES phase.
Karlsson et al[32] Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two doses Supplemental analgesic medication was permitted throughout the study. Paracetamol* up to 2,000 mg/day was allowed.	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week before visit 1	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				dizziness (15.9%).
Conaghan et al[33] Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol* 1,000 mg orally four times daily vs codeine/ paracetamol* 8/500 mg or 30/500 mg orally one or two tablets four times daily Supplemental analgesic medication was permitted throughout the study. Ibuprofen up to 1,200 mg/day was allowed.	AC, MC, OL, PG, RCT Patients ≥60 years of age with a clinical diagnosis of OA of the hip and/or knee with severe pain and taking the maximum tolerated dose of paracetamol (four or more 500 mg tablets each day)	N=220 10 weeks of titration period followed by 12 weeks of assessment period	Primary: Average pain score over the last 24 hours on Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, laxative use, sleep parameters on the Medical Outcome Study-Sleep Scale, time to achieve stable pain control, length of time on anti-emetics, discontinuation rate during the titration period and safety	Primary: In the ITT analysis, the treatment difference between buprenorphine plus paracetamol and codeine/paracetamol with regard to the average daily pain score was -0.07 (95% CI, -0.67 to 0.54; P value not reported), demonstrating that buprenorphine plus paracetamol was non-inferior to codeine/paracetamol. Secondary: In the per-protocol analysis, patients receiving buprenorphine plus paracetamol required 33% fewer supplemental analgesic medications compared to those receiving codeine/paracetamol. The treatment difference was -0.98 (95% CI, -1.55 to -0.40; P=0.002). Fifty percent of patients in each treatment group required laxatives during the study (P value not reported). In the per-protocol analysis, the mean sleep disturbance score on the Medical Outcome Study-Sleep Scale decreased from 33.90±22.09 at baseline to 24.30±25.32 at the end of the study in the buprenorphine plus paracetamol group, while the score decreased from 41.8±28.6 to 32.9±26.1 in the codeine/paracetamol group (P value not reported). Patients receiving buprenorphine plus paracetamol reported improvement in sleep adequacy, with an increase in score from 50.80±25.35 at baseline to 62.50±28.26 at the end of the study, whereas the score increased from 56.10±25.84 to 59.10±26.41 in patients receiving codeine/paracetamol (P value not reported). There was no difference in the number of hours slept between the two groups. The number of patients with optimal sleep slightly increased in the buprenorphine plus paracetamol group and slightly decreased in the codeine/paracetamol group. The snoring score did not change with buprenorphine plus paracetamol and slightly improved with codeine/paracetamol. Neither treatment had any effect on shortness of breath, headache or somnolence (P values not reported for all parameters). The mean time to achieve stable pain control during the titration period was 19.5±11.5 days for buprenorphine plus paracetamol and 21.80±13.76 days for codeine/paracetamol (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The median percentage of days on which anti-emetics were used during the titration period was 18.5% (interquartile range, 0 to 70.6) for buprenorphine plus paracetamol and 0% (interquartile range, 0 to 26.8) for codeine/paracetamol (P value not reported). Forty-three of 110 patients in the buprenorphine plus paracetamol group withdrew from the study during the titration period; 34 patients withdrew due to adverse events and five patients withdrew due to lack of therapeutic effect. In the codeine/paracetamol group, 63 of 110 patients withdrew during the titration period; 23 patients withdrew were due to adverse events and 12 patients withdrew due to lack of therapeutic effect. Eighty-six percent and 82% of patients in the buprenorphine plus paracetamol and codeine/paracetamol groups, respectively, reported treatment emergent adverse events. The most commonly reported adverse events in the buprenorphine plus paracetamol group were nausea, application site reaction and constipation.
Agarwal et al[34] Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	OL, PRO Patients >18 years of age with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in PI and daily activity Secondary: Pain relief, cognition, physical function and mood	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in PI. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in PI in the peripheral neuropathy group compared to the CRPS-1 (P=0.06) and postamputation (P=0.07) groups among the ITT population. Among completers, fentanyl was more effective in reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (P<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (P<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in PI and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6%, 37.5% and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (P value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (P value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (P value not significant).
Finkel et al[35] Fentanyl transdermal system 12.5 to 100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment; changes in pain level, PPS, and CHQ and safety Secondary: Not reported	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily PI levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of 11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Mercadante et al[36] Fentanyl transdermal patch 12 µg/hour, doses were titrated according to the clinical response Morphine (5 mg) was allowed for breakthrough pain.	OL, OS Opioid-naïve patient with advanced cancer and moderate pain	N=50 4 weeks	Primary: PI, opioid-related adverse events, doses, quality of life Secondary: Not reported	Primary: Thirty-one patients completed all four weeks of the trial. Pain control was achieved within 1.7 days after the start of therapy. PI significantly decreased from baseline through the remaining weekly evaluations (P<0.001). Significant differences in doses were observed after two weeks and were almost doubled at four weeks. The mean fentanyl escalation index was 4.04% and 0.012 mg, respectively. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. The pain mechanism did not significantly affect the changes in PI and doses of fentanyl. The mean fentanyl escalation index was similar in patients presenting difference pain mechanisms. There were significant changes in opioid-related symptoms and quality of life between weekly evaluations. Secondary: Not reported
Park et al[37] Fentanyl transdermal patch 12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	OL, PRO Patients ≥19 years of age, with overall good health, and complaining of chronic pain of the spine and limbs that scored >4 points on a numerical	N=65 12 weeks	Primary: Percentage of change in PI from before the administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's	Primary: Changes in average PI, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual PI, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; P<0.001). The pain intensities evaluated by the patients, at rest and when moving, were decreased from 5.40 to 1.95 (63.9%; P<0.0001). Secondary: Within three visits, the sum of patients who answered "very satisfied" or "satisfied" was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of 'very satisfied' and "satisfied" measured in week four and the rates on the last visit constituted a significant increase (P<0.05). The determinants of the patient's satisfaction with pain

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	rating scale 72 hours prior to baseline data		function/sleep interference, dose, safety	treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (P<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (P<0.0001). The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (P<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al[38] Fentanyl transdermal system 25 to 100 µg/hour every 72 hours vs placebo	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects of pain relief affecting mobility and quality of life	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; P=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (P=0.009 and P=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (P=0.051 and P=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; P=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; P<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all P<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (P=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; P=0.041).
Ahmedzai et al[39] Fentanyl transdermal system replaced every 72 hours for 15 days vs morphine SR (MST-Continus™) every 12 hours for 15 days	MC, OL, RCT, XO Patients 18 to 89 years of age with cancer who required strong opioid analgesia and were receiving a stable dose of morphine for ≥48 hours	N=202 30 days	Primary: Pain control, effect on sedation and sleep, bowel function, treatment preference and adverse events Secondary: Not reported	Primary: No significant differences on any of the pain scales were detected between the fentanyl and morphine phases. During the fentanyl phase, patients used more rescue medications than during the morphine phase. Rescue medication was used for 53.9% of days during treatment with fentanyl, compared to 41.5% of days for morphine (P=0.0005) throughout the whole of the phases. A sizeable proportion of patients required upward titration of study medication (47.1% required ≥1 fentanyl dose change and 27.4% required ≥1 morphine dose change). One patient required a downward titration in fentanyl dose. Fentanyl was associated with significantly less daytime drowsiness than morphine (mean percent area under the curve, 34.0; 95% CI, 29.1 to 38.9; vs 43.5; 95% CI, 38.5 to 48.5; respectively, as assessed by VAS in the patient diaries). Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine (mean scores, 32.4; 95% CI, 26.9 to 37.9; vs 22.4; 95% CI, 17.8 to 27.1; for fentanyl and morphine, respectively). The only difference in diary data was that patients reported shorter sleep duration when on fentanyl compared to when on morphine over the whole 15-day treatment period (mean, 8.1; 95% CI, 7.9 to 8.3 hours; vs 8.3; 95% CI, 8.0 to 8.5 for morphine). Fentanyl treatment was associated with significantly less constipation than morphine (P<0.001). At the end of the trial, significantly more patients indicated that fentanyl had caused less interruption to their daily activities, and the activities of family and care takers, and had been more convenient to take than the morphine tablets. The percentages expressing preference were as follows: less interruption of daily activities, 55.2% fentanyl; 20.4% morphine; less interruption to care givers, 49.0% fentanyl; 22.3% morphine; and more convenient medication, 58.3% fentanyl; 22.3% morphine. Of the 202 patients who entered the study, 136 felt able to express an opinion about the two treatments. Of these, 14 (10%) had no preference, 73 (54%) preferred fentanyl, and 49 (36%) preferred

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the morphine tablets (P=0.037). The EORTC quality of life questionnaire revealed no other significant differences between the two treatments. When scores for nausea and vomiting were separated, the mean score for nausea was significantly lower in the fentanyl group (1.7; 95% CI, 1.5 to 1.8; vs 1.8; 95% CI, 1.7 to 2.0; P=0.04). Although more adverse events were reported during fentanyl treatment, the end of treatment questionnaire indicated that significantly fewer patients considered that fentanyl caused adverse events compared to morphine (40.4 vs 82.5%; P<0.001). Secondary: Not reported
Allan et al[40] Fentanyl transdermal system 25 µg/hour replaced every 72 hours; dosage was titrated based on pain levels vs morphine SR 30 mg every 12 hours; dosage was titrated based on pain levels	MC, OL, PG, RCT Adults patients with chronic lower back pain requiring regular strong opioid treatment	N=673 13 months	Primary: Comparison of pain relief achieved with each treatment and incidence of constipation Secondary: SF-36 quality of life, treatment assessment, investigator's overall assessment of disease progression, number of working days lost and adverse events	Primary: Pain relief achieved with both treatments was similar. Mean VAS scores at study endpoint was 56.0±1.5 and 55.8±1.5 for fentanyl and morphine. Based on the 95% CI, the difference between groups established noninferiority (-3.9 to 4.2). After one week of treatment, pain relief was evident with VAS scores being 58.5±1.3 and 59.9±1.4 for fentanyl and morphine. Fentanyl was associated with significantly less constipation than morphine. Baseline levels of constipation were similar, but at endpoint 31% of fentanyl patients (93/299) and 48% of morphine patients (145/298) were constipated (P<0.001). Secondary: Mean SF-36 quality of life scores improved to a similar extent in both treatment groups between baseline and endpoint for all domains of overall physical health (P<0.001), physical functioning, role-physical, bodily pain, vitality, social functioning and role-emotional. However, the scores for overall mental health did not change significantly from baseline to endpoint in either group (P=0.937 for fentanyl and P=0.061 for morphine). The mean dose of fentanyl on day one was 25 µg/hour (range 25 to 50 µg/hour) and the mean dose at study end was 57 µg/hour (range 12.5 to 250 µg/hour). The mean dose of morphine on day one was 58 mg (range 6 to 130 mg) and the mean dose at study end was 140 mg (range 6 to 780 mg). The proportion of patients who improved by at least one pain category (e.g., from severe to moderate) during the course of the trial was 50 to

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				70% in both treatment groups. While patients in the fentanyl group improved more than the patients in the morphine group for pain during the day and pain at rest, the groups improved to a similar degree for pain on movement and pain at night. The dose of supplemental medication for breakthrough pain did not differ significantly between the treatment groups. Investigator ratings of disease progression were similar across treatment groups. At endpoint, investigators considered that 49% of fentanyl and 45% of morphine patients had stable disease; 10 and 8%, respectively, had deteriorated and 21 and 23%, respectively, had improved. Based on the number of patients with jobs, loss of working days was applicable to a small population of patients. The proportion of patients reporting >3 weeks off at baseline decreased from 34 and 25% of fentanyl and morphine to 16% for both groups. No differences between treatment groups in patients with lower back pain were observed. Most participants (95%) reported at least one adverse event during the study. The proportion of patients receiving fentanyl and morphine who reported adverse events that were considered to be at least possibly related to the trial medication were 87 and 91%. Adverse events led to discontinuation of trial medication in 37% of the fentanyl group and 31% of the morphine group (P=0.098). The most common adverse events leading to discontinuation were nausea (37% of discontinuations in each group), vomiting (24% fentanyl and 20% morphine) and constipation (11% fentanyl and 23% morphine).
Clark et al[41] Fentanyl transdermal system, initially 25 µg/hour every 72 hours, with dosage adjustments to achieve adequate pain control vs	Systematic review (8 trials) Patients ≥18 years of age with defined and documented chronic non-cancer pain (including lower back pain, pain due to rheumatoid	N=2,525 28 days to 13 months	Primary: Pain results and adverse events Secondary: Not reported	Primary: Treatment with fentanyl and morphine was equally effective in improving average pain from baseline to Day 28 (mean changes in scores were -21.8 and -20.6, respectively). In the subgroup analysis, both treatments were similarly effective in improving the average pain scores (-24.5 vs -25.9, respectively in the cancer pain subgroup and -21.0 and -17.7, respectively in the non-cancer pain subgroup). Improvements in pain “right now” scores between baseline and day 28 were significant for both treatment groups, and for both cancer pain patients and non-cancer pain patients (all measures P<0.001). The changes in pain “right now” from baseline to day 28 were significantly greater in the fentanyl treatment group compared to the morphine treatment group in the total patient sample (P=0.017). The cancer pain subgroup showed a similar trend towards better pain relief from baseline to day 28 with fentanyl treatment

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morphine SR, initially 15 to 30 mg every 12 hours, with dosage adjustments to achieve adequate pain control	arthritis, or OA of the knee or hip) or cancer pain, that had reached a stage requiring treatment with a strong opioid			but this was not statistically significant (P=0.171). Overall the type of pain did not influence the incidences of adverse events. However, in the total patient sample, as well as in both pain type subgroups, significantly fewer adverse events occurred in the fentanyl treatment group compared to the morphine treatment group (all measures P<0.001). Additionally, serious adverse events were also reported significantly less frequently in the fentanyl treatment group (P=0.006). The highest rate of serious adverse events was reported in patients with cancer pain and included 61 deaths. Constipation was the most commonly reported adverse event in the morphine treatment group, and significantly fewer patients reported nausea during the first 28 days of treatment with fentanyl compared to morphine (P<0.001). Patients treated with fentanyl also reported less somnolence compared to morphine-treated patients (P<0.001). Secondary: Not reported
Rauck, et al[42] Hydrocodone extended-release 20 to 100 mg every 12 hours vs placebo	DB, MC, PC, RCT Diagnosis of moderate to severe chronic low back pain, 18 to 75 years of age, average pain score of at least 4 on the NRS for 24 hour period prior to screening	N=302 12 weeks	Primary: Change in mean daily PI score from baseline ± SD Secondary: Percentage of treatment responders, mean increase in SGAM scores ± SD from baseline to end of treatment	Primary: The mean change from baseline in daily PI scores ± SD was significantly lower for hydrocodone extended-release vs placebo (0.48 ± 1.56 vs 0.96 ± 1.55; P=0.008, respectively). Secondary: There was a significantly higher percentage of treatment responders in the hydrocodone extended-release group vs placebo (68% vs 31%; P<0.001, respectively) at the end of treatment. In addition, mean SGAM scores ± SD increased from baseline to end of treatment in the hydrocodone extended-release group vs placebo (0.8 ± 1.3 vs 0.0 ± 1.4; P<0.0001, respectively).
Hale et al[43] Hydromorphone ER 12 to 64 mg QD vs	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a	N=268 12 weeks (DB phase only)	Primary: Mean change from baseline to week 12 or final visit in weekly PI based on patient	Primary: Hydromorphone significantly reduced PI compared to placebo (P<0.001). Secondary: The change from baseline in PI over the entire 12 weeks was statistically significant for hydromorphone compared to placebo (P<0.001). A significantly larger increase in mean

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placebo Patients were enrolled in a 2 to 4 week OL enrichment phase (conversion and titration), followed by a randomized withdrawal phase for opioid-tolerant patients. Hydromorphone IR was allowed as rescue medication during all phases of the study.	documented diagnosis of moderate-to-severe chronic lower back pain for ≥3 hours/day and ≥20 days/month for six months and had their pain classified as non-neuropathic or neuropathic		diary numeric rating scale scores Secondary: Mean change from baseline to week 12 in weighted mean PI number rating scale score, mean change from baseline to each visit in PI during the 12 weeks of treatment recorded in the office, time to treatment failure, mean change from baseline in patient global assessment, rescue medication use, mean changes from baseline in RMDQ total scores and the proportion of total study dropouts in each treatment group	PI numeric rating scale scores was seen in the placebo group compared to hydromorphone (1.2 vs 0.4; P<0.001). Weekly office visit number rating scale scores showed greater improvement following treatment with hydromorphone compared to placebo beginning at visit one and continued throughout the 12 weeks of treatment. The difference between the groups was significant (P<0.05) at every office visit except week three. Discontinuations due to treatment failure occurred sooner (P<0.001) and more frequently among patients in the placebo group. The difference was apparent by two weeks and the difference in discontinuation rates increased over the entire 12 weeks of treatment. Treatment with hydromorphone significantly improved patient global assessment scores at week 12 or at the final visit (P<0.001). A higher proportion of patients rated their treatment as good, very good or excellent compared to placebo at week 12 or final visit (80.5 vs 62.4%). The overall percentage of patients requiring rescue medication at least once over the 12 week course was similar between hydromorphone and placebo groups (96.2 vs 97.0%). The mean number of rescue medication tablets used per day at the week 12 visit also was similar between the groups (P=0.49). Weekly RMDQ scores were “superior” in patients treated with hydromorphone compared to placebo. Hydromorphone-treated patients showed a median change from baseline to week 12 or final visit of 0 on this measure; placebo-treated patients showed a median change of 1, indicating that placebo patients’ self-reported functional status was significantly worse compared to hydromorphone (P<0.005). Significant differences were seen at weeks one, two, three, eight and 12 (or final visit). The difference between treatment groups was not statistically significant at weeks four, six or ten. A significantly higher proportion of patients in the placebo group discontinued the study compared to patients in the hydromorphone group (67.2% [90/134] vs 50.7% [68/134]; P<0.01).
Hale et al[44] Hydromorphone	MC, OL, PG Patients ≥18	N=147 6 weeks	Primary: Mean pain relief score at end point	Primary: The mean (SD) pain relief score was 2.30 (0.95) in the hydromorphone group and 2.30 (1.00) in the oxycodone group. The 1-sided 95% CI for the difference of means was -

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ER 8 to 64 mg QD vs oxycodone ER 10 to 80 mg BID	years of age who met ACR clinical criteria for OA of the knee or hip for ≥3 months before enrollment, with a mean daily pain rating at the affected joint of moderate to severe, despite chronic use of stable doses (≥30 days with no regimen change) of NSAIDs or other nonsteroidal, nonopioid therapies (with or without as-needed opioids)		Secondary: Change from baseline to end point in the mean pain relief score; mean PI score at end point; change from baseline to end point in mean PI score; change from baseline to end point in mean total daily dose of study medication; change from baseline to end point in mean daily number of tablets of study medication; and changes from visit one to subsequent visits in the MOS sleep scale, investigator and patient global evaluations and WOMAC	0.30 to infinity. Secondary: The mean changes in pain relief from baseline to end point are reported in graphic form; as such the results could not be accurately interpreted. The mean time to the third day of moderate to complete pain relief was 6.20 (4.00) days in the hydromorphone group and 5.50 (2.57) days in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.31 to infinity. The mean (SD) changes in PI from baseline to end point were -0.6 (0.80) points in the hydromorphone ER group and -0.4 (1.15) in the oxycodone ER group; the 1-sided 95% CI for the difference of means was -0.53 to infinity. The results of the patient and investigator global evaluations indicated that both treatments were considered clinically effective. Patient global evaluations improved from baseline by a mean (SD) of 1.20 (1.01) points in the hydromorphone group and by 1.00 (1.33) points in the oxycodone group. The magnitude of change was not significantly different between groups. The overall effectiveness of treatment was rated as good, very good or excellent by 67.2% of patients in the hydromorphone group and 66.7% of patients in the oxycodone group. The mean patient global evaluation scores at end point were similar in the two groups (2.90 [1.06] and 2.90 [1.11], respectively). Similarly, investigator global evaluations improved by 1.20 (1.01) and 1.10 (1.16) points, with a median of one point in each group. The effectiveness of treatment was rated as good, very good or excellent by 71.9% of investigators for hydromorphone and by 70.0% for oxycodone. Mean investigator global evaluation scores at end point were similar between groups (3.00 [0.95] and 3.10 [1.08]). At end point, the mean (SD) change in WOMAC total score was -2.00 (1.90) points in the hydromorphone group and -1.80 (2.14) points in the oxycodone group (P value not reported). Mean changes in WOMAC pain scale scores were -2.10 (1.96) in the hydromorphone and -2.00 (2.03) in the oxycodone group (P value not reported). The mean changes in WOMAC stiffness and physical function scale scores were not significantly different between the two groups (P values not reported). At end point, scores on the MOS Sleep Problem Index I indicated significantly less sleep

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				disruption and daytime somnolence in the hydromorphone group compared to the oxycodone group (mean [SD], 25.70 [17.82] and 35.30 [22.56], respectively; P<0.012). Both agents were associated with numerical improvements, the change from baseline was significantly greater for hydromorphone (-13.30 [21.10] vs -5.20 [22.09]; P<0.045). Changes on the MOS Sleep Problems Index II were comparable in the two groups.
Quigley et al[45] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting or placebo or non-opioids	MA (48 RCTs) Patients of any age suffering from any illness with either acute or chronic pain, including cancer pain and postoperative pain	N=3,293 Duration not reported	Primary: Pain relief and safety Secondary: Not reported	Primary: Overall, studies varied in quality and methodology. The review did not demonstrate any clinically significant difference between hydromorphone and other strong opioids. Compared to meperidine, hydromorphone appeared more effective in achieving acute pain relief without an increase in adverse events. For the treatment of chronic pain, two studies showed that hydromorphone CR and morphine CR achieved similar pain relief; however, one of the studies showed that patients taking hydromorphone CR required more doses of rescue medication and were more likely to experience withdrawal compared to morphine. Diarrhea was more commonly seen with hydromorphone. No significant differences were seen in other adverse events. In studies comparing hydromorphone to morphine for the treatment of acute pain, hydromorphone-to morphine equianalgesic ratio was shown to vary from 7:1 to 5:1 for parenteral and spinal administration. Both drugs were associated with nausea, sleepiness and pruritus. Less anger and anxiety but lower cognitive function was associated with hydromorphone compared to morphine. One study comparing patient-controlled hydromorphone, morphine and sufentanil showed that morphine was superior with regard to time to treatment failure and was associated with the lowest incidence of adverse events. No significant differences were seen in chronic pain relief between hydromorphone CR and oxycodone SR. One study showed that transmucosal fentanyl led to greater improvement in pain and anxiety compared to hydromorphone. Studies comparing different formulations and/or routes of administration of hydromorphone found no differences in chronic pain relief between IR vs CR tablets,

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				subcutaneous bolus vs subcutaneous infusion, intravenous vs subcutaneous and oral vs intramuscular. For the treatment of acute pain, epidural hydromorphone was associated with higher incidence of pruritus compared to intravenous or intramuscular hydromorphone. For the treatment of acute pain, hydromorphone IR was associated with greater pain relief compared to placebo, and there were no significant differences in adverse events between hydromorphone and placebo. One study showed that subcutaneous hydromorphone and intravenous indomethacin were equally effective in pain relief, although the duration of nausea and vertigo was longer following hydromorphone. Secondary: Not reported
Felden et al[46] Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; P=0.006). No differences were observed for the treatment of chronic pain relief (P=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (P=0.005) and vomiting (P=0.001). Secondary: Not reported.
Pigni et al[47] Hydromorphone, long- or short-acting vs strong opioids, long- or short-	Systematic review (9 RCTs, 4 non-RCTs) Patients ≥18 years of age with chronic cancer pain who had not taken a strong opioid in	N=1,208 Duration not specified	Primary: Pain relief and safety Secondary: Not reported	Primary: MA was not performed due to study heterogeneity. Overall, the review supported the use of hydromorphone in the treatment of moderate to severe cancer pain as an alternative to morphine and oxycodone. There was no clinically significant difference between hydromorphone and morphine. The majority of the studies showed similar safety and efficacy in pain relief between hydromorphone and morphine or oxycodone. The following agents of different formulations were found comparable in safety and efficacy: hydromorphone IR vs morphine IR; hydromorphone CR or SR vs morphine CR or SR, hydromorphone IR vs

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acting	the past			intramuscular morphine and hydromorphone SR vs oxycodone SR. In one non-RCT, hydromorphone SR was shown to have similar analgesia with more vomiting and less constipation compared to transdermal fentanyl and buprenorphine. Two studies comparing hydromorphone IR to SR demonstrated similar pain relief and safety profile between the two formulations. Other studies comparing different routes of administration of hydromorphone also showed similar safety and efficacy between the following routes: intravenous vs subcutaneous, intravenous vs oral and intramuscular vs oral. Secondary: Not reported
Morley et al[48] Methadone 10 to 20 mg/day vs placebo In Phase 1 of the study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total). In Phase 2 of the study, patients were instructed to take methadone 10	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous drug regimens	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum PI by 16.00 (P=0.013) and VAS average PI by 11.85 (P=0.020) and increased VAS pain relief by 2.16 (P=0.015). Analgesic effects, by lowering VAS maximum PI and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (P=0.065 and P=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum PI by 12.02 (P=0.010), a lowering of VAS average PI by 10.46 (P=0.026), and an increase in VAS pain relief by 0.94 (P=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who completed the trial. Secondary: Not reported

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mg BID or placebo on odd days and to take no medication on even days (20 days total).				
Bruera et al[49] Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for breakthrough pain vs slow-release morphine 15 mg BID, in addition to IR morphine 5 mg every 4 hours as needed for breakthrough pain	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed consent	N=103 4 weeks	Primary: Difference in PI Secondary: Change in toxicity and patient-reported global benefit	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; P=0.50). Secondary: The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; P=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI, 38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).
Musclow et al (abstract)[50] Morphine long acting 30 mg BID for 3 days vs placebo	DB, PC, RCT Patients undergoing total hip or knee replacement surgery	N=200 3 days	Primary: Decrease in pain scores by 2 points on a 10 point rating scale Secondary: Acute confusion, pain-related interferences in function and sleep, length of	Primary: Most pain scores did not reach the predetermined improvement for clinical significance. Secondary: There was an increase in opioid usage (P<0.0001) and over sedation (P=0.08). There were no significant changes in function or sleep. Improved satisfaction with pain management was minimal (P=0.052). There was an increase in vomiting (P=0.0148).

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			stay, patient satisfaction, safety	
Caldwell et al[51] Morphine ER (Avinza®) 30 mg in the morning plus placebo in the evening vs placebo in the morning plus morphine ER (Avinza®) 30 mg in the evening vs morphine CR (MS Contin®) 15 mg BID vs placebo	DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with both a clinical diagnosis and grade II-IV radiographic evidence of OA of the hip and/or knee; have had prior suboptimal analgesic response to treatment with NSAIDs and acetaminophen or had previously received intermittent opioid analgesic therapy; and have a baseline VAS PI score of ≥40 mm in the index joint	N=295 4 weeks	Primary: Analgesic efficacy of morphine ER QD compared to placebo and safety of morphine ER QD compared to morphine CR BID Secondary: Physical functioning; stiffness; sleep measures; and analgesic efficacy of morphine ER in the morning, morphine ER in the evening and morphine CR	Primary: Overall, a statistically significant reduction in pain from baseline was demonstrated by morphine ER in the morning (17%; P≤0.05) and in the evening (20%; P≤0.05), and morphine CR BID (18%; P≤0.05), as compared to placebo (4%). Morphine ER in the morning (26%) and in the evening (22%) and morphine CR BID (22%) reduced overall arthritis PI as compared to placebo (14%), but these differences were not statistically significant. PI (measured on a 100-mm scale) was reduced by approximately 20 to 23 mm in the morphine ER and CR groups compared to 14 mm in the placebo group. Decreases in PI were apparent in all treatment groups by week one and further reductions in pain throughout the four week period were observed as compared to baseline. Secondary: Statistically significant differences in physical function were not achieved among the treatment groups. Mean improvements in physical function (total score, 0 to 1,700 mm) at Week four were as follows: morphine ER in the morning (207 mm, 18%) and in the evening (205 mm, 19%), morphine CR (181 mm, 14%) and placebo (97 mm, 8%). Reductions in stiffness were also observed for all treatment groups. The changes were not large enough to achieve statistical significance. Active treatment groups provided greater improvements in all sleep measures compared to placebo. Morphine ER in the morning provided statistically significant improvements compared to placebo for overall quality of sleep, less need for sleep medication, increases hours of sleep and less trouble falling asleep because of pain (P values not reported). Morphine ER in the evening provided statistically significant improvements compared to placebo for overall quality of sleep and duration of sleep each night. Relative to placebo, morphine CR provided statistically significant improvements in overall quality of sleep and patients had less trouble falling asleep because of pain (P values not reported). Morphine ER in the morning demonstrated a statistically significant improvement in overall quality of sleep compared to morphine CR (P value not reported) and no significant differences were observed between morphine ER in the morning and the evening (P value not reported).

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				A total of 197 patients (67%) experienced at least one adverse event during this trial, with constipation and nausea reported most frequently. Adverse events were higher in all active treatment groups compared to the placebo group. Among the 33 pair-wise comparisons the only significant differences observed were a higher rate of constipation with morphine ER in the morning (49%) vs morphine CR (29%), a higher rate of vomiting with morphine ER in the evening (16%) vs morphine ER in the morning (6%) and a higher rate of asthenia with morphine CR (9%) vs morphine ER in the morning (1%).
Allan et al[52] Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	MC, OL, RCT, XO Patients >18 years of age with chronic non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate pain control with a stable dose of oral opioid for seven days before the trial	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment assessment, rescue drug use, SF-36 quality of life, and safety	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; P<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief. Secondary: Patients treated with fentanyl reported on average lower PI scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; P<0.001), irrespective of the order of treatment. More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; P=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (P<0.001). The corresponding percentages from the patient assessments were 60% for fentanyl and 36% for morphine (P<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; P<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (P<0.001), vitality (P<0.001), social functioning (P=0.002), and

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				mental health (P=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
Wiffen et al[53] Morphine, long- or short-acting vs Opioids or non-opioid analgesics	MA (54 RCTs) Adults and children with cancer pain requiring opioid treatment	N=3,749 3 days to 6 weeks	Primary: Pain relief and adverse events Secondary: Not reported	Primary: The review showed that morphine was comparable to other opioids in achieving cancer pain relief, and different formulations of morphine were effective. Limited evidence suggested that transmucosal fentanyl may provide more rapid pain relief for breakthrough pain compared to morphine. Thirteen studies (n=939) compared long-acting morphine to other opioids of either long- or short-acting formulation. There were no significant differences in pain relief and adverse events between long-acting morphine and long- or short-acting oxycodone, long-acting hydromorphone or tramadol. Pain relief was similar between morphine and transdermal fentanyl, though patients in the transdermal fentanyl group required more rescue medication and reported less sedation and constipation. Compared to methadone, morphine was associated with similar pain relief and fewer adverse events. Six studies (n=973) compared short-acting morphine to other opioids. One study comparing morphine to transmucosal fentanyl for breakthrough pain showed that PI scores were significantly lower with transmucosal fentanyl at all time points compared to morphine. No differences in pain relief were seen between morphine and methadone, short-acting oxycodone or tramadol. Compared to methadone, morphine was associated with more dry mouth and fewer headaches. Morphine was also associated with more nausea than oxycodone. Fifteen studies (n=460) compared long- to short-acting morphine and demonstrated that the two formulations were comparable in pain relief and adverse events. No carry-over effects were observed with long-acting morphine. One study showed long-acting morphine was associated with greater improvement in sleep quality. Twelve studies (n=1,010) compared long-acting morphine of different dosage strengths, dosing intervals or dosage formulations. Results from these studies showed no significant differences in pain relief or adverse events between the following comparisons: 12-hourly vs eight-hourly dosing, 12-hour-release capsule (M-Eslon®†) vs

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				tablet (MS Contin®), 24-hour-release capsule or tablet (Kadian®, Kapenol®†, Morcap®† or MXL®†) vs 12-hour-release tablet (MS Contin®) and long-acting tablet vs long-acting suspension. One study showed that long-acting morphine suppository caused less nausea compared to long-acting morphine oral tablet. Another study showed rectal administration of morphine solution led to faster and greater pain relief compared to oral solution. In one study, oral and epidural morphine achieved similar pain relief. Patients on epidural morphine reported significantly fewer adverse events Secondary: Not reported
Caraceni et al[54] Morphine, long- or short-acting vs opioids	MA (16 RCTs and 1 MA) Patients ≥18 years of age with chronic cancer pain	N=2,487 Duration not reported	Primary: Pain relief and adverse events Secondary: Not reported.	Primary: No significant differences in pain relief were observed when long- and short-acting morphine was compared to diamorphine†, hydromorphone, methadone, oxycodone or transdermal fentanyl. No clinically significant differences were observed between morphine and other opioids; however, transdermal fentanyl was associated with a lower incidence of constipation, and patients on methadone were more likely to withdraw from the study due to sedation. Secondary: Not reported
Katz et al (abstract)[55] Morphine/ naltrexone vs placebo All patients received morphine/ naltrexone, titrated	DB, MC, RCT Patients with chronic, moderate to severe, OA (hip or knee) pain	N=547 12 weeks	Primary: Change from baseline in diary average-pain scores to the last seven days of the trial Secondary: Remaining BPI scores, WOMAC OA index, opioid withdrawal	Primary: Combination therapy maintained pain control better than placebo (mean change from baseline dairy average-pain score: -0.2±1.9 vs ±0.3±2.1; P=0.045). Change from baseline for combination therapy pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks two to 12 (P<0.05). Secondary: WOMAC composite score change from baseline was superior at most visits. Combination therapy was generally well tolerated, with a typical morphine safety profile. No patient taking combination therapy as directed experienced withdrawal symptoms.

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to 20/160 mg/day, prior to randomization. Patients randomized to placebo were tapered off morphine/ naltrexone over a two week period.			symptoms	
Gimbel et al[56] Oxycodone CR (OxyContin®) 10 to 60 mg BID vs placebo	DB, MC, PC, PG, RCT Adult diabetic patients with a history of stable diabetes mellitus and a HbA1c ≤11.0%, painful symmetrical distal polyneuropathy, a history of pain in both feet for more than half the day for ≥3 months prior to enrollment, and at least moderate pain in the absence of any opioid analgesic therapy for three	N=159 6 weeks	Primary: Average daily PI during the past 24 hours obtained during the study period from days 28 to 42 Secondary: Patient reported scores for average PI from days one to 27, current and worst pain, satisfaction, and sleep quality from days one to 42; total and subscale scores from the 14-item BPI; scores for validated measures of psychological state, physical	Primary: In the ITT cohort, the efficacy analysis of the primary endpoint showed that oxycodone provided "superior" analgesia compared to placebo (P=0.002). Least squares mean scores for overall average daily PI from days 28 to 42 were 4.1 and 5.3 for the oxycodone and placebo groups. The primary efficacy results from the per protocol cohort confirmed these results: least squares mean scores for overall average daily PI from days 28 to 42 in this cohort was 4.2 and 2.3 for the oxycodone and placebo groups (P=0.009). Secondary: Oxycodone produced significant improvements in overall scores for average PI from days one to 27 (P<0.001), pain right now (P=0.002), worst pain (P=0.001), satisfaction with study medication (P<0.001) and sleep quality from days one to 42 (P=0.024). Significant improvements in all pain measurements (except worst pain) and in sleep quality were observed within one week of initiation of oxycodone therapy. An improvement from baseline in nine out of 14 items (average PI [P=0.004], pain right now [P<0.001], worst pain [P=0.001], least pain [P=0.004], pain relief [P<0.001], interference score [P=0.015], relations with other people [P=0.023], sleep [P<0.001] and enjoyment of life [P=0.016]) were significant and improved in the oxycodone group compared to placebo. No significant improvements occurred for the five remaining items which included physical function score, general activity, mood, walking ability and normal work. There were no significant differences between treatments in physical functioning,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	days before receiving the study treatment		functioning, and general health status; the proportion of patients who discontinued study medication due to lack of efficacy; and time to mild pain, number of days with mild pain and proportion of days with mild pain	general health and mental health subscales of the SF-36 Health Survey or in the seven subscales of the Rand Mental Health Inventory. A significant difference in ambulation, a subscale of the Sickness Impact Profile, was observed between oxycodone and placebo at the final visit. Of the 12 patients discontinuing study medication due to inadequate pain control, one patient was in the oxycodone group and 11patients were in placebo group (P=0.002). The median time to achieve mild pain was shorter for the patients treated with oxycodone (six days) compared to placebo-treated patients (17 days; P=0.017). Patient treated with oxycodone had more days with mild pain: mean (SD) of 20.0 (16.6) days vs 12.5 (16.0) days for the placebo (P=0.007). Oxycodone-treated patients reported a higher mean (±SD) percentage of days with mild pain (47%±39%) compared to placebo-treated patients (29%±37%; P=0.006).
Ma et al[57] Oxycodone CR 5 to 10 mg or larger dosages every 12 hours vs placebo	DB, PRO, RCT Patients 40 to 70 years of age with a history of chronic refractory neck pain for >6 months, a MRI or computer topography scan suggesting a degenerative disease process, with a frequency of acute pain flares occurring >3 times/day that are VAS >4 for 3 days	N=116 4 weeks	Primary: Frequency of pain flares, PI, quality of life, quality of sleep, adverse events and SF-36 Secondary: Not reported	Primary: Compared to the pretreatment and placebo group, the frequency of acute pain flares (>3 times/day) in the oxycodone group decreased significantly on day three and day seven (P<0.05). Only 20.7% of patients (12/58) continued to have acute flare pain (>3 times/day) on day seven, and 21 days later no patient complained of acute flare pain in the oxycodone group (P<0.01). Patients treated with oxycodone had a stepwise reduction in PI during the first week compared to their baseline. The VAS decreased from 6.82±1.83 to 3.35±1.57 on day three, and to 3.24±0.92 on day seven (P<0.05). Patients in the oxycodone group had lower scores for PI compared to patients in the placebo group (P<0.05). The oxycodone group had dramatic improvements in performance status and performance status scale scores after seven days of treatment. Compared to pretreatment levels and the placebo group, performance status decreased from 2.74±1.01 to 1.25±0.42 on day seven, and to 0.28±0.07 on day 28, respectively (P<0.05). Similarly, performance status scale increased from 3.21±0.68 to 4.74±0.95 on day seven and to 7.23±1.44 on day 28 (P<0.05). Bad quality of sleep was 63.8% before treatment and was decreased to 15.5% on day three, 8.6% on day seven, and 5.6% on day 14 in patients treated with oxycodone. Additionally, there was significant improvement in the quality of sleep, with 13.8% as the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline for good quality of sleep, rising to 46.6%, 50.0%, and 58.3% on day three, seven and 14 respectively after oxycodone treatment (P<0.01). Adverse events, including mild-to-moderate nausea (31.0%) constipation (22.4%), pruritus (18.9%) and dizziness (27.6%) were only seen on day seven of the treatment in oxycodone patients (P<0.05). However, events diminished starting from day 14 of the treatment until day 28; only two patients had persistent constipation. Most domains of SF-36 were effective positively in patients treated with oxycodone. The score for physical functioning, pain index, vitality, social functioning, emotional role and mental health index were significantly better in the oxycodone group compared to placebo at the end of the study (P<0.05). Secondary: Not reported
Watson et al[58] Oxycodone CR (OxyContin®) 10 to 40 mg BID vs active placebo (Benztropine® 0.25 to 1 mg BID)	DB, RCT, XO Adult diabetic patients in stable glycemic control; with painful symmetrical distal sensory neuropathy; at least moderate pain in the lower extremities; a medical history of moderate daily pain for previous three months; one or more symptoms of diabetic neuropathy; and	N=36 8 weeks	Primary: PI, SF-36 and PDI Secondary: Not reported	Primary: Oxycodone resulted in significantly lower VAS (P=0.0001) and ordinal (P=0.0001) pain scores and better pain relief (P=0.0005) compared to placebo during the last week of treatment assessed in patients' daily diaries. There was no evidence of sequence effect (P=0.2098). Steady (P=0.0001), brief (P=0.0001) and skin pain (P=0.0001) were significantly reduced with oxycodone treatment compared to placebo. For the SF-36, results were significantly better during the oxycodone treatment phase compared to active placebo for Physical Functioning (P=0.0029), Pain Index (P=0.0001), Vitality (P=0.0005), Social Functioning (P=0.0369) and Mental Health Index (P=0.0317) domains. All variables in the PDI were significantly better in the oxycodone treatment phase (P≤0.0005 and P≤0.05) with the exception of sexual behavior, which showed no difference between the two treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	signs of reduced sensation, strength or tendon reflexes not attributable to any other cause			
Bruera et al[59] Oxycodone CR (OxyContin®) and placebo every 12 hours for 7 days vs morphine CR (MS Contin®) and placebo every 12 hours for 7 days	DB, DD, PC, RCT, XO Patients ≥18 years of age who had cancer pain and who were receiving treatment with an oral opioid analgesic during study entry and who gave informed consent	N=32 2 weeks	Primary: PI, overall effectiveness, and adverse events Secondary: Not reported	Primary: There were no significant differences between treatments in pain-intensity VAS scores when tested by day of treatment, time of day, or overall (P=0.43) or between categorical scores pain-intensity scores by day of treatment, time of day, or overall (P=0.36). For both formulations, there was a significant (P=0.02) difference in rescue use with respect to doses taken during the night (2 to 6 AM) as compared to the remainder of the 24-hour day. The rate of rescue use during the night was 55 and 67% of that used during the daytime in the oxycodone and morphine groups, respectively. The average daily number of rescue doses in a 24-hour period was 2.3±2.3 for oxycodone and 1.7±2.1 for morphine (P=0.01). There were no significant differences in sedation or nausea between oxycodone CR and morphine. Secondary: Not reported
King et al[60] Oxycodone vs strong opioids	Systematic Review (14 RCTs, 1 MA, 10 OS) Patients ≥18 years of age with moderate to severe cancer pain	N=3,875 3 days to 3 months	Primary: Pain relief and adverse events Secondary: Not reported	Primary: This review found no significant differences in safety and cancer pain relief between oxycodone and hydromorphone, morphine or oxymorphone. The MA included in this review showed no difference in analgesia and safety between oxycodone and morphine or hydromorphone (pooled standardized mean difference, 0.04; 95% CI, -0.29 to 0.36; P=0.8). Similarly, results from RCT and PRO OS also showed no difference between oxycodone and hydromorphone, morphine or oxymorphone. Studies that compared short- to long-acting oxycodone showed similar pain relief and safety profile between the two formulations. Studies comparing intravenous vs rectal and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				intramuscular vs oral oxycodone also demonstrated similar safety and efficacy between different routes of administration. Secondary: Not reported
Slatkin et al[61](abstract) Oxymorphone ER Patients who had been taking oxymorphone ER continued the dose established in a previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of oxymorphone ER.	Post-hoc analysis of 2 ES, OL Patients with cancer	N=80 12 months	Primary: Current, average, worst and least pain scores normalized to a 100-point scale Secondary: Patients rated global assessment of study medication and adverse events	Primary: Of the 80 patients who were entered into the ES, 26 patients completed 52 weeks, seven patients discontinued owing to loss of effectiveness, and 20 patients discontinued owing to adverse events (most unrelated to the study drug). No significant increase in mean (SD) average PI was observed from baseline (30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; P=0.37). Secondary: The most common adverse events were concomitant disease progression (28.8%; n=23), nausea (22.5%; n=18), dyspnea (16.3%; n=13), fatigue (16.3%; n=13) and edema of the lower limb (15%; n=12). Patient rated global assessment of study medication was not reported in the abstract.
Sloan et al[62] Oxymorphone ER Patients were stabilized for ≥3 days on morphine CR (MS Contin®) or oxycodone CR (OxyContin®), and then treated for 7 days at their stabilized dose	MC, MD, OL, PRO, XO Patients 18 to 80 years of age with a history of chronic cancer pain requiring ≥20 mg of oxycodone or the analgesic equivalent of ≥30 mg of oral	N=63 7 days (Period 2)	Primary: Efficacy Secondary: Not reported	Primary: Mean daily PI scores were comparable during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain was achieved with oxymorphone as with oxycodone. The average scheduled daily dose of study medication and the average total daily dose decreased after XO to oxymorphone. There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for the treatment groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Period 1). Patients were then crossed over for 7 days of treatment at an estimated equianalgesic dosage of oxymorphone ER (Period 2).	morphine per day			Not reported
Kivitz et al[63] Oxymorphone ER 10 mg every 12 hours for 2 weeks vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 40 mg every 12 hours for 1 week vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 50 mg every 12 hours for 1 week	DB, DR, MC, PG, RCT Patients ≥18 years of age with OA (defined by the presence of typical knee or hip joint symptoms [pain, stiffness, and disability] and signs [bony crepitus], and radiographic evidence of OA [grade II-IV in the index joint on the Kellgren-Lawrence scale]); who are regularly taking acetaminophen, NSAIDs or opioid analgesics for	N=370 2 weeks	Primary: Mean change in arthritis PI Secondary: Change in pain, stiffness, and physical function subscales of WOMAC OA index and WOMAC composite index; SF-36 quality of life, CPSI and tolerability	Primary: In the ITT population, the least squares mean change in arthritis PI from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for oxymorphone 10, 40 and 50 mg; and placebo, respectively. The least squares mean differences in change from baseline compared to placebo were -4.3 (95% CI, -12.8 to -4.3; P value not significant), -11.1 (95% CI, -19.7 to -2.5; P=0.012) and -12.2 (95% CI, -20.9 to -3.5; P=0.006) for oxymorphone 10, 40 and 50 mg, respectively. Compared to placebo, arthritis PI scores were improved by 62.8% and 70.9% after treatment with oxymorphone 40 or 50 mg every 12 hours, respectively (P=0.012 and P=0.006). Secondary: Overall, improvements in WOMAC scores were two- to three-fold greater in oxymorphone compared to placebo. From baseline to the final visit, two-fold greater decreases in WOMAC pain subscale scores were found in all three oxymorphone groups compared to the placebo group (P≤0.025). Improvements in WOMAC physical function subscale scores also were significantly greater for each of the oxymorphone groups compared to the placebo group (P≤0.025). Improvements in the WOMAC stiffness subscale score were significant compared to placebo only for the oxymorphone 40 and 50 mg groups (P≤0.001). With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone groups found significantly greater improvements in each oxymorphone group (P≤0.025). All patients who received oxymorphone, irrespective of the dose, had significant improvements in the SF-36 quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with oxymorphone 10, 40 and 50 mg; and placebo, respectively (P<0.001).

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vs placebo	90 days before the screening visit with suboptimal analgesic response			Improvements in the CPSI scores for overall sleep quality were two-fold greater in patients who received oxymorphone 40 and 50 mg than in the placebo group (P≤0.05). The most frequently reported adverse event in the oxymorphone groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%) and headache (14.7%).
Schwartz et al[64] Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3 days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg increments every 3 days (within dose range of 100 to 250 mg BID).	DB, PC, PG, RCT Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with the following: HbA1c ≤11.0%, ≥3-month history of analgesic use for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average PI score ≥5 on an	N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (main-tenance phase after a 3-week titration phase)	Primary: The change from baseline in average PI over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in PI of at least 30% and 50% at week 12 (i.e., responder rate), PGIC at weeks two, six, and 12, and safety measures	Primary: The least square mean change in average PI from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in PI, and 0.0 in the tapentadol ER group, indicating no change in PI. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P<0.001). Secondary: The mean changes in average PI scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in PI was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017). At least a 50% improvement in PI from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032). Of the patients who achieved ≥ 30% improvement in PI (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in PI (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acetaminophen ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.	11-point rating scale, and effective method of birth control (if applicable)			Of those patients who were randomized to placebo after achieving ≥30%improvement in PI (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in PI during the maintenance phase. Among patients who achieved ≥50% improvement in PI (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in PI (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (P<0.001). The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Afilalo et al[65] Tapentadol ER 100 mg BID vs placebo vs oxycodone CR 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current analgesic regimen, and had a baseline PI score ≥5 during the 3 days prior to randomization	N=1,030 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change in average PI at week-12 of the maintenance period compared to baseline Secondary: Change in average PI over the entire 12-week maintenance period compared to baseline	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (P-values not reported). The average PI rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average PI at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least a 50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023). Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P<0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3 consecutive days) was permitted.				The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019). The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al[66] Tapentadol ER 100 mg BID vs oxycodone CR 20 mg BID vs placebo Initial treatment with tapentadol ER 50 mg BID or	AC, DB, MC, PC, PRO, RCT Patients ≥18 years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and	N=981 12 weeks (main-tenance phase after a 3-week titration phase)	Primary: Change from baseline in mean PI at week-12 of the maintenance period Secondary: Change from baseline in mean PI over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in PI at	Primary: Throughout the 12-week maintenance period, average PI scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo. The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P<0.001). The mean change in PI from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P<0.001). Secondary: The mean PI was also reduced for the oxycodone CR group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3 consecutive days) was permitted.	whose previous opioid daily doses, if applicable, were equivalent to ≤160 mg of oral morphine		week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	Reductions in mean PI were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline PI. Significantly greater reductions in mean PI with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline PI and severe baseline PI. Reductions in mean PI were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline PI at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (P=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (P=0.090). A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in PI at week-12 compared to baseline (P<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo responded with 50% improvement in PI at week-12 compared to baseline (P<0.016). The percentage of patients in the oxycodone CR group with ≥30% improvement in PI at week-12 compared to baseline was 30.4% (P=0.365) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with ≥50% improvement in PI at week-12 compared to baseline was 23.3% (P=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (P<0.001) and oxycodone CR (P<0.001) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score. The percentage of patients with “any pain today other than everyday kinds of pain” on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group. The percentage of patients who reported “at least 50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared to the placebo group. The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.
Imanaka et al[67] Tapentadol ER 25 to 200 mg BID vs oxycodone CR 5 to 40 mg BID Treatment was initiated with either tapentadol ER 25 mg BID or oxycodone CR 5 mg BID with dose escalation allowed on treatment day three based upon 24-hour PI scores and the need for rescue medication at least three times per day. The maximum doses were tapentadol ER 200 mg BID and oxycodone CR 40 mg BID.	AC, DB, MC, PRO, RCT Men and women ≥20 years of age experiencing chronic malignant tumor-related pain that had an average PI score over the past 24 hours ≥4 on an 11 point numerical rating scale in Japan and South Korea. Patients must not have taken opioid analgesics (other than codeine or dihydrocodeine for cough) within 28 days before screening, patients must have had pain requiring an	N=343 4 weeks	Primary: Mean change in the average PI score from baseline to the last 3 days of study drug administration Secondary: PGIC, rescue medication use and responder rates achieving at least 30% and at least 50% decreases in PI score from baseline	Primary: Mean change from baseline in PI scores for oxycodone CR was -2.69 and -2.57 for tapentadol ER. The least squares mean difference between tapentadol ER and oxycodone CR was -0.06, 95% CI, -0.506 to 0.383. The efficacy of tapentadol ER was shown to be non-inferior to oxycodone CR based upon the upper limit of the 95% CI of <1 (predefined non-inferiority threshold). Secondary: The percentage of subjects reporting “very much improved,” “much improved,” or “minimally improved” on the PGIC was 89.7% (N=113/126) for tapentadol ER and 82.7% (N=115/139) for oxycodone CR. The percentage of subjects reporting at least a 30% improvement in PI scores from baseline for tapentadol ER was 63.5% (N=80/126) and 59.0% (N=82/139) for the oxycodone CR group. The percentage of subjects reporting at least a 50% improvement in PI scores from baseline for tapentadol ER was 50.0% (N=63/126) and 42.4% (N=59/139) in the oxycodone CR group. The mean (SD) of the average number of doses of morphine IR 5 mg per day used for breakthrough pain in the tapentadol ER group was 1.4 (0.46) compared to 1.4 (0.43) for oxycodone CR. The mean (SD) of the average total daily dose of morphine IR used was 7.0 mg (2.30) for tapentadol ER compared to 6.7 mg (2.15) for oxycodone CR. Morphine IR was used by 74.6% (N=94/126) of subjects treated with tapentadol ER compared to 74.1% (N=103/139) of subjects in the oxycodone CR group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	opioid analgesic and patients must have been dissatisfied with the pain relief experienced with their current pain regimen.			
Wild et al[68] Tapentadol 100 to 250 mg BID vs oxycodone CR 20 to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or low back pain (non-malignant) with a ≥ 3 month history of pain, who were dissatisfied with current analgesic therapy, and had a PI score ≥4 on an 11-point rating scale after therapy washout	N=1,121 51 weeks (main-tenance phase)	Primary: Safety and tolerability Secondary: Change in mean PI score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone CR group, respectively. The incidence of pruritis was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone CR groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxycodone CR 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Occasional pain relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and acetaminophen ≤1,000 mg/day (up to a max of 7 consecutive days and no more that 14 out of 30 days) were permitted.				group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean PI scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of "excellent," "very good," or "good" among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was "much improved" for both the tapentadol ER and oxycodone CR groups (35.7 and 32.8%, respectively). A rating of "very much improved" or "much improved" was reported by 48.1 and 41.2%, respectively.
Bekkering et al (2011)[69] Strong opioids vs placebo or strong opioids	Systematic review (56 RCTs) Patients ≥18 years of age with cancer-related or non-cancer-related chronic pain	N=not reported ≥24 hours	Primary: Change of PI Secondary: Safety	Primary: Morphine vs another strong opioids One trial favored other opioids, one trail favored morphine, and the remaining eight trials did not find any difference between the two treatments. In the subgroup of trials with a duration between one week and one month, morphine was more effective than other opioids (eight trials: weighted mean difference, -5.8; 95% CI, -9.5 to -2.1). Other differences were not significant. Network analyses showed that fentanyl (weighted mean difference, 6.3; 95% CI, 1.8 to 10.9) and hydromorphone (weighted mean difference, 5.1; 95% CI, 0.5 to 9.6) were less effective compared to morphine. Also placebo was less effective (weighted mean difference, 10.7; 95% CI, 7.2 to 14.1). No differences with morphine were found for oxycodone (weighted mean difference, 2.9; 95% CI, -0.4 to 6.2), methadone (weighted mean difference, 3.3; 95% CI, -4.6 to 11.3), oxymorphone (weighted mean difference, 0.4; 95% CI, -5.5 to 6.3) and buprenorphine (weighted mean difference, 3.0; 95% CI, -3.0 to 9.0). Differences between morphine and fentanyl and between morphine and hydromorphone were not significant (3.6; 95% CI, -2.0 to 9.3 and 4.8; 95% CI, -0.1 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				9.8). No differences were found when excluding trials examining opioids in neuropathic pain. Secondary: No difference between morphine and other strong opioids were found for risk of treatment discontinuation due to any reasons (ten trials: RR, 1.06; 95% CI, 0.88 to 1.29), treatment discontinuation due to lack of efficacy (nine trials: RR, 0.83; 95% CI, 0.55 to 1.25), or treatment discontinuation due to adverse events (nine trials: RR, 1.05; 95% CI, 0.67 to 1.65). Network analyses showed no difference between morphine and any other strong opioid or placebo in treatment discontinuation when all reasons for discontinuation were pooled. Patients using buprenorphine and those using placebo are more likely to discontinue treatment due to lack of efficacy (OR, 2.32; 95% CI, 1.37 to 3.95; OR, 4.12; 95% CI, 2.66 to 6.38). Patients using methadone are more likely to discontinue due to adverse events (OR, 3.09; 95% CI, 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR, 0.29; 95% CI, 0.17 to 0.50), buprenorphine (OR, 0.30; 95% CI, 0.16 to 0.53), and placebo (OR, 0.12; 95% CI, 0.08 to 0.18). After excluding trials with reversed design, oxymorphone showed increased risk for treatment discontinuation for any reason (OR, 2.32; 95% CI, 1.49 to 3.63) whereas this was nonsignificant in the overall analysis (OR, 1.00; 95% CI, 0.70 to 1.44). No differences were found when excluding trials examining opioids in neuropathic pain. Three trials comparing morphine to another strong opioid reported serious adverse events; no differences in risk was found in the pair-wise MA (RR, 1.15; 95% CI, 0.79 to 1.67). The network analysis also found no difference in risk of serious adverse events for patients using morphine compared to those using oxycodone, fentanyl, placebo, buprenorphine, oxymorphone, and hydromorphone. Limitations: Patients with non-cancer pain and cancer pain were included; therefore, differences in patient populations exist among included trials. Some trials included patients with moderate pain which may not require a strong opioid. Use of RCTs is less suitable for evaluating adverse events, and the majority of trials were industry funded.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Conclusion: Current evidence is moderate, both in respect to the number of directly comparative trials and in the quality of reporting of these trials. No clear superiority in efficacy and tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.
Whittle et al[70] Opioids vs placebo, opioids or NSAIDs	MA (11 RCTs) Patients ≥18 years of age with a diagnosis of rheumatoid arthritis	N=672 <24 hours (four studies) 1 to 6 weeks (seven studies)	Primary: Percentage of patients with pain relief ≥30% and number of withdrawals due to adverse events Secondary: Percentage of patients with pain relief ≥50%, changes in function, quality of life, withdrawals due to inadequate analgesia and adverse events	Primary: Data from the four single-dose studies were not included in the MA. A review of these studies showed that single-dose aspirin, acetaminophen, caffeine/phenacetin/ isopropylantipyrine†, codeine, codeine/aspirin, codeine/aspirin/phenacetin†, dextropropoxyphene/acetaminophen†, pentazocine and propoxyphene† were all associated with greater pain relief compared to placebo. No significant differences in efficacy were found between these agents. Five of the remaining seven studies that were at least one week in duration compared codeine/acetaminophen, morphine CR, pentazocine, tilidine/naloxone† and tramadol/ acetaminophen to placebo. One study compared dextropropoxyphene/aspirin† to aspirin, and one study compared codeine/acetaminophen plus diclofenac to diclofenac. None of these studies reported data on percentage of patients with pain relief of ≥30%. The rate of withdrawal due to adverse events was higher with opioids but not significantly different from placebo (RR, 2.67; 95% CI, 0.52 to 13.75). Secondary: One study showed that 60% of patients receiving codeine/acetaminophen achieved ≥50% pain relief compared to 26% with placebo (RR, 2.28; 95% CI, 0.99 to 5.25). Three studies showed that opioids were associated with greater improvement in CGI within the first six weeks compared to placebo (RR, 1.44; 95% CI, 1.03 to 2.03; NNT, 6). There were no significant differences between opioids and placebo with regard to changes in function, as measured by HAQ (weighted mean difference, -0.10; 95% CI, -0.33 to 0.13). One study showed that codeine/acetaminophen led to a greater improvement in self-reported disability scale compared to placebo (P=0.04). The number of withdrawals due to inadequate analgesia was similar between opioids

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and placebo (RR, 0.82; 95% CI, 0.34 to 2.01). The risk of adverse events was higher in patients receiving opioids compared to patients receiving placebo (OR, 3.90; 95% CI, 2.31 to 6.56; NNH, 4). The most commonly reported adverse events were nausea, vomiting, dizziness, lightheadedness and constipation. When a net efficacy was adjusted for risk, opioids provided no additional benefit compared to placebo (RR, 1.20; 95% CI, 0.89 to 1.61). Moreover, there were no significant differences in efficacy and safety between opioids and NSAIDs.
Eisenberg et al[71] Opioids vs placebo, opioids or non-opioid analgesics	MA (23 RCTs) Patients ≥18 years of age with neuropathic pain	N=727 Short-term: <24 hours (14 RCTs) Intermediate-term: 8 to 70 days (nine RCTs)	Primary: Change in PI Secondary: Safety	Primary: Among the 14 short-term studies (n=267), the following opioids were compared to placebo: morphine, alfentanil, fentanyl, meperidine and codeine. Six trials showed greater pain relief with opioids compared to placebo; five trials showed equivalent efficacy between opioids and placebo; two trials demonstrated mixed efficacy and one trial showed a reduction in the affective but not the sensory component of pain. MA was performed on six trials and showed that opioids were associated with a lower PI score by 16 points on a 100-point VAS compared to placebo (95% CI, -23 to -9; P<0.001). When analyzed separately for peripheral and central pain, the differences in PI between opioids and placebo were 15 (95% CI, -23 to -7; P<0.001) and 18 points (95% CI, -30 to -5; P=0.006), respectively. MA on two trials using percentage of pain reduction showed an additional 26% reduction in pain with opioids vs placebo (95% CI, 17 to 35; P<0.00001). Among the nine intermediate-term studies (n=460), the following opioid analgesics were compared to placebo: morphine, oxycodone, methadone and levorphanol. Three of the trials also compared opioids to carbamazepine, nortriptyline, desipramine and gabapentin. Two of the trials compared different dosages of the same opioid, including methadone and levorphanol. MA of seven studies showed PI score was 13 points lower with opioids than placebo (95% CI, -16 to -9; P<0.00001). Evoked PI was measured in two studies, which showed that PI was 24 points lower with opioids than placebo (95% CI, -33 to -15). Two studies showed a 6-point reduction in PI with morphine or methadone compared to non-opioid analgesics (95% CI, -12 to 0). A dose-dependent analgesic effect was found with methadone and levorphanol (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When comparing opioids to placebo, there was a higher incidence of nausea (33 vs 9%; NNH, 4.2; 95% CI, 3.2 to 5.6), constipation (33 vs 10%; NNH, 4.2; 95% CI, 3.3 to 5.9), drowsiness (29 vs 12%; NNH, 6.2; 95% CI, 4.3 to 10.0), dizziness (21 vs 6%; NNH, 7.1; 95% CI, 5.0 to 11.1) and vomiting (15 vs 3%; NNH, 8.3; 95% CI, 5.6 to 14.3). In four intermediate-term studies, 11 and 4% of patients in the opioid and placebo groups withdrew due to adverse events (NNH, 16.7; 95% CI, 9.1 to 100.0).
Acute Pain				
Singla et al[72] Oxycodone/ acetaminophen ER every 12 hours vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age scheduled to undergo bunionectomy surgery considered healthy or with mild systemic disease states	N=303 48 hours	Primary: SPID over the first 48 hours after bunionectomy surgery Secondary: SPID from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours; TOTPAR from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours; time to perceptible, meaningful and confirmed pain relief; percentage of patients with a 30% or greater reduction in PI scores	Primary: The mean SPID from baseline to 48 hours was significantly higher in the oxycodone/acetaminophen ER (114.9) group compared to placebo (66.9), resulting in a treatment difference of 48.0 (95% CI, 27.3 to 68.6; *P*<0.001) Secondary: The mean SPID from baseline (0 hours) to 4 hours for the oxycodone/acetaminophen ER group was 8.1 versus 1.7 for placebo, resulting in a treatment difference of 6.5 (95% CI, 4.4 to 8.6; *P*<0.001). The mean SPID from 0 to 12 hours for oxycodone/acetaminophen ER was 15.5 versus 2.5 for placebo, resulting in a treatment difference of 13.0 (95% CI, 7.7 to 18.2; *P*<0.001). Mean SPID scores for oxycodone/acetaminophen ER and placebo from 0 to 24 hours were 41.0 and 13.2, respectively, for a treatment difference of 27.7 (95%CI, 17.2 to 38.2; *P*<0.001). The mean SPID score from 0 to 36 hours was 76.0 for oxycodone/acetaminophen ER versus 36.2 for placebo, which resulted in a treatment difference of 39.7 (95% CI, 24.1 to 55.3; *P*<0.001). The mean SPID score from 12 to 24 hours was 25.5 for oxycodone/acetaminophen ER versus 10.7 for placebo, which resulted in a treatment difference of 14.8 (95% CI, 8.3 to 21.3; *P*<0.0001). Mean SPID scores for oxycodone/acetaminophen ER and placebo for 24 to 36 hours were 35.0 versus 23.0, respectively, which results in a treatment difference of 12.0 (95% CI, 5.8 to 18.3; *P*=0.0002). The mean SPID from 36 to 48 hours for the oxycodone/acetaminophen ER group was 38.9 versus 30.7 for placebo, resulting in a treatment difference of 8.3 (95% CI, 1.8 to 14.7; *P*=0.0118). From 0 to 4 hours, oxycodone/acetaminophen ER had a mean TOTPAR value of 6.8 versus 3.4 for placebo, resulting in a treatment difference of 3.4 (95% CI, 2.4 to 4.4; *P*<0.001). Mean TOTPAR values from 0 to 12 hours for oxycodone/acetaminophen and placebo were 16.5 and 11.2, respectively, which resulted in a treatment difference of 5.3 (95% CI, 2.9 to 7.7; *P*<0.001). The mean TOTPAR value for oxycodone/acetaminophen

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ER from 0 to 24 hours was 38.4 versus 26.8 for placebo, resulting in a treatment difference of 11.6 (95% CI, 7.1 to 16.2; *P*<0.001). From 0 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 64.2 versus 47.5 for placebo, which resulted in a treatment difference of 16.8 (95% CI, 9.8 to 23.8; *P*<0.001). Mean TOTPAR values for oxycodone/acetaminophen ER and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). From 12 to 24 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 21.9 versus 15.6 for placebo, resulting in a treatment difference of 6.3 (95% CI, 3.4 to 9.2; *P*<0.0001). From 24 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 25.8 versus 20.7 for placebo, which resulted in a treatment difference of 5.2 (95% CI, 2.1 to 8.2; *P*=0.0009). The mean TOTPAR value for oxycodone/acetaminophen ER from 36 to 48 hours was 27.1 versus 23.4 for placebo, resulting in a treatment difference of 3.7 (95% CI, 0.4 to 7.0; *P*=0.0276). The median time to perceptible pain relief for oxycodone/acetaminophen ER was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen ER group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/acetaminophen ER versus 27.2% for placebo (*P*<0.0001).
Detoxification				
Madlung-Kratzer et al[73] Morphine slow-release vs methadone Patients continued their previous maintenance	DB, MC, PG, RCT Patients ≥18 years of age with a confirmed diagnosis of opioid addiction, who have received maintenance treatment with either morphine	N=202 22 days	Primary: Non-inferiority of dose reduction regimens Secondary: Patient-reported outcomes and safety	Primary: Completion rate per treatment group was 51 and 49% in the morphine and methadone groups, resulting in a difference in completion rates between treatment groups of 2% (95% CI, -12 to 16). According to the prior-defined non-inferiority margin of -15%, morphine is non-inferior to methadone for detoxification. Secondary: At study entry, signs and symptoms of withdrawal were mild but deteriorated steadily over time (day 0 vs day 22; P<0.001). Craving for opiates varied considerably but was generally rated as moderate. No changes became evident during the detoxification phase and there were no significant differences between treatment groups over time, respectively (morphine: day 0,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment for 3 consecutive days and then were randomized to treatment based on previous drug for maintenance treatment and dose level. Dose reduction regimens were started and maintained for 3 consecutive days under DB conditions. Thereafter, detoxification was initiated by tapered dose reductions over a period of 16 days in order to reach abstinence for 3 days.	slow-release or methadone at constant doses for ≥1 month			35.4±35.1 mm; day 22, 32.0±35.1 mm; P=0.442; and methadone: day 0; 38.7±38.6 mm, day 22; 36.8±36.5 mm; P=0.813). Cravings for alcohol, cocaine and cannabis were low throughout detoxification without any significant differences between groups or over time (P values not reported). The proportion of patients reporting at least one adverse event was 16 and 13% in the morphine and methadone groups (P=0.586). The majority of adverse events were gastrointestinal system disorders (nausea, vomiting, and dentalgia), followed by psychiatric disorders (dysphoria, agitation, depression and panic attacks).

*Synonym for acetaminophen.
†Agent not available in the United States.
Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, MD=multi-dose, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single-arm, XO=crossover
Miscellaneous abbreviations: ACR=American College of Rheumatology, $AUCMB_{avg}$=average area under the curve of VAS scores overtime between baseline and end of study, BDI=Beck depression inventory, BPI=Brief Pain Inventory, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, CPSI=Chronic Pain Sleep Inventory, CRPS=Complex Regional Pain Syndrome, EORTC=European Organization for Research and Treatment of Cancer, HAQ=Health Assessment Questionnaire, HbA1c=glycosylated hemoglobin, MOS=Medical Outcomes Study, MPI=multidimensional pain inventory, MRI=magnetic resonance imaging, NNH=number needed to harm, NNT=number needed to treat, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, OR=odds ratio, PDI-Pain Disability Index, PGIC=Patient's Global Impression of Change, PI=Pain Intensity, PPS=Play Performance Scale, SF-36=short form 36 health assessment questionnaire, RMDQ=Roland Morris Disability Questionnaire, RR=relative risk, SGAM=Subject global assessment of medication, SD=standard deviation, SPID= summed pain intensity difference, TOTPAR=total pain relief, VAS=visual analog scale, WOMAC index=Western Ontario and McMaster Universities Index

Special Populations

Table 5. Special Populations[1-17]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in severe hepatic dysfunction.	C	Yes (% low); breast-feeding is not advised.
Fentanyl	Use with caution in the elderly. Approved for use in opioid-tolerant children ≥2 years of age.	Insufficient information exists; use with caution.	Insufficient information exists; use with caution.	C	Yes (% not reported); do not use in nursing women.
Hydrocodone	It is recommended that elderly patients start at lower doses and be closely monitored. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal impairment can increase hydrocodone concentra-tions. Lower initial doses are recommended with close monitoring for patients with renal dysfunction.	No adjustment in initial dose is necessary for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment should start at the lowest dose (10 mg) and be monitored closely.	C	Yes (% low); risk vs benefit should be weighed in order to either discontinue the medication or nursing, taking into account the importance of the medication to the mother.
Hydromorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Renal dose adjustment is required in moderate renal impairment.	Hepatic dose adjustment is required in moderate and severe hepatic impairment.	C	Yes (% not reported); breast-feeding is not advised.
Methadone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; due to the metabolism of methadone,	C	Yes (% not reported); benefits and risks should be

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established.		patients with liver impairment may be at risk of accumulating methadone after multiple dosing.		evaluated before use in nursing women.
Morphine sulfate	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required.	Hepatic dose adjustment is required.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Oxycodone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required and dose titration should follow a conservative approach.	Hepatic dose adjustment is required and careful dose titration is warranted.	B	Yes (% not reported); breast-feeding is not advised.
Oxymorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Caution should be used in patients with moderate to severe renal impairment, starting with lower doses and titrating the dosage slowly.	Caution should be used in patients with mild hepatic impairment; starting with the lowest dose and titrating the dosage slowly. Contra-indicated in moderate and severe hepatic impairment.	C	Unknown; caution should be exercised.
Tapentadol	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been	Not recommended in patients with severe renal impairment.	Use with caution in patients with moderate hepatic impairment; not	C	Insufficient/ limited information on the excretion of tapentadol in human

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	established.		recommended in patients with severe hepatic impairment.		breast milk; should not be used during breast feeding.
Combination Products					
Morphine sulfate/ naltrexone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required in severe renal impairment.	Hepatic dose adjustment is required in severe hepatic impairment.	C	Yes (morphine sulfate; % variable); benefits and risks should be evaluated before use in nursing women.
Oxycodone/ acetaminophen	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required due to higher plasma oxycodone concentrations.	Start with one tablet dose for hepatic impairment and adjust as needed.	C	Yes (both; oxycodone % not reported, acetamino-phen 1 to 2%)

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-17]

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Central Nervous System											
Abnormal gait	-	✔	-	-	-	<5	<1	-	-	-	-
Agitation	-	✔	-	-	✔	<5	<1	<1	-	-	-
Anxiety	✔	3 to 10	≥1 to <10	0 to 4	-	<5 to 6	1 to 5	≥1 to <10	2	2.2	-
Aphasia	-	<1	-	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	<5	-	-	-	-	-
Balance disorder	-	-	-	<2	-	-	-	-	-	-	-
Central nervous system depression	-	-	-	-	-	-	-	<1	-	-	-
Cognitive disorder	-	-	-	<2	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<5	-	-	-	-	-
Convulsions	-	✔	-	<2	-	<5	-	-	-	-	-
Coordination abnormal	-	✔	-	<2	-	-	-	-	-	<1	-
Depressed level of consciousness	-	-	-	<2	-	-	-	<1	-	<1	-
Depression	✔	3 to 10	≥1 to <10	3	-	<3 to 10	<1	≥1 to <10	1	≥1 to <10	-
Difficulty in walking	-	-	-	<2	-	-	-	-	-	-	-
Disturbance in attention	-	-	-	<2	-	-	-	-	1	<1	-
Dizziness	2 to 16	3 to 10	2 to 3	2 to 11	✔	6	13	4.8 to 17.8	17	1.2 to 7.7	13
Drowsiness	-	-	-	-	-	9	-	-	-	-	-
Dysarthria	-	-	-	<2	-	-	-	-	-	-	-
Dysgeusia	-	-	-	<2	-	-	-	-	-	-	-
Dyskinesia	-	-	-	<2	-	-	-	-	-	-	-
Encephalopathy	-	-	-	<2	-	-	-	-	-	-	-
Foot drop	-	-	-	-	-	<3	-	-	-	-	-
Headache	5 to 16	3 to 10	4	5 to 12	✔	<3 to >10	7	2.9 to 12.2	15	2.3 to 6.9	-
Hostility	-	<1	-	-	-	-	-	-	-	-	10
Hyperesthesia	-	-	-	<2	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	<1	-	-	-	-
Hyperreflexia	-	-	-	<2	-	-	-	-	-	-	-
Hypertonia	-	<1	-	-	-	-	-	-	-	-	-
Hypoesthesia	2	-	-	<2	-	-	<1	-	-	-	-
Hypotonia	-	<1	-	-	-	-	<1	-	-	-	-
Irritability	-	-	-	-	-	-	-	-	-	≥1 to <10	-
Loss of concentration	-	-	-	-	-	<3	-	-	-	-	-
Memory impairment	-	-	-	<2	-	-	-	-	✔	<1	-
Mental impairment	-	-	-	-	-	-	-	<1	-	<1	-
Migraine	✔	-	≥1 to <10	-	-	-	<1	-	-	-	-
Myoclonus	-	-	-	<2	-	<3	-	-	-	-	-
Paresthesia	2	✔	≥1 to <10	<2	-	<3 to 10	<1	-	-	<1	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Psychomotor hyperactivity	-	-	-	<2	-	-	-	-	-	-	-
Sedation	-	-	-	<2	✔	-	-	5.9	-	≥1 to <10	-
Seizures	-	-	-	-	✔	<3	<1	-	-	-	-
Somnolence	2 to 14	>10	1 to 5	1to 15	-	>10	23	1.9 to 19.1	12	1.2 to 13.9	4
Stupor	-	<1	-	-	-	-	<1	-	-	<1	-
Speech disorder	-	✔	-	-	-	<3	<1	-	-	-	-
Tremor	2	✔	3	<2	-	<5	<1	-	1	≥1 to <10	-
Vertigo	-	<1	-	<2	-	<5	<1	-	2	-	-
Visual disturbances	-	-	-	-	✔	-	<1	-	1	-	-
Dermatological											
Application site reaction	2 to 15	✔	-	-	-	-	-	-	-	-	-
Blister	-	-	-	-	-	-	-	-	-	-	1
Clamminess	-	-	-	-	-	-	-	<1	-	-	-
Cold sweat	-	-	-	-	-	-	-	-	-	<1	-
Decubitus ulcer	-	-	-	-	-	<3	-	-	-	-	-
Dermatitis	-	-	-	-	-	-	-	<1	-	-	-
Dry skin	-	-	-	-	-	<5	<1	-	-	-	-
Edema	-	✔	1 to 3	-	✔	<5	<1	≥1 to <10	-	-	-
Erythema	-	✔	-	<2	-	-	-	-	-	-	1
Excoriation	-	-	-	-	-	-	-	-	-	-	1
Exfoliative dermatitis	-	<1	-	-	-	-	<1	-	-	-	-
Hemorrhagic urticaria	-	-	-	-	✔	-	-	-	-	-	-
Hyperhidrosis	4	-	≥1 to <10	1 to 6	-	-	-	-	5	3.4	-
Itching	-	✔	-	-	-	-	-	-	-	-	-
Night sweats	-	-	≥1 to <10	-	-	-	-	-	-	<1	-
Other skin rashes	-	-	-	-	✔	-	-	-	-	-	-
Papules	-	✔	-	-	-	-	-	-	-	-	-
Piloerection	-	-	-	-	-	-	-	-	-	<1	-
Pruritus	4	3 to 10	3	1 to 8	✔	<3	-	0 to 15.2	5	5.6 to 6.2	1
Pustules	-	<1	-	-	-	-	-	-	-	-	-
Rash	2	✔	≥1 to <10	3	-	<3 to 10	1 to 5	-	1	<1	2
Skin reaction localized	-	✔	-	-	-	-	-	-	-	-	-
Skin laceration	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Sweating	-	>10	-	-	✔	5 to 10	5	8.6 to >10.0	-	-	-
Urticaria	-	-	-	-	✔	<5	<1	<1	-	-	-
Gastrointestinal Disorders											
Abdominal distention	-	<1	-	<2	-	-	-	<1	-	<1	-
Abdominal discomfort	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Abdominal pain	-	3 to 10	2 to 3	2 to 5	✔	<3 to 10	1 to 5	≥1 to <10	-	-	-
Abdominal pain; lower	-	-	-	-	-	-	-	-	-	<1	-
Abdominal pain; upper	-	-	-	-	-	-	-	-	-	1.1 to 2.3	-
Abdominal tenderness	-	-	-	-	-	-	-	-	-	<1	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Abnormal feces	-	-	-	<2	-	-	-	-	-	-	-
Anal fissure	-	-	-	<2	-	-	-	-	-	-	-
Anorexia	2	3 to 10	-	1 to 6	✔	<3 to 10	1 to 5	-	-	≥1 to <10	-
Bezoar	-	-	-	<2	-	-	-	-	-	-	-
Biliary colic	-	-	-	-	-	<3	-	-	-	-	-
Biliary pain	-	-	-	-	-	<5	-	-	-	-	-
Biliary tract spasm	-	-	-	-	✔	✔	-	-	-	-	-
Constipation	3 to 14	>10	11 to 12	7 to 31	✔	9 to >10	23	5.7 to 27.6	17	7.0 to 31.2	4
Cramps	-	-	-	-	-	✔	-	-	-	-	-
Decreased appetite	-	-	-	-	-	-	-	≥1 to <10	2	≥1 to <10	-
Delayed gastric emptying	-	-	-	-	-	<3	-	-	-	-	-
Diarrhea	3	3 to 10	-	3 to 8	-	<3 to 10	1 to 5	≥1 to <10	-	1.1 to 7.0	≥1
Diverticulum	-	-	-	<2	-	-	-	-	-	-	-
Dry mouth	7	>10	3	1 to 5	✔	<3 to 10	6	≥1 to <10	7	1.8 to 5.7	≥1
Duodenitis	-	-	-	<2	-	-	-	-	-	-	-
Dyspepsia	3	3 to 10	-	4	-	<5	1 to 5	≥1 to <10	3	≥1 to <10	≥1
Dysphagia	-	-	-	<2	-	<5	<1	-	-	-	-
Eructation	-	-	-	<2	-	-	<1	-	-	-	-
Fecaloma	-	-	-	-	-	-	-	-	-	<1	-
Flatulence	-	✔	-	<2	-	-	<1	-	-	≥1 to <10	-
Gastritis	-	-	-	-	-	-	1 to 5	-	-	-	-
Gastroenteritis	-	-	-	<2	-	<5	-	-	-	-	-
Gastro-esophageal reflux	-	-	≥1 to <10	-	-	<3	-	-	-	-	-
Gastrointestinal motility disorder	-	-	-	<2	-	-	<1	-	-	-	-
Glossitis	-	-	-	-	✔	-	-	-	-	-	-
Hematochezia	-	-	-	<2	-	-	-	-	-	-	-
Hemorrhoids	-	-	-	<2	-	-	-	-	-	-	-
Ileus	-	-	-	<2	-	-	<1	<1	-	-	-
Increased appetite	-	-	-	<2	-	-	<1	-	-	-	-
Intestinal obstruction	-	-	-	<2	-	-	-	-	-	-	-
Large intestine perforation	-	-	-	<2	-	-	-	-	-	-	-
Nausea	8 to 23	>10	7 to 10	9 to 28	✔	7 to >10	23	2.9 to 33.1	21	11.1 to 22.2	31
Pancreatitis	-	-	-	-	-	-	-	-	-	<1	-
Painful defecation	-	-	-	<2	-	-	-	-	-	-	-
Rectal disorder	-	-	-	-	-	<5	-	-	-	-	-
Stomach atony disorder	-	-	-	-	-	<3	-	-	-	-	-
Stomach discomfort	2	-	-	-	-	-	-	-	-	≥1 to <10	-
Stomatitis	-	-	-	-	-	-	<1	-	-	-	-
Thirst	-	-	-	-	-	<5	<1	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Vomiting	2 to11	>10	3 to 5	6 to 14	✔	<3 to >10	12	0 to 15.6	8	4.1 to 8.4	9
Weight gain	-	-	-	-	✔	-	-	-	-	-	-
Weight loss	-	✔	-	1 to 3	-	<5	-	≥1 to <10	✔	-	-
Laboratory Values											
Abnormal liver function tests	-	-	-	-	-	<5	-	-	-	-	-
Alanine aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Anemia	-	-	-	-	-	<5	-	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Blood amylase increased	-	-	-	<2	-	-	-	-	-	-	-
Blood potassium decreased	-	-	-	<2	-	-	-	-	-	-	-
Blood testosterone decreased	-	-	-	<2	-	-	-	-	-	-	-
Gynecomastia	-	-	-	-	-	<3	-	-	-	-	-
Hepatic enzyme increased	-	-	-	<2	-	-	-	-	-	-	≥1
Hypokalemia	-	-	≥1 to <10	-	✔	-	-	-	-	-	-
Hypomagnesemia	-	-	-	-	✔	-	-	-	-	-	-
Hyponatremia	-	-	-	-	-	<3	<1	-	-	-	-
Increased blood cholesterol	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Increased gamma-glutamyltransferase	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	<3	-	-	-	-	-
Oxygen saturation decreased	-	-	-	<2	-	-	-	<1	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	-	-	-	-	-	-	<1	-	-	-	-
Thrombocytopenia; reversible	-	-	-	-	✔	<5	-	-	-	-	-
Psychiatric Disorders											
Abnormal dreams	-	✔	-	<2	-	<5	1 to 5	-	1	<1	-
Aggression	-	-	-	<2	-	-	-	-	-	-	-
Amnesia	-	✔	-	-	-	<5	<1	-	-	-	-
Apathy	-		-	-	-	<3	-	-	-	-	-
Confusional state	2	>10	-	<2	✔	<5	1 to 5	≥1 to <10	-	<1	-
Crying	-	-	-	<2	-	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Delirium	-	-	-	-	-	<5	-	-	-	-	-
Depersonalization	-	<1	-	-	-	-	<1	-	-	-	-
Disorientation	-	-	-	-	✔	-	-	≥1 to <10	-	<1	-
Dysphoria	-	-	-	<2	✔	-	-	<1	-	-	-
Emotional lability	-	-	-	-	-	-	<1	-	-	-	-
Euphoric mood	-	3 to 10	-	<2	✔	<5	1 to 5	<1	✔	<1	-
Hallucination	-	3 to 10	-	<2	✔	<5	<1	<1	-	<1	-
Insomnia	3	3 to 10	≥1 to <10	3 to 7	✔	<3 to 10	1 to 5	≥1 to <10	4	1.3 to 2.9	≥1
Listless	-	-	-	<2	-	-	-	-	-	-	-
Mental status changes	-	-	-	-	-	-	-	<1	-	<1	-
Mood altered	-	-	-	<2	-	-	-	-	-	-	-
Mood swings	-	-	-	-	-	-	-	-	-	<1	-
Nervousness	-	3 to 10	-	<2	-	<5	1 to 5	≥1 to <10	-	<1	-
Panic attack	-	-	-	<2	-	-	-	-	-	-	-
Paranoid reaction	-	✔	-	<2	-	-	-	-	-	-	-
Restlessness	-	-	-	<2	-	-	-	≥1 to <10	-	≥1 to <10	-
Suicide ideation	-	-	-	<2	-	-	-	-	-	-	-
Thinking abnormal	-	✔	-	-	-	<5	1 to 5	-	✔	<1	-
Other											
Abnormal ejaculation	-	-	-	-	-	<5	-	-	-	-	-
Accidental injury	-	✔	-	-	-	<3 to 10	<1	-	-	-	-
Allergic reaction	-	✔	-	-	-	-	-	<1	-	-	-
Amblyopia	-	<1	-	-	-	<5	-	-	-	-	-
Amenorrhea	-	-	-	-	✔	<3	<1	-	-	-	-
Anaphylactic reaction	-	-	-	-	-	-	<1	-	-	-	-
Anorgasmia	-	✔	-	-	-	-	-	-	-	-	-
Apnea	-	3 to 10	-	-	-	-	-	-	-	-	-
Arrhythmia	-	✔	-	-	✔	-	-	-	-	-	-
Arthralgia	2	-	≥1 to <10	2 to 6	-	<3	-	-	-	≥1 to <10	-
Asthenia	-	>10	-	1 to 11	✔	<3 to 10	6	-	2	<1	-
Asthma	-	<1	-	-	-	<3	-	-	-	-	-
Atelectasis	-	-	-	-	-	<3	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	<3	-	-	-	-	-
Back pain	3	3 to 10	1 to 4	3 to 4	-	<3 to 10	-	-	-	-	-
Bladder pain	-	<1	-	-	-	-	-	-	-	-	-
Bone pain	-	-	-	-	-	<3	-	-	-	-	-
Bradycardia	-	<1	-	<2	✔	<5	-	<1	-	-	-
Bronchitis	-	✔	-	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	<2	-	-	-	-	-	-	-
Cardiomyopathy	-	-	-	-	✔	-	-	-	-	-	-
Chest discomfort	-	-	-	2	-	-	-	-	-	-	-
Chest pain	-	✔	-	-	-	<3	<1	-	-	-	-
Chills	-	-	-	<2	-	<3	1 to 5	-	1	≥1 to <10	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Conjunctivitis	-	-	-	-	-	<3	-	-	-	-	-
Contusion	-	-	≥1 to <10	<2	-	-	-	-	-	-	-
Coughing	-	✔	≥1 to <10	-	-	-	<1	-	-	-	≥1
Decreased libido	-	✔	-	<2	✔	<5	<1	-	-	-	-
Dehydration	-	-	≥1 to <10	<2	-	-	<1	≥1 to <10	-	-	-
Depressed cough reflex	-	-	-	-	-	<3	-	-	-	-	-
Diaphoresis	-	-	-	-	-	<3	-	-	-	-	-
Difficult micturition	-	-	-	-	-	-	-	<1	-	-	-
Drug withdrawal syndrome	-	-	-	2 to 10	-	<5	<1	-	-	<1	-
Diplopia	-	-	-	<2	-	<3	-	-	-	-	-
Dry eye	-	-	-	<2	-	-	-	-	-	-	-
Dyspnea	3	3 to 10	≥1 to <10	3	-	<3 to 10	1 to 5	≥1 to <10	1	<1	-
Dysuria	-	-	-	<2	-	<5	<1	-	-	<1	1
Electrocardiogram abnormalities	-	-	-	-	✔	-	-	-	-	-	-
Edema peripheral	7	-	-	2 to 5	-	<3 to 10	<1	-	-	≥1 to <10	1
Ejaculatory difficulty	-	✔	-	-	-	-	-	-	-	-	-
Erectile dysfunction	-	-	-	<2	-	-	-	-	1	<1	-
Extrasystoles	-	-	-	<2	✔	-	-	-	-	-	-
Eye pain	-	-	-	-	-	<5	-	-	-	-	-
Facial edema	-	-	-	-	-	-	<1	-	-	-	-
Facial flushing	-	-	-	-	-	<3	-	-	-	-	-
Fall	4	-	≥1 to <10	2	-	-	-	-	-	-	-
Fatigue	5	3 to 10	1 to 4	-	-	-	-	≥1 to <10	9	4.1	≥1
Feeling abnormal	-	-	-	<2	-	-	-	-	-	-	-
Feeling drunk	-	-	-	<2	-	-	-	-	-	-	-
Feeling hot and cold	-	-	-	<2	-	-	-	-	-	-	-
Feeling jittery	-	-	-	<2	-	-	-	<1	-	<1	-
Foot fracture	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Fever	-	3 to 10	-	-	-	<3 to 10	1 to 5	-	-	-	-
Flu syndrome	-	-	-	-	-	<3 to 10	-	-	-	-	-
Fluid retention	-	-	-	<2	-	-	-	-	-	-	-
Flushing	-	✔	-	<2	✔	<3	-	≥1 to <10	-	<1.0 to 2.3	-
Hangover	-	-	-	<2	-	-	-	-	-	-	-
Heart failure	-	-	-	-	✔	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	<1	-	-	-	-
Hemoptysis	-	✔	-	-	-	-	-	-	-	-	-
Hiccups	-	✔	-	-	-	<5	1 to 5	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	<1	-	-	1
Hot flush	-	-	≥1 to <10	-	-	-	-	-	2	≥1 to <10	-
Hypersensitivity	-	-	-	-	-	-	-	<1	✔	-	-
Hypertension	✔	✔	-	<2	-	<5	-	≥1 to <10	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Hyperuricemia	-	-	-	<2	-	-	-	-	-	-	-
Hyperventilation	-	-	-	<2	-	-	-	-	-	-	-
Hypogonadism	-	-	-	<2	-	-	-	-	-	-	-
Hypotension	-	-	-	<2	✔	<5	-	<1	-	<1	-
Hypothermia	-	-	-	<2	-	-	-	-	-	-	-
Hypoventilation	-	3 to 10	-	-	-	<5	-	-	-	-	-
Hypoxia	-	-	-	<2	-	<3	-	<1	-	-	-
Impotence	-	-	-	-	-	<5	<1	-	-	-	-
Infection	-	-	-	-	-	5 to 10	-	-	-	-	-
Influenza-like symptoms	✔	3 to 10	-	-	-	-	-	-	-	-	-
Joint injury	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint sprain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint swelling	3	-	-	-	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	✔	✔	-	-	-	-	-
Lethargy	-	-	≥1 to <10	-	-	<5	-	≥1 to <10	1	≥1 to <10	-
Lymphadenopathy	-	-	-	-	-	-	<1	-	-	-	-
Malaise	-	-	-	<2	-	<5	<1	-	-	<1	-
Micturition disorder	-	-	-	<2	-	-	-	-	-	-	-
Miosis	-	-	-	<2	-	<3	-	<1	-	-	-
Muscle spasms	-	-	1 to 3	1 to 3	-	-	-	-	-	≥1 to <10	-
Muscle strain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	-	<1	-
Musculoskeletal pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Myalgia	✔	-	≥1 to <10	<2	-	-	-	-	-	<1	-
Neck pain	✔	-	≥1 to <10	-	-	-	<1	-	-	-	-
Non-cardiac chest pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Non-cardiogenic pulmonary edema	-	-	-	-	-	<3	-	-	-	-	-
Nystagmus	-	-	-	-	-	<3	-	-	-	-	-
Oliguria	-	<1	-	-	-	<5	-	-	-	-	-
Orthostatic hypotension	-	-	-	-	-	-	-	-	-	<1	-
Osteoarthritis	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Overdose	-	-	-	<2	-	-	-	-	-	-	-
Pain	✔	3 to 10	≥1 to <10	2	-	<3	<1	-	-	-	-
Pain in extremity	3	-	≥1 to <10	3	-	-	-	-	-	-	-
Pallor	-	-	-	-	-	<3	-	-	-	-	-
Palpitations	-	-	-	<2	✔	<5	-	<1	-	-	-
Pharyngitis	-	3 to 10	-	-	-	-	<1	-	-	-	-
Polyuria	-	-	-	-	-	-	<1	-	-	-	-
Postural hypotension	-	-	-	-	-	-	1 to 5	<1	-	-	-
Pulmonary edema	-	-	-	-	✔	-	-	-	-	-	-
Pyrexia	-	-	≥1 to <10	2	-	-	-	≥1 to <10	-	-	-
QT interval prolongation	-	-	-	-	✔	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Respiratory depression	-	✔	-	<2	✔	-	-	<1	-	-	-
Respiratory disorder	-	<1	-	-	-	-	-	-	-	-	-
Respiratory distress	-	-	-	<2	-	-	-	<1	-	-	-
Respiratory insufficiency	-	-	-	-	-	<3	-	-	-	-	-
Respiratory rate decreased	-	-	-	-	-	-	-	<1	✔	-	-
Rhinorrhea	-	-	-	<2	-	-	-	-	-	<1	-
Rhinitis	-	✔	-	-	-	<3	-	-	-	-	-
Rigors	-	✔	-	-	-	-	-	-	-	-	-
Sexual dysfunction	-	-	-	<2	-	-	-	-	✔	-	-
Sinusitis	-	✔	-	-	-	-	-	-	-	-	-
Skeletal muscle rigidity	-	-	-	-	-	<5	-	-	-	-	-
Sneezing	-	-	-	<2	-	-	-	-	-	-	-
ST depression	-	-	-	-	-	-	<1	-	-	-	-
Stertorous breathing	-	<1	-	-	-	-	-	-	-	-	-
Syncope	-	✔	-	<2	✔	<5	<1	<1	-	-	-
T-wave inversion	-	-	-	-	✔	-	-	-	-	-	-
Tachycardia	-	✔	-	<2	✔	<5	-	<1	-	-	-
Taste perversion	-	-	-	-	-	<5	<1	-	-	-	-
Tinnitus	-	-	-	<2	-	-	<1	-	-	-	-
Torsade de pointes	-	-	-	-	✔	-	-	-	-	-	-
Twitching	-	-	-	-	-	-	1 to 5	-	-	-	-
Upper respiratory tract infection	✔	3 to 10	1 to 3	-	-	-	-	-	-	-	-
Urinary abnormality	-	-	-	-	-	<3	-	-	-	-	-
Urinary frequency	-	<1	-	<2	-	-	-	-	-	-	-
Urinary hesitancy	-	-	-	<2	✔	<3	-	-	✔	-	-
Urinary retention	-	-	-	<2	✔	<5	<1	<1	-	<1	-
Urinary tract infection	3	-	1 to 5	-	-	5 to 10	-	-	-	-	-
Urination impaired	-	-	-	-	-	-	<1	-	-	-	-
Vasodilation	-	-	-	-	-	<5	<1	-	-	-	-
Ventricular fibrillation	-	-	-	-	✔	-	-	-	-	-	-
Ventricular tachycardia	-	-	-	-	✔	-	-	-	-	-	-
Vision blurred	-	✔	-	<2	-	<3	-	≥1 to <10	-	<1	-
Voice alteration	-	-	-	-	-	<5	<1	-	-	-	-
Weakness	-	-	-	-	-	✔	-	≥1 to <10	-	-	-

APAP=Acetaminophen
*During dosage titration and maintenance therapy.
†At least one dosage formulation.
✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-17]

Contraindication(s)	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Bronchial asthma or hypercarbia, acute or severe	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days	-	-	-	-	-	-	-	-	✔	-	-
Hypersensitivity reactions including anaphylaxis have been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	✔
Hypersensitivity to any components or the active ingredient	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Management of acute pain or in patients who require opioid analgesia for a short period of time	-	✔	-	-	-	-	-	-	-	-	-
Management of intermittent pain (e.g., use on an as-needed basis)	-	✔	-	-	-	-	-	-	-	-	-
Management of mild pain	-	✔	-	-	-	-	-	-	-	-	-
Management of postoperative pain, including use after out-patient or day surgeries	-	✔	-	-	-	-	-	-	-	-	-
Moderate and severe hepatic impairment	-	-	-	-	-	-	-	✔	-	-	-
Opioid non-tolerant patients	-	✔	-	✔	-	-	-	-	-	-	-
Preexisting gastrointestinal surgery or narrowing of gastrointestinal tract	-	-	-	✔	-	-	-	-	-	-	-
Respiratory depression, significant	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Suspected or documented paralytic ileus	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

APAP=Acetaminophen

Boxed Warnings

Boxed Warning for Butrans® (buprenorphine)[1]

WARNING

Abuse Potential
Butrans® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Butrans®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of BUTRANS. Monitor for respiratory depression, especially during initiation of BUTRANS or following a dose increase. Misuse or abuse of BUTRANS by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.

Accidental Exposure
Accidental exposure to Butrans®, especially in children, can result in a fatal overdose of buprenorphine.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of BUTRANS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Duragesic® (Fentanyl)[2]

WARNING

Abuse Potential
Duragesic® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Duragisc®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Duragesic®, even when used as recommended. Monitor for respiratory depression, especially during initiation of Duragesic® or following a dose increase. Because of the risk of respiratory depression, Duragesic® is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain.

Accidental Exposure
Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to Duragesic®. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Duragesic®, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and

WARNING

requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Duragesic® with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving Duragesic® and any CYP3A4 inhibitor or inducer.

Exposure To Heat
Exposure of the Duragesic® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl and death. Patients wearing Duragesic® systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of Duragesic® to avoid overdose and death.

Boxed Warning to Zohydro® (hydrocodone extended-release)[3]

WARNING

Addiction, Abuse, and Misuse
Zohydro ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Zohydro ER®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Zohydro ER®. Monitor for respiratory depression, especially during initiation of Zohydro ER® or following a dose increase. Instruct patients to swallow Zohydro ER® capsules whole; crushing, chewing, or dissolving Zohydro ER capsules can cause rapid release and absorption of a potentially fatal dose of hydrocodone.

Accidental Exposure
Accidental consumption of even one dose of Zohydro ER®, especially by children, can result in a fatal overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome
For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Zohydro ER®. The co-ingestion of alcohol with Zohydro ER® may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

Boxed Warning for Exalgo® (hydromorphone)[4]

WARNING
Addiction, Abuse, and Misuse Exalgo® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing EXALGO, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Exalgo®. Monitor for respiratory depression, especially during initiation of Exalgo® or following a dose increase. Instruct patients to swallow Exalgo® tablets whole; crushing, chewing, or dissolving Exalgo® tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone. Accidental Ingestion Accidental ingestion of even one dose of Exalgo®, especially by children, can result in a fatal overdose of hydromorphone. Neonatal Opioid Withdrawal Syndrome Prolonged use of Exalgo® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Dolophine®, Methadose® tablet, solution (methadone)[5-7]

WARNING
Addiction, Abuse, and Misuse Dolophine®/Methadose® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Dolophine®/Methadose®, and monitor all patients regularly for the development of these behaviors or conditions Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Dolophine®/Methadose®. Monitor for respiratory depression, especially during initiation of DOLOPHINE or following a dose increase. Accidental Ingestion Accidental ingestion of even one dose of Dolophine®/Methadose®, especially by children, can result in a fatal overdose of methadone. Life-threatening QT Prolongation QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients for changes in cardiac rhythm during initiation and titration of Dolophine®/Methadose®. Neonatal Opioid Withdrawal Syndrome

WARNING
Prolonged use of Dolophine®/Methadose® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration.

Boxed Warning for Methadose® concentrate, dispersible tablet (methadone)[8,9]

WARNING
Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8: Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8:
Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program

WARNING
approval, and injunction precluding operation of the program.

Boxed Warning for Avinza®, Kadian® (morphine sulfate extended-release capsules)[10,11]

WARNING
Addiction, Abuse, and Misuse Avinza®/Kadian® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Avinza®/Kadian®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Avinza®/Kadian®. Monitor for respiratory depression, especially during initiation of Avinza®/Kadian® or following a dose increase. Instruct patients to swallow Avinza®/Kadian® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow immediately without chewing. Crushing, chewing, or dissolving Avinza®/Kadian® can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of even one dose of Avinza®/Kadian®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of Avinza®/Kadian® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Avinza®/Kadian®. The co-ingestion of alcohol with AVINZA may result in increased plasma levels and a potentially fatal overdose of morphine.

Boxed Warning for MS Contin® (morphine sulfate controlled-release)[12]

WARNING
Addiction, Abuse, and Misuse MS Contin® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS Contin®, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of MS Contin®. Monitor for respiratory depression, especially during initiation of MS Contin® or following a dose increase. Instruct patients to swallow MS Contin® tablets whole; crushing, chewing, or dissolving MS Contin® tablets can cause rapid release and absorption of a potentially fatal dose of morphine.

WARNING
Accidental Ingestion Accidental ingestion of even one dose of MS Contin®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of MS Contin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning to OxyContin® (oxycodone controlled-release)[13]

WARNING
Addiction, Abuse, and Misuse OxyContin® exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OxyContin® and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of OxyContin®. Monitor for respiratory depression, especially during initiation of OxyContin® or following a dose increase. Instruct patients to swallow OxyContin® tablets whole; crushing, chewing, or dissolving OxyContin® tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone. Accidental Ingestion Accidental ingestion of even one dose of OxyContin®, especially by children, can result in a fatal overdose of oxycodone. Neonatal Opioid Withdrawal Syndrome Prolonged use of OxyContin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Cytochrome P450 3A4 Interaction The concomitant use of OxyContin® with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OxyContin® and any CYP3A4 inhibitor or inducer .

Boxed Warning for Opana ER® (oxymorphone extended-release)[14]

WARNING
Addiction, Abuse, and Misuse Opana ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Opana ER®, and monitor all patients regularly for the development of these behaviors or conditions.

WARNING

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Opana ER®. Monitor for respiratory depression, especially during initiation of Opana ER® or following a dose increase. Instruct patients to swallow Opana ER® tablets whole; crushing, chewing, or dissolving Opana ER® tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental Ingestion
Accidental ingestion of even one dose of Opana ER®, especially by children, can result in a fatal overdose of oxymorphone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Opana ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be availablel.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Opana ER®. The co-ingestion of alcohol with Opana ER® may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Boxed Warning for Nucynta ER® (tapentadol extended-release)[15]

WARNING

Addiction, Abuse, and Misuse
NUCYNTA® ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing NUCYNTA® ER, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA® ER. Monitor for respiratory depression, especially during initiation of NUCYNTA® ER or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole; crushing, chewing, or dissolving NUCYNTA® ER tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Ingestion
Accidental ingestion of even one dose of NUCYNTA® ER, especially by children, can result in a fatal overdose of tapentadol.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of NUCYNTA® ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

WARNING
Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA® ER. The co-ingestion of alcohol with NUCYNTA® ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Boxed Warning for Embeda® (morphine sulfate/naltrexone)[16]

WARNING
Abuse Potential Embeda® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Embeda®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Embeda® for signs of misuse, abuse, and addiction during treatment. Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Embeda®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Embeda® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Embeda® or following a dose increase. Instruct patients to swallow Embeda® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Embeda®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Embeda® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Embeda® therapy.

Boxed Warning for Xartemis XR® (oxycodone/acetaminophen)[17]

WARNING
Addiction, Abuse, and Misuse XARTEMIS XR® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing XARTEMIS XR®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMIS XR®. Monitor for respiratory depression, especially during initiation of XARTEMIS XR® or following a dose increase. Instruct patients to swallow XARTEMIS XR® tablets whole; crushing, chewing, or dissolving XARTEMIS XR® can cause rapid release and absorption of a potentially fatal dose of oxycodone.

WARNING

Accidental Exposure
Accidental ingestion of XARTEMIS XR®, especially in children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of XARTEMIS XR® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Hepatotoxicity
XARTEMIS XR® contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limit, and often involve more than one acetaminophen-containing product.

Warnings and Precautions

Table 8. Warnings and Precautions[1-17]

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Accidental exposure; can result in a fatal overdose, especially in children	✔	✔	✔	-	-	✔	✔	-	✔	-	-
Acute abdominal conditions; administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions	-	-	✔	-	✔	-	✔	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule III controlled substance.	✔	-	-	-	-	-	-	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule II controlled substance.	-	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Ambulatory surgery and postoperative use; not indicated for pre-emptive analgesia and only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time	-	-	-	-	-	-	-	✔	-	-	-
Anaphylaxis have been reported	✔	-	✔	-	-	✔	-	-	-	✔	-
Application of external heat; avoid	✔	✔	-	-	-	-	-	-	-	-	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
exposing the application site and surrounding area to direct external heat sources											
Application site skin reactions	✔	-	-	-	-	-	-	-	-	-	-
Cardiac disease; may produce bradycardia	-	✔	-	-	-	-	-	-	-	-	-
Central nervous system depression; may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma	✔	✔	✔	-	-	-	-	-	✔	-	-
Coadministration of anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone; dose should be adjusted accordingly	-	-	-	-	✔	-	-	-	-	-	-
Cordotomy	-	-	-	-	-	✔ (Kadian®)	-	-	-	✔	-
Cytochrome P450 inducers; should be monitored for evidence of withdrawal effects	-	✔	✔	-	✔	-	✔	-	-	-	✔
Cytochrome P450 inhibitors; may result in an increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression	-	✔	✔	-	✔	-	✔	-	-	-	✔
Difficulty in swallowing and risk for obstruction in patients at risk for a small gastrointestinal lumen	-	-	-	-	-	-	✔	✔	-	-	✔
Driving and operating machinery	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Gastrointestinal obstruction; do not administer to patients with gastrointestinal obstruction, especially paralytic ileus	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Head injury and increased intracranial pressure	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hepatic or renal disease; clearance may be reduced in patients with hepatic dysfunction, while the clearance of its metabolites may be decreased in renal dysfunction	-	✔	-	-	-	✔	✔	✔	✔	-	-
Hepatotoxicity	✔	-	-	-	-	-	-	-	-	-	✔
Hypotensive effect; may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
drugs											
Impaired respiration/respiratory depression	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Interactions with alcohol and drugs of abuse; additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Interactions with mixed agonist/antagonist opioid analgesics; may reduce the analgesic effect and/or may precipitate withdrawal symptoms	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	-
Interactions with other central nervous system depressants; may result in respiratory depression, hypotension, and profound sedation or coma	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Monoamine oxidase inhibitors; not recommended for use in patients who have received monoamine oxidase inhibitors within 14 days	-	-		✔	✔	-	-	-	-	-	-
Neonatal opioid withdrawal syndrome; prolonged maternal use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Pancreatic/biliary tract disease; use with caution in patients with biliary tract disease, including acute Pancreatitis	-	✔	-	✔	-	✔	✔	✔	✔	✔	-
Patients with fever; patients should be monitored for opioid adverse events and the dose should be adjusted if necessary	✔	✔	-	-	-	-	-	-	-	-	-
Precipitation of withdrawal; mixed agonist/antagonist analgesics should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic	-	✔	✔	✔	✔	✔	-	-	✔	✔	-
QTc prolongation	✔	-	-	-	✔	-	-	-	-	-	-
Seizures	✔	-	-	✔	✔	✔	✔	✔	✔	✔	-
Risk of relapse; abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms	-	-	-	-	✔	-	-	-	-	-	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Skin reactions, serious have rarely been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	✔
Serotonin syndrome risk	-	-	-	-	-	-	-	-	✔	-	-
Special risk groups; should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients; caution should be exercised in the administration to patients with central nervous system depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure disorders	✔	-	✔	✔	✔	✔	✔	✔	✔	✔	-
Sulfites; contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes	-	-	-	✔	-	-	-	-	-	-	-
Tolerance and physical dependence may develop	-	✔	✔	-	✔	✔	✔	-	-	✔	-
Use in addiction treatment; has not been studied and is not approved for use in the management of addictive disorders	✔	-	-	-	-	-	-	-	-	-	-
Use in elderly, cachectic and debilitated patients; life-threatening respiratory depression is more likely to occur in these patient populations; monitor these patients closely, especially when initiating and titrating doses	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Use in patients with chronic pulmonary disease; monitor patients for respiratory depression, particularly when initiating therapy and titrating therapy	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Use with other acetaminophen-containing products should not be used if total acetaminophen dose is ≥4,000 mg/day	-	-	-	-	-	-	-	-	-	-	✔

Drug Interactions

Table 9. Drug Interactions[1-17,29]

Drug	Interacting Medication	Potential Result
All long-acting opioids	Mixed agonist/antagonist and partial agonists	Effects of long-acting opioid may be reduced
All long-acting opioids	CNS depressants (alcohol, benzodiazepines)	Increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients carefully.
Buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone oxycodone/ acetaminophen, oxymorphone, tapentadol	Anticholinergics	May result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Burenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 Inducers (amiodarone, phenytoin, carbamazepine, diltiazem St. John's wort, etc.)	May cause increased clearance of oxycodone/acetaminophen, leading to decreased concentrations and lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. Monitor and adjust dose as needed.
Buprenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 inhibitors (azole antifungals, macrolides, protease inhibitors, etc.)	The pharmacologic effects and adverse reactions of certain opioid analgesics may be increased.
Buprenorphine, methadone	Arrhythmogenic Agents (class I and III anti-arrhythmics, some neuroleptics and tricyclics, calcium channel blockers)	Cardiac conduction changes when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Monitor closely when used together.
Buprenorphine morphine, morphine/ naltrexone, oxycodone, oxycodone/ acetaminophen, oxymorphone,	Neuromuscular blocking agents	May enhance the effects of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Drug	Interacting Medication	Potential Result
tapentadol		
Fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone/ acetaminophen	Monoamine Oxidase Inhibitors (MAOIs)	Enhanced effects of at opioid drugs causing anxiety, confusion, and significant depression of respiration or coma. Avoid use during and 14 days after stopping MAOIs.
Morphine, morphine/ naltrexone, oxymorphone	Cimetidine	Cimetidine can potentiate opioid-induced respiratory depression.
Morphine, morphine/ naltrexone, oxymorphone	Diuretics	Reduced efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.
Morphine, morphine/ naltrexone	P-Glycoprotein Inhibitors	PGP inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.
Oxycodone, Tapentadol	Serotonergic Drugs SSRIs and SNRIs).	The risk of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may be increased.

Dosage and Administration

When selecting an individualized initial dose for any of the long-acting opioids, taking into account the patient's prior opioid and non-opioid analgesic treatment, consideration should be given to the general condition and medical status of the patient, the daily dose, potency and kind of analgesic(s) the patients has been taking, the reliability of the conversion estimate used to calculate the dose of the new long-acting opioid, the patient's opioid exposure and opioid tolerance (if any), any safety issues associated with the specific long-acting opioid, and the balance between pain control and adverse outcomes. The specific dosing for each of long-acting opioids are listed in Table 10 below.[1-17]

Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven.[1-2] Buprenorphine patches are applied for a 7-day cycle on the right or left outer arm, upper chest, upper back or side of chest. The same location for application should not be reused within 21 days.[1] Each fentanyl system may be worn continuously for 72 hours on areas such as the chest, back, flank or upper arm and then removed and disposed of immediately. The next fentanyl transdermal system should be applied to a different skin site.[2] Buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1] If problems with adhesion to either occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, waterproof or semipermeable adhesive dressings or transparent adhesive film dressing may be used on buprenorphine patches or fentanyl transdermal systems respectively.[1-2]

Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-17] The only exceptions are the morphine-containing capsules (Avinza®, Kadian® and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[10,11,16] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[11] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[10,11,16] It is recommended to give only one Zohydro ER®

(hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,13-15]

Almost all oral, long-acting opioids are dosed twice daily. Exalgo® ER (hydromorphone) tablets and Avinza® (morphine) capsules, however, are dosed once daily.[4,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[11,16] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[5-9,12] The remaining long-acting agents are dosed twice daily only (OxyContin® [oxycodone], Opana ER® [oxymorphone], Nucynta ER® [tapentadol], Xartemis XR® [oxycodone/acetaminophen]).[3,14,15,17] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[10]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, or if taking other acetaminophen products, a maximum of 4,000 mg/day.[17]

Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-17] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

Methadone differs from many of the other long-acting opioids due to pharmacokinetic properties; high interpatient variability in absorption, metabolism, and relative analgesic potency. For these reasons, it is necessary that a cautious and highly individualized approach to prescribing methadone is practiced.[5-9] The concentrate and dispersible tablets are only indicated for the detoxification treatment or maintenance treatment of opioid addiction.[8,9] When methadone is used for the treatment of opioid addiction in detoxification or maintenance programs, it is only to be dispensed by opioid treatment programs certified by the Substance Abuse and Mental Health Service Administration and approved by the designated state authority. Also, these programs must only dispense oral formulations of methadone according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12).[5-9] The methadone solution and concentrate are for oral administration only and should never be injected.[7,8]

Table 10. Dosing and Administration[1-17]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Transdermal patch: initial (opioid-naïve)†, 5 µg/hour; maintenance and titration, titrate only after 72 hours of continuous exposure to current dose; maximum, 20 µg/hour Application sites: Right or left outer arm, upper chest, upper back or side of chest	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-	Approved for use in opioid-tolerant children ≥2 years of	Transdermal system‡: 12 µg/hour§

Generic Name	Adult Dose	Pediatric Dose	Availability
	term opioid treatment and for which alternative treatment options are inadequate*: Transdermal system: initial, dose conversion instructions should be consulted; maintenance/titration, titrate after three days based on the daily dose of supplemental opioid analgesics required in the second or third day of application; maximum, no maximum Application sites: Right or left chest, back, flank or upper arm	age. The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*: Transdermal system: initial, dosage is based upon oral morphine sulfate dose; maintenance, dose may be increased after three days based on the daily dose of supplemental opioid analgesics required by the patients in the second or third day of initial application	25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve or no opioid tolerance)[†], 10 mg every 12 hours; maintenance/titration, titrate 10 mg every 12 hours every three to seven days as necessary; maximum, no maximum dose.	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate*: Extended release tablets: initial, once daily, dose conversion instructions should be consulted ; maintenance/titration, titrate every three to four days; maximum, no maximum	Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Tablet, extended release[‡]: 8 mg 12 mg 16 mg 32 mg
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for	Safety and efficacy in pediatric patients <18 years of age have not	Concentrate solution, oral (sugar-free

Generic Name	Adult Dose	Pediatric Dose	Availability
	which alternative treatment options are inadequate: Oral solution, extended release tablet: initial (opioid-naïve)†, 2.5 to 10 mg every eight to 12 hours; maintenance/titration, titrate every 24 to 48 hours; maximum, no maximum For detoxification treatment of opioid addiction (heroin or other morphine-like drugs): Oral concentrate solution, dispersible tablet for oral suspension, oral solution, extended release tablet (first day of treatment): initial, single 20 to 30 mg dose to suppress withdrawal symptoms; maintenance, an additional 5 to 10 mg may be provided if withdrawal symptoms have not been suppressed; maximum, 40 mg/day Oral concentrate solution, dispersible tablet for oral suspension, oral solution, extended release tablet (short-term detoxification): titrate total daily dose to 40 mg administered in divided doses; maintenance, stabilization should be continued for two to three days after which the dose should be gradually decreased For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services: Oral concentrate solution, dispersible tablet for suspension, oral solution, extended release tablet: maintenance, 80 to 120 mg/day	been established.	available): 10 mg/mL Dispersible tablet for oral suspension: 40 mg Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Biphasic extended release biphasic capsule (Avinza®): initial (opioid-naïve or no opioid tolerance)†, 30 mg once daily; maintenance/titration, titrate every three to four days; maximum, 1,600 mg/day Extended release capsule (Kadian®):	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended release: 10 mg 20 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	initial (opioid-naïve)†, not recommended, start with instant release morphine and convert to once daily dose after; initial (no opioid tolerance)†, 30 mg once daily; maintenance/titration, dose conversion instructions should be consulted for once or twice daily dose; maximum, no maxium Extended release tablet (MS Contin®): initial (opioid-naïve or no opioid tolerance)†, 15 mg every eight to 12 hours; maintenance/titration, titrate every one to two days for every eight to 12 hour dose; maximum, no maximum		30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid naïve or no opioid tolerance)†, 10 mg every 12 hour dose; maintenance/titration, titrate every one to two days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 5 mg every 12 hours; maintenance/titration, titrate five to 10 mg every 12 hours every three to seven days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to three days; maximum, 500 mg/day Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to three days; maximum, 500 mg/day		
Combination Products			
Morphine sulfate/ naltrexone	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve)†, 20 mg/0.8 mg once or twice daily ; maintenance/titration, titrate every one to two days for once or twice daily dose; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡
Oxycodone/ Acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve), 15/650 mg every 12 hours; maximum, 15/650 mg every 12 hours	Safety and efficacy in pediatric patients <18 years of age have not been established.	Biphasic tablet, extended release: 7.5 mg/325 mg

*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†For patients already taking opioids, initial dose should be calculated by consulting dose conversion instructions.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.

Clinical Guidelines

The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole. In terms of specific etiologies of pain, opioids are recognized as a possible treatment option for the treatment of noncancer pain, osteoarthritis pain, lower back pain, gout pain and neuropathic pain. Only weak opioids are recommended for the treatment of pain associated with fibromyalgia; strong opioids are not recommended in these patients.

Specific to the long-acting opioids, proposed benefits of these agents when administered around-the-clock include more consistent control of pain, improved adherence, and lower risk of abuse or addiction; however, to date, no well-conducted clinical trials have clearly proven these benefits.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Treatment Guidelines from The Medical Letter: **Drugs for Pain**	• Nociceptive pain can be treated with nonopioid analgesics or opioids. • Neuropathic pain is less responsive to opioids and is often treated with adjuvant drugs such as antidepressants and antiepileptics. • Combining different types of analgesics may provide an additive analgesic

Clinical Guideline	Recommendations
(2013)[23]	effect without increasing adverse events. • Nonopioid analgesics such as aspirin, acetaminophen and NSAIDs are preferred for initial treatment of mild to moderate pain. • For moderate acute pain, most NSAIDs are more effective than aspirin or acetaminophen and some have shown equal or greater analgesic effect than an oral opioid combined with acetaminophen, or even injected opioids. The selective cyclooxygenase-2 inhibitor celecoxib appears to cause less severe gastrointestinal toxicity compared to non-selective NSAIDs. • Moderate pain that does not respond to nonopioids can be treated with a combination of opioid and nonopioid analgesics. • For treatment of most types of severe pain, full opioid agonists are the drugs of choice. Unlike NSAIDs, morphine and the other full agonists generally have no dose ceiling for their analgesic effectiveness except that imposed by adverse events. • Patients who do not respond to one opioid may respond to another. Meperidine use should be discouraged because of the high rate of central nervous system (CNS) toxicity and the availability of less toxic, longer-acting alternatives. • Tolerance to most of the adverse events of opioids, including respiratory and CNS depression, develops at least as rapidly as tolerance to the analgesic effect; tolerance can usually be surmounted and adequate analgesia restored by increasing the dose. • When frequent dosing becomes impractical, long-acting opioids may be helpful.
National Comprehensive Cancer Network: **Adult Cancer Pain (2014)**[75]	• Pain is one of the most common symptoms associated with cancer. • The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine. • This guideline is unique it that it contains the following components: o In order to maximize patient outcomes, pain is an essential component of oncology management. o There is an increasing amount of evidence that survival is linked to effective pain control. o Analgesic therapy must be administered in conjunction with management of multiple symptoms or symptom clusters and complex pharmacologic therapies that patients with cancer are generally prescribed. o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect. o Persistent cancer pain often requires treatment with regularly scheduled analgesics with supplemental doses of analgesics provided as needed to manage breakthrough pain. o A multidisciplinary team may be needed for comprehensive pain management.

Clinical Guideline	Recommendations
	○ Psychosocial support must be available. ○ Specific educational material must be provided to the patient. • The pain management algorithm distinguishes three levels of pain intensity, based on a zero to 10 numerical rating scale: severe pain (seven to 10), moderate pain (four to six) and mild pain (one to three). • Pain associated with oncology emergency should be addressed while treating the underlying condition. • Patients considered to be opioid tolerant are those who are taking >60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer. Patients not meeting this definition are considered opioid naïve. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as patient and family education. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. • Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. • Opioid-naïve patients experiencing mild pain intensity should receive nonopioids analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids. • Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration as preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice at an initial oral dose of 5 to 15 mg. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (fentanyl, morphine, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. • Due to the ease of titration, opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid.

Clinical Guideline	Recommendations
	• Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. Methadone use should be initiated by physicians with experience and expertise in its use. • At a maximum dose of 400 mg/day, tramadol is less potent than other opioids and is approximately 1/10 as potent as morphine. • Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. • The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” • “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. • For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate, 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended. • Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. • If the pain decreases to 4 to 6, the same dose of opioid is repeated and reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered “as needed” over the initial 24 hours before proceeding to subsequent management strategies. • No single opioid is optimal for all patients. When considering opioid

Clinical Guideline	Recommendations
	rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse events, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new "rescue dose" must be increased by 10 to 20%. • Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families. • Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. • Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic

Clinical Guideline	Recommendations
	interventions. Attention should also be focused on psychosocial support and providing education to patients and families.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[76]	• Comprehensive assessment and documentation is recommended prior to initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. • Screening for opioid use is recommended, despite limited evidence for reliability and accuracy, as it will identify opioid abusers and reduce opioid abuse. • Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. • Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. • Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. Use caution in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. • Patients should be stratified as low, medium, or high risk. • A pain management consult may assist non-pain physicians, if high-dose opioid therapy is utilized. • Establish medical necessity prior to initiation or maintenance of opioid therapy. • Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. • Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain not amenable to short-acting or moderate doses of long-acting opioids, as there is no difference between long-acting and short-acting opioids for their effectiveness or adverse events. • An agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. • Opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid adverse events. • Up to 40 mg of morphine equivalent is considered as low dose, 41 to 90 mg of morphine equivalent as a moderate dose and greater than 91 mg of morphine equivalence as high dose. • In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. • Methadone is recommended for use after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. • Monitoring recommendation for methadone include electrocardiogram prior to initiation, at 30 days and yearly thereafter. • In order to reduce prescription drug abuse and doctor shopping, adherence monitoring by UDT and prescription drug monitoring programs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. • Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary.

Clinical Guideline	Recommendations
	• Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse events.
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[77]	• Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. • Clinicians may consider a trial of chronic opioid therapy as an option for chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. • A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during chronic opioid therapy. • When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy. • Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education. • Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate. • Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids. • Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics, and should be initiated and titrated cautiously, by clinicians familiar with its use and risks. • Clinicians should reassess patients on chronic opioid therapy periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies. • In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • In patients on chronic opioid therapy not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. • Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultations with a mental health or addiction specialist. • Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management, or

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>discontinuation of chronic opioid therapy.
• When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and reassess benefits relative to harms.
• In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.
• Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse events or inadequate benefit despite dose increases.
• Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse events.
• Clinicians should anticipate, identify, and treat common opioid-associated adverse events.
• As chronic non-cancer pain is often a complex biopsychosocial condition, clinicians who prescribe chronic opioid therapy should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies.
• Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment.
• Patients on chronic opioid therapy should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe chronic opioid therapy, but should coordinate consultation and communication among all clinicians involved in the patient's care.
• Clinicians should pursue consultation, including interdisciplinary pain management, when patients with chronic non-cancer pain may benefit from additional skills or resources that they cannot provide.
• In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk.
• Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of chronic opioid therapy during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn.
• Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of chronic opioid therapy for chronic non-cancer pain.</td></tr>
<tr><td></td><td>•</td></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American</td><td>• Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.
• The potential interventions for low back pain are outlined below:
<table>
<tr><th colspan="3">Interventions for the Management of Low Back Pain</th></tr>
<tr><th>Intervention Type</th><th>Acute pain</th><th>Subacute</th></tr>
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Clinical Guideline	Recommendations
Pain Society: **Diagnosis and Treatment of Low Back Pain (2007)**[78]	

		(duration <4 weeks)	or chronic pain (duration >4 weeks)
Self-care	Advice to remain active	Yes	Yes
	Application of superficial heat	Yes	No
	Book, handouts	Yes	Yes
Pharmacologic Therapy	Acetaminophen	Yes	Yes
	Tricyclic antidepressants	No	Yes
	Benzodiazepines	Yes	Yes
	NSAIDs	Yes	Yes
	Skeletal muscle relaxants	Yes	No
	Tramadol, opioids	Yes	Yes
Non-pharmacologic Therapy	Acupuncture	No	Yes
	Cognitive behavior therapy	No	Yes
	Exercise therapy	No	Yes
	Massage	No	Yes
	Progressive relaxation	No	Yes
	Spinal manipulation	Yes	Yes
	Yoga	No	Yes
	Intensive interdisciplinary rehabilitation	No	Yes

Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

- Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
- In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first-line options.
- Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
- Skeletal muscle relaxants are associated with central nervous system effects (primarily sedation).These agents should be used with caution.
- Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance.
- Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs.

Clinical Guideline	Recommendations
	Evidence is insufficient to recommend one opioid over another. • Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution.
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[79]	<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u> • It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> • It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs.

Clinical Guideline	Recommendations
	o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents.

Clinical Guideline	Recommendations
	○ Receive walking aids, as needed. • No recommendation is made regarding the following: ○ Participation in balance exercises, either alone or in combination with strengthening exercises. ○ Participation in tai chi. ○ Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: ○ Acetaminophen. ○ Oral NSAIDs. ○ Tramadol. ○ Intraarticular corticosteroid injections. • It is conditionally recommend that patients with hip osteoarthritis not use the following: ○ Chondroitin sulfate. ○ Glucosamine. • No recommendation is made regarding the use of the following: ○ Topical NSAIDs. ○ Intraarticular hyaluronate injections. ○ Duloxetine. ○ Opioid analgesics.
American Academy of Orthopaedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[80]	<u>Nonpharmacological/surgical therapy</u> • Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. • Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. • Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. • Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. • It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. • Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. <u>Pharmacological therapy</u> • Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol. • There is a lack of compelling evidence to recommend for or against the

Clinical Guideline	Recommendations
	use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. • There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. • There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[81]	<u>Painful polyneuropathy</u> • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <u>PHN</u> • Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies. <u>Trigeminal neuralgia</u> • Recommended first-line treatments include carbamazepine and oxcarbazepine. • Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable adverse events may be prescribed lamotrigine but should also be considered for a surgical intervention. <u>Central pain</u> • Recommended first-line treatments include amitriptyline, gabapentin or pregabalin. • Tramadol may be considered second-line. • Strong opioids are recommended as second- or third-line if chronic treatment is not an issue. • Lamotrigine may be considered in central post-stroke pain or spinal cord injury pain with incomplete cord lesion and brush-induced allodynia and cannabinoids in multiple sclerosis only if all other treatments fail.
American Academy of Neurology/	<u>Anticonvulsants</u>

Clinical Guideline	Recommendations
American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[82]	• If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options • Capsaicin and isosorbide dinitrate spray should be considered for treatment. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options • Percutaneous electrical nerve stimulation should be considered for treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[83]	Neuropathy • All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. • Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. • Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. • Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. • Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. • When treating patients with cardiac autonomic neuropathy, strategies

Clinical Guideline	Recommendations
	appropriate for protection against cardiovascular disease should be utilized. • Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. • Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. • Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[84]	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[85]	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.
European League Against Rheumatism: **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[86]	• Tramadol is recommended for the management of pain in fibromyalgia. • Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. • Corticosteroids and strong opioids are not recommended. • Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. • Tropisetron, pramipexole and pregabalin reduce pain and are recommended for the treatment of fibromyalgia.

Conclusions

Opioids have been the mainstay of pain treatment for a number of years and there is well documented evidence of their effectiveness. Oral morphine sulfate is the standard for comparison for all other opioid agents currently available. Starting in March 2014, all long-acting opioid labels were updated with an indication change. Long-acting opioids are now indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[18] Methadone is the only long-acting opioid to also be FDA-approved for the treatment of opioid addiction (maintenance or detoxification treatment).[5-9]

The current formulations of OxyContin® (oxycodone extended-release), Opana® ER (oxymorphone extended-release), and Embeda® (morphine sulfate/naltrexone) were developed to deter abuse; however, there is no well-documented clinical evidence to demonstrate these formulations prevent abuse.[13,14,16]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which is a Schedule III controlled substance.[1-17] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy for all long-acting opioids which includes the availability of training regarding proper prescribing practices by manufacturers, as well as the distribution of educational materials on the safe use of these agents.[22]

In general, all of the long-acting opioids are similar in terms of associated effectiveness, adverse events, warnings, and contraindications.[1-17] Head-to-head trials demonstrate similar efficacy among the agents in the class, and current clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain.[75-86] Main differences among the individual agents and formulations are due to dosing requirements and generic availability. Several generic long-acting opioids exist, including fentanyl transdermal systems; hydromorphone extended release tablets; methadone extended release tablets, oral solution, and oral concentrate solution; morphine sulfate extended release tablets and capsules; oxycodone extended release tablets; and oxymorphone extended release tablets. Unlike other non-opioid analgesics, full opioid agonists generally have no ceiling for their analgesic effectiveness, except that imposed by adverse events.[20] Even though no true ceiling dose exists, dosing intervals are important with these agents; mainly due to their associated adverse events and risks.[21]

Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[11,16] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[5-9,12] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,14,15,17] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[10]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[17]

Most solid, long-acting opioid formulations (tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-17] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, Embeda®), which can all be opened and the pellets sprinkled on applesauce and then swallowed whole.[10,11,16] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[11] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[10,11,16] It is recommended to only swallow one Zohydro ER®

capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,13-15]

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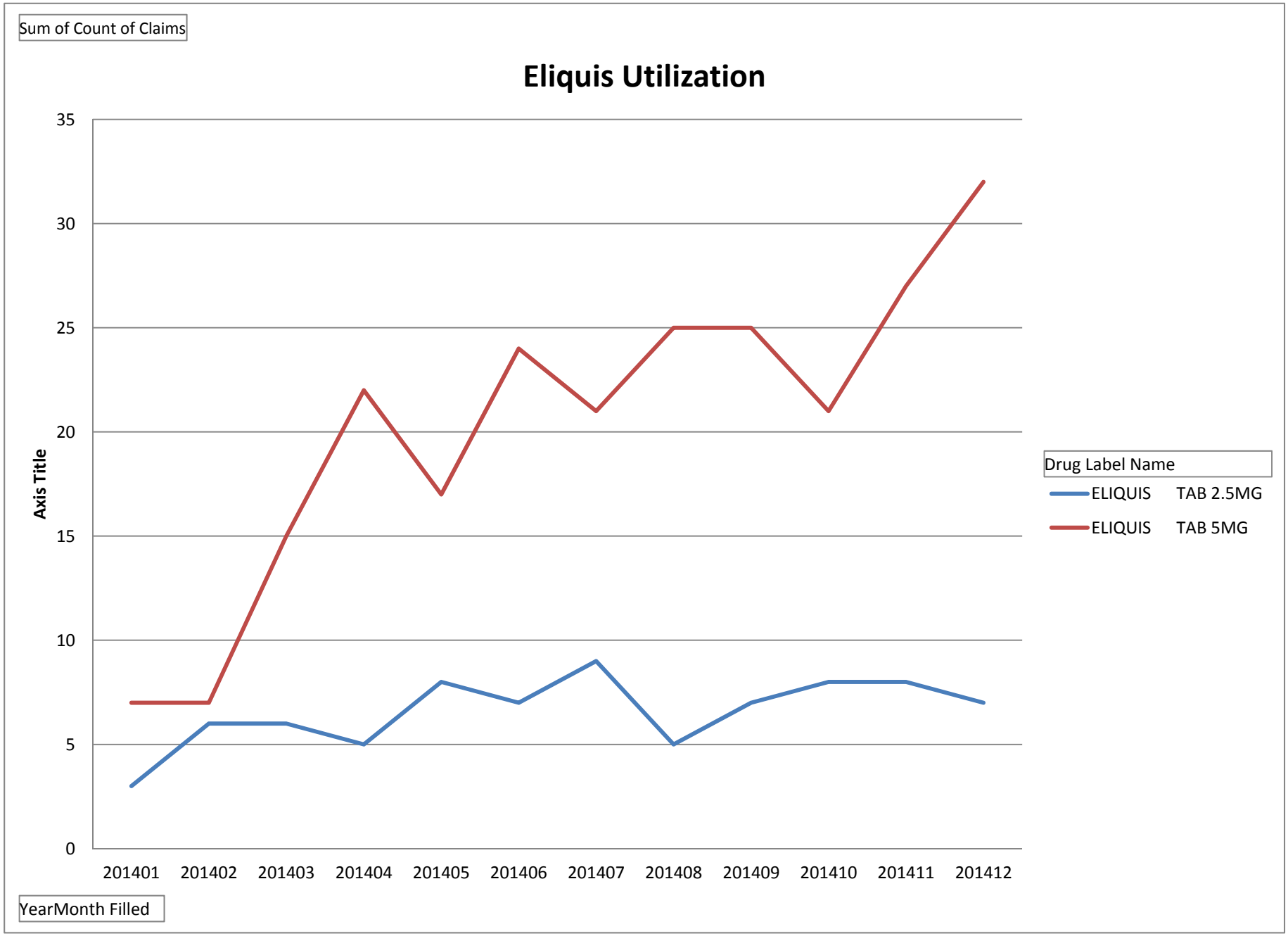
Eliquis Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201401	ELIQUIS TAB 2.5MG	3	3	180	90	$ 285.41
201401	ELIQUIS TAB 5MG	7	7	420	210	$ 297.06
201402	ELIQUIS TAB 2.5MG	6	5	360	180	$ 298.96
201402	ELIQUIS TAB 5MG	7	7	388	194	$ 568.92
201403	ELIQUIS TAB 2.5MG	6	5	360	240	$ 21.60
201403	ELIQUIS TAB 5MG	15	14	960	490	$ 1,517.62
201404	ELIQUIS TAB 2.5MG	5	5	241	121	$ 22.11
201404	ELIQUIS TAB 5MG	22	20	1,256.00	643	$ 3,646.65
201405	ELIQUIS TAB 2.5MG	8	8	392	196	$ 336.51
201405	ELIQUIS TAB 5MG	17	15	749	390	$ 1,694.52
201406	ELIQUIS TAB 2.5MG	7	7	482	241	$ 332.91
201406	ELIQUIS TAB 5MG	24	23	1,650.00	840	$ 3,084.92
201407	ELIQUIS TAB 2.5MG	9	9	570	330	$ 632.45
201407	ELIQUIS TAB 5MG	21	20	1,168.00	599	$ 2,535.83
201408	ELIQUIS TAB 2.5MG	5	5	268	134	$ 319.40
201408	ELIQUIS TAB 5MG	25	25	1,470.00	750	$ 4,271.10
201409	ELIQUIS TAB 2.5MG	7	7	540	330	$ 476.51
201409	ELIQUIS TAB 5MG	25	24	1,830.00	930	$ 4,271.10
201410	ELIQUIS TAB 2.5MG	8	8	720	420	$ 778.76
201410	ELIQUIS TAB 5MG	21	21	1,184.00	607	$ 4,029.05
201411	ELIQUIS TAB 2.5MG	8	7	600	360	$ 1,077.41
201411	ELIQUIS TAB 5MG	27	19	1,189.00	595	$ 4,235.72
201412	ELIQUIS TAB 2.5MG	7	7	510	270	$ 1,121.41
201412	ELIQUIS TAB 5MG	32	30	2,050.00	1,025	$ 4,951.68


Sum of Count of Claims
Eliquis Utilization
35
30
25
20
15
10
5
0
Axis Title
201401
201402
201403
201404
201405
201406
201407
201408
201409
201410
201411
201412
Drug Label Name
ELIQUIS TAB 2.5MG
ELIQUIS TAB 5MG
YearMonth Filled

FF. Pradaxa® (dabigatran etexilate); Eliquis® (apixaban); Xarelto® (rivaroxaban)

Therapeutic Class: Thrombin Inhibitors
Last Reviewed by the DUR Board: July 25, 2013

Pradaxa® (dabigatran etexilate), Eliquis® (apixaban) and Xarelto® (rivaroxaban) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations:

Approval will be given if the following criteria are met and documented.

a. Pradaxa® (dabigatran etexilate)

1. An ICD-9 code for an FDA approved indication for dabigatran is ~~of 427.31 (Atrial Fibrillation)~~ documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient having all of the following and:

a. The recipient has a diagnosis of ~~nonvalvular Atrial Fibrillation~~ for an FDA approved indication for dabigatran;
and

b. The recipient does not have an active pathological bleed; and

c. The recipient does not have a mechanical prosthetic heart valve.

b. Eliquis® (apixaban)

1. An ICD-9 code ~~of 427.31 (Atrial Fibrillation)~~ for an FDA approved indication for apixaban is documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient having all of the following:

a. The recipient has a diagnosis of ~~nonvalvular Atrial Fibrillation~~ an FDA approved indication for apixaban;
and

b. The recipient does not have an active pathological bleed.

c. Xarelto® (rivaroxaban)

1. ~~1.~~ An ICD-9 code ~~of 427.31 (Atrial Fibrillation) or an ICD-9 code beginning with 415.1 (Pulmonary Embolism and Infarction) or an ICD-9 code~~ for an FDA approved indication for rivaroxaban documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient meeting all of the following:

   a. The recipient has a diagnosis for an FDA approved indication for rivaroxaban

   b. The recipient does not have an active pathological bleed.

2. Prior Authorization Guidelines

   a. Prior Authorization approval will be for up to one year.

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

FF. Pradaxa® (dabigatran etexilate); Eliquis® (apixaban); Xarelto® (rivaroxaban)

Therapeutic Class: Thrombin Inhibitors
Last Reviewed by the DUR Board: July 25, 2013

Pradaxa® (dabigatran etexilate), Eliquis® (apixaban) and Xarelto® (rivaroxaban) are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations:

Approval will be given if the following criteria are met and documented.

a. Pradaxa® (dabigatran etexilate)

1. An ICD-9 code of 427.31 (Atrial Fibrillation) documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient having all of the following and:

a. The recipient has a diagnosis of nonvalvular Atrial Fibrillation; and

b. The recipient does not have an active pathological bleed; and

c. The recipient does not have a mechanical prosthetic heart valve.

b. Eliquis® (apixaban)

1. An ICD-9 code of 427.31 (Atrial Fibrillation) documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient having all of the following:

a. The recipient has a diagnosis of nonvalvular Atrial Fibrillation; and

b. The recipient does not have an active pathological bleed.

c. Xarelto® (rivaroxaban)

1. An ICD-9 code of 427.31 (Atrial Fibrillation) or an ICD-9 code beginning with 415.1 (Pulmonary Embolism and Infarction) or an ICD-9 code

beginning with 453.4 (Acute Venous Embolism and Thrombosis of Deep Vessels of Lower Extremity) documented on the prescription and transmitted on the claim; or

2. An approved Prior Authorization documenting the recipient meeting all of the following:

a. The recipient has a diagnosis of nonvalvular Atrial Fibrillation, or Deep Vein Thrombosis (DVT), or Pulmonary Embolism (PE), or treatment is needed for the reduction in the risk of recurrence of the DVT or PE; and

b. The recipient does not have an active pathological bleed.

2. Prior Authorization Guidelines

a. Prior Authorization approval will be for up to one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Oral Anticoagulants

Therapeutic Class

- **Overview/Summary:** Apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for various cardiovascular indications.[1-4] All four agents can be used to manage thromboembolic complications associated with non-valvular atrial fibrillation. Specifically, rivaroxaban and apixaban are also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.[1,3] Rivaroxaban and dabigatran etexilate mesylate have the indication of treatment and reduction in the risk of recurrence of DVT and PE in patients who have previously been treated.[2,3] Warfarin has the unique indication of prophylaxis of thromboembolic complications associated with cardiac valve replacement, prophylaxis and treatment of patients with DVT or PE, and to reduce the risk of recurrent myocardial infarction and thromboembolic events after myocardial infarction.[4] Warfarin, a vitamin K antagonist, has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all FDA-approved indications.[4,5] Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor. While the data for apixaban, dabigatran etexilate mesylate and rivaroxaban are not as substantial as compared to warfarin, the newer oral anticoagulants are associated with several advantages. Unlike warfarin, apixaban, dabigatran etexilate mesylate and rivaroxaban are not associated with a narrow therapeutic window, numerous drug-drug and -food interactions, or monitoring requirements. It has been stated that due to the lack of surrogate markers to measure the efficacy of anticoagulation with the new oral anticoagulants, clinicians may find it difficult to find an objective way to assess a patient's adherence to therapy, and whether a fixed-dose regimen can be universally applied to all patients. Currently, there is no antidote to reverse bleeding with apixaban, dabigatran etexilate mesylate or rivaroxaban.[6,7] Warfarin does not require a dosage adjustment in patients with renal impairment, while a lower dose of apixaban, dabigatran etexilate mesylate and rivaroxaban (atrial fibrillation only) is recommended.[1-4] Moreover, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1] Apixaban and dabigatran etexilate mesylate are approved for twice-daily dosing while rivaroxaban and warfarin are dosed once daily.[1-4] Currently, warfarin is the only oral anticoagulant that is available generically.[8]

Table 1. Current Medications Available in the Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Apixaban (Eliquis®)	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery	Tablet: 2.5 mg 5 mg	-
Dabigatran etexilate mesylate (Pradaxa®)	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation‡; treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days; reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism in patients who have been previously treated	Capsule: 75 mg 150 mg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Rivaroxaban (Xarelto®)	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery; reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation†; treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial six months of treatment for DVT and/or PE§	Tablet: 10 mg 15 mg 20 mg	-
Warfarin (Coumadin®*, Jantoven®*)	Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement; prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism; reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction	Tablet: 1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg	✔

* Generic available in at least one dosage form and/or strength.
† There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
‡ Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
§ Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE

Evidence-based Medicine

- As it has been the principle oral anticoagulant for more than 60 years, the clinical evidence derived from meta-analyses and Cochrane Reviews demonstrating the safety and efficacy of warfarin in Food and Drug Administration-approved indications is well established.[3,9-19]
- The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the AVERROES and ARISTOTLE trials.[20,21]
- In AVERROES (N=5,599), patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with aspirin (1.6 vs 3.7% per year; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.62; *P*<0.001).
    - There was no difference in major bleeding between the apixaban and aspirin treatment groups (*P*=0.57). The incidences of intracranial bleeding (*P*=0.69), extracranial bleeding (*P*=0.42), gastrointestinal bleeding (*P*=0.71), non gastrointestinal bleeding (*P*=0.22) and fatal bleeding (*P*=0.53) were similar between the treatment groups.[20]
- In ARISTOTLE (N=18,201), patients were randomized to receive apixaban 5 mg twice daily or dose-adjusted warfarin (to target an International Normalized Ratio [INR] of 2.0 to 3.0). The incidence of stroke or systemic embolism, the primary endpoint, was significantly reduced in patients treated with apixaban compared to patients treated with warfarin (1.27 vs 1.60% per year; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority).
    - Treatment with apixaban was associated with a significantly lower incidence of major intracranial bleeding (*P*<0.001), and major bleeding at other locations (*P*=0.004) compared to warfarin treatment. There was no difference in the rate of major gastrointestinal bleeding with apixaban compared to warfarin (*P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin treatment groups (*P*=0.37); however, apixaban treatment

significantly reduced death from any cause compared to warfarin treatment (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047).[21]

- Approval of apixaban for use as prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, was established after being compared to enoxaparin in three large, multi-centered, double-blind, double-dummy, randomized control trials: ADVANCE-1, ADVANCE-2, and ADVANCE-3.[22-24]
    - In ADVANCE-1, the statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. DVT, non-fatal PE, and all-cause death occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2 to 2.4; P<0.001).[22]
    - In ADVANCE-2, apixaban was had statistically significant reduction in risk compared to enoxaparin once-daily for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). Absolute risk reduction was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided P<0.0001 for non-inferiority).[23]
    - In ADVANCE-1, There was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053) as opposed to ADVANCE-2, where there was no difference in major bleeding rates between enoxaparin daily and apixaban (P=0.3014).[22,23]
    - In ADVANCE-3 there was a statistically significant reduction in asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause with apixaban 2.5 mg twice dialy compared with enoxaparin 40 mg daily (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The absolute risk reduction with apixaban was 2.5% (95% CI, 1.5% to 3.5%).[24]
- Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence derived from the non inferiority, RE-LY trial (N=18,113). After a median follow-up of two years, dabigatran etexilate mesylate 110 mg twice-daily was associated with a similar rate of stroke and systemic embolism compared to warfarin (*P*=0.34), while dabigatran etexilate mesylate 150 mg twice-daily was associated with a significantly lower rate (*P*<0.001). Rates of major bleeding were similar between warfarin and dabigatran etexilate mesylate 150 mg twice-daily (*P*=0.31) but significantly less with dabigatran etexilate mesylate 110 mg twice-daily (*P*=0.003).[25]
    - No differences were observed between the two treatments with regard to death from any cause and pulmonary embolism (PE); however, the rate of MI was significantly higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization significantly lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[26]
    - A 2012 subgroup analysis of RE-LY demonstrated a nonsignificant increase in MI with dabigatran etexilate mesylate compared to warfarin, but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of dabigatran etexilate mesylate were consistent in patients at higher and lower risk of myocardial ischemic events.[23] In contrast, a meta-analysis published in 2012 demonstrated that dabigatran etexilate mesylate is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute venous thromboembolism [VTE], ACS, short term prophylaxis of deep venous thrombosis [DVT]) compared to different controls (warfarin, enoxaparin, or placebo).[27]
- The RE-COVER study found dabigatran etexilate mesylate to be noninferior to warfarin in preventing recurrent VTE who had presented with acute symptoms of DVT or PE (P<0.001), with the RE-COVER II study also confirming the results (P<0.001).[28,29] Patients who participated in the RE-COVER or RE-COVER II study and received dabigatran etexilate mesylate and had additional risk factors could elect for long term VTE prophylaxis in two follow up studies, RE-MEDY or RE-SONATE. RE-MEDY was and active-control study whereas RE-SONATE was placebo-controlled. Dabigatran

etexilate mesylate was found to be noninferior to warfarin and superior to placebo in long-term VTE prophylaxis (P=0.01 and P<0.001 respectively).[30]

- Approval of rivaroxaban for use in AF was based on the clinical evidence for safety and efficacy derived from the non inferiority, ROCKET-AF trial (N=14,264). Results demonstrated that rivaroxaban (15 or 20 mg/day) is non inferior to warfarin for the prevention of stroke or systemic embolism (*P*<0.001 for non inferiority), with no increased risk of major bleeding (*P*=0.44). Within ROCKET-AF, intracranial and fatal bleeding were significantly less frequent with rivaroxaban (*P*=0.02).[31]
    - In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or transient ischemic attack, it was revealed that the relative efficacy and safety of rivaroxaban compared to warfarin was not different between these two patient populations. Ultimately, results support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent as well as initial stroke in patients with AF.[32]
- Approval of rivaroxaban for prophylaxis of DVT was based on the clinical evidence for safety and efficacy derived from the global program of clinical trials known collectively as RECORD (1 [N=4,541], 2 [N=2,509], 3 [2,531], and 4 [N=3,148]). All four trials compared rivaroxaban to enoxaparin for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries.[33-36]
    - In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin, with no increased risk of major bleeding, any bleeding, and hemorrhagic wound complications.
- The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and PE was based on two open-label, non inferiority trials. In EINSTEIN-DVT, 3,449 patients with an acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg subcutaneously twice daily plus warfarin or acenocoumarol adjusted to maintain an INR of 2.0 to 3.0. The occurrence of symptomatic, recurrent VTE was 2.1% in the rivaroxaban group and 3.0% in the standard therapy group (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority and *P*=0.08 for superiority).[37]
    - Clinically relevant (first major or clinically relevant non major) bleeding was similar between the treatment groups (*P*=0.77). In a 12-month extension, EINSTEIN-EXT, symptomatic, recurrent VTE occurred in eight patients receiving rivaroxaban and 42 patients receiving placebo (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001).[37]
- In 4,832 patients with an acute, symptomatic PE, with or without symptomatic DVT (EINSTEIN-PE), there was a symptomatic recurrence of VTE in 50 patients treated with rivaroxaban compared to 44 patients treated with standard-therapy (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority).[38]
    - There was no difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant non major bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - A recent Science Advisory for Healthcare Professionals by the American Heart Association and American Stroke Association states that the choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range (if taking warfarin). Apixaban, dabigatran etexilate mesylate and rivaroxaban are recommended as an alternative to warfarin in patients with atrial fibrillation and at least one additional risk factor for stroke.[39]
    - Atrial fibrillation:
        -
        - The 2012 American College of Chest Physicians recommends oral anticoagulation in patients at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose vitamin K antagonist therapy.[40]

        - The 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society guideline recommends warfarin, or either apixaban, rivaroxaban or dabigatran as an alternative to warfarin for non-valvular atrial fibrillation. Patients who already have excellent INR control would likely gain little by switching to the newer agents. They recommend not using the newer agents in end-stage chronic kidney disease or on hemodialysis due to lack of evidence regarding the risk versus benefit. A specific recommendation to avoid the use of dabigatran for patients with a mechanical heart valve is also made.[41]
    - Thromboprophylaxis:
        - The 2012 American College of Chest Physicians guideline recommends dabigatran etexilate mesylate, rivaroxaban, and adjusted-dose vitamin K antagonist therapy, along with low molecular weight heparin, fondaparinux, apixaban, low dose unfractionated heparin, aspirin, and an intermittent pneumatic compression device, for thromboprophylaxis in total hip and knee arthroplasty. Low molecular weight heparin is suggested in preference to other recommended agents for this indication.[40]
        - In general, other current guidelines are in line with the American College of Chest Physicians.
    - Secondary prevention in post-myocardial infarction:[40,42,43]
        - Warfarin is recommended in post-myocardial infarction patients who have an indication for anticoagulation; however, the evidence surrounding its use in these patients is still evolving.
- Other Key Facts:
    - Rivaroxaban for use in atrial fibrillation:[3]
        - The approved package labeling for rivaroxaban acknowledges the low percentage of "time in International Normalized Ratio range" for patients randomized to warfarin within the ROCKET-AF trial as compared to other clinical trials, and states that it is unknown how rivaroxaban compares when patients are well controlled on warfarin.
        - Within the ROCKET-AF trial, an increased incidence of adverse clinical events were noted when patients were transitioned off of rivaroxaban to warfarin or to another vitamin K antagonist.
    - The prescribing information for apixaban, dabigatran and rivaroxaban contain a Black Box Warning regarding an increased risk of thromboembolic events following the discontinuation of treatment.[1-3]
    - Apixaban has demonstrated a significant reduction in the risk of stroke and systemic embolism, major bleeding and all-cause mortality compared to warfarin in patients with atrial fibrillation.[21]
    - Dabigatran etexilate mesylate 150 mg has demonstrated a significant reduction in the risk of stroke and systemic embolism compared to warfarin in patients with atrial fibrillation; the risk of major bleeding and all-cause mortality was similar between treatments.[25]
    - Rivaroxaban was non inferior to warfarin with regard to the reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation (per-protocol analysis) with a similar incidence of major bleeding.[31]
    - All three new oral anticoagulants are associated with a significant reduction in intracranial hemorrhage compared to warfarin.[21,25,31]
    - Warfarin is available generically.[8]

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Therapeutic Class Review
Oral Anticoagulants

Overview/Summary

Apixaban (Eliquis®) dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®) are oral anticoagulants that are Food and Drug Administration (FDA)-approved for the various cardiovascular indications outlined in Table 2.[1-4] Warfarin, has been the principle oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy in all of its FDA-approved indications.[5-7] Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran etexilate mesylate is a direct thrombin inhibitor (DTI). All are novel oral anticoagulants that are approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-3] Rivaroxaban and apixaban are also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.[1,3] Rivaroxaban and dabigatran etexilate mesylate have the indication of treatment and reduction in the risk of recurrence of DVT and PE in patients who have previously been treated.[2,3]

Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors and anticoagulant proteins C and S. Specifically, warfarin inhibits the vitamin K epoxide reductase enzyme complex, resulting in the blockade of the regeneration of vitamin K_1 epoxide.[4-7] Conversely, the new oral anticoagulants target a single enzyme involved in the coagulation cascade. Dabigatran etexilate mesylate is a prodrug that is converted to dabigatran, a potent, competitive inhibitor of thrombin. As a DTI, dabigatran inhibits the conversion of fibrinogen into fibrin; thereby, inhibiting the development of a thrombus. Both free and fibrin-bound thrombin and thrombin-induced platelet aggregation are inhibited by dabigatran etexilate mesylate.[2,6,7] Apixaban and rivaroxaban both selectively inhibit factor Xa, thereby preventing the generation of thrombin and ultimately preventing platelet activation and the formation of fibrin clots.[1,3,6,7] Warfarin is available generically while apixaban, dabigatran etexilate mesylate and rivaroxaban are branded oral anticoagulants.[8]

The evidence demonstrating the efficacy of warfarin for FDA-approved indications, including reducing the risk of stroke and systemic embolism in patients with AF, is well established, and warfarin has been considered the standard of care in high-risk patients with AF.[9] Warfarin therapy is associated with several challenges including a slow onset and offset of action, significant and unpredictable inter-individual variability in pharmacologic response, a narrow therapeutic window necessitating frequent monitoring and numerous food and drug interactions. Moreover, maintenance of a therapeutic level of anticoagulation may be difficult for some patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.[5,10,11] In comparison to warfarin, treatment with apixaban, dabigatran etexilate mesylate or rivaroxaban does not require routine monitoring, but clinicians may discover it difficult to find an objective way to assess a patient's adherence to therapy, and whether a fixed-dose regimen can be universally applied to all patients. Apixaban and dabigatran etexilate mesylate require twice-daily dosing compared to rivaroxaban and warfarin which are administered once daily.[1-4] Warfarin does not require a dosage adjustment in patients with renal impairment, while a lower dose of apixaban, dabigatran etexilate mesylate and rivaroxaban (in AF only) is recommended.[1-4] Moreover, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1] In situations where a major bleed occurs, no specific antidote is currently available for the new oral anticoagulants.[11] The overall bleeding risk appears to be comparable overall between apixaban and aspirin. Clinical trials comparing apixaban to warfarin have demonstrated a lower incidence of major intracranial bleeding and major bleeding at other locations with apixaban, with a similar incidence of gastrointestinal bleeding.[1,12] In clinical trials, warfarin was associated with more intracranial bleeding, while dabigatran etexilate mesylate was associated with more gastrointestinal bleeding.[2,13] In the clinical trial that was the basis for FDA-approval of dabigatran etexilate mesylate, the incidence of myocardial infarction (MI) was higher with dabigatran etexilate mesylate compared to warfarin.[15] Whether or not this is a true risk associated with the agent is unclear; however, a subanalysis of the trial did not demonstrate an increase in MI with either dose of dabigatran etexilate

mesylate compared to warfarin.[14] In the trial that was the basis for FDA-approval of rivaroxaban for use in AF, there was no difference in major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin, but like dabigatran etexilate mesylate, rivaroxaban and apixaban were associated with a lower risk of intracranial bleeding. Rivaroxaban had a higher incidence of gastrointestinal bleeding, while apixaban had similar rates, compared to warfarin.[12,32] In clinical trials for DVT prophylaxis, rivaroxaban and apixaban demonstrated a comparable bleeding profile to enoxaparin, a low molecular weight heparin (LMWH) agent; enoxaparin dosed once daily was associated with similar rates of major bleeding and hemorrhagic wound complications when compared to either rivaroxaban or apixaban.[16-19,63,64] However, when apixaban was compared to twice daily enoxaparin, there was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053).[62] In trials evaluating the use of rivaroxaban for treatment of DVT and PE and for the reduction in the risk of recurrence, there were comparable rates of clinically relevant bleeding between patients receiving rivaroxaban or standard therapy with enoxaparin.[20,21]

The current clinical guidelines support the use of the oral anticoagulants for their respective FDA-approved indications.[22-31] The American College of Chest Physicians and The American College of Cardiology/The American Heart Association/Heart Rhythm Society and published updated guidelines in 2012 and 2014 respectively regarding antithrombotic therapy and prevention of thrombosis. With regards to management of AF, oral anticoagulation is recommended in patients at intermediate to high risk of stroke.[9,22] Depending on indication, warfarin has the strongest level of evidence, followed by either dabigatran etexilate mesylate, rivaroxaban, or apixaban. [9] A 2012 Science Advisory for Healthcare Professionals by the American Heart Association and American Stroke Association regarding the use of oral anticoagulants states that the choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range (if taking warfarin). Apixaban, dabigatran etexilate mesylate and rivaroxaban are all recommended as an alternative to warfarin in patients with AF and at least one additional risk factor for stroke.[31]

Apixaban, dabigatran etexilate mesylate, rivaroxaban, and adjusted-dose VKA therapy are recommended, along with LMWH, fondaparinux, apixaban, low dose unfractionated heparin, aspirin, and an intermittent pneumatic compression device, for thromboprophylaxis in total hip and knee arthroplasty. According to the American College of Chest Physicians, LMWH is suggested in preference to other recommended agents for this indication. For patients who decline or who are uncooperative with injections or intermittent pneumatic compression devices, apixaban or dabigatran etexilate mesylate is recommended over alternative forms of thromboprophylaxis, with rivaroxaban or adjusted-dose VKA therapy recommended if these two therapies are unavailable. Parenteral anticoagulation (LMWH, fondaparinux, or unfractionated heparin) is recommended for a minimum of five days for the treatment of acute DVT or PE, with the addition of early initiation of VKA therapy. The duration of anticoagulation after treatment of an acute event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor and if it was the first or second thromboembolic event.[22]

For secondary prevention in post-MI patients, the American College of Cardiology recommends the use of warfarin in aspirin-allergic patients who have an indication for anticoagulation. Depending on whether a patient is allergic to aspirin or a stent is implanted, warfarin may also be appropriate as combination therapy with aspirin or clopidogrel in post-MI patients. The American College of Cardiology recommends that post-MI patients with persistent or paroxysmal AF receive warfarin, and therapy with warfarin is recommended if evidence of a thrombus is present following an MI. For this indication, warfarin therapy may last at least three months or indefinitely, depending on the patient's risk of bleeding. Despite these recommendations, the role of long-term warfarin therapy in post-MI patients remains controversial, and aspirin remains the preferred antithrombotic.[23,24] The American College of Chest Physicians also provides recommendations for the use of warfarin in this indication, particularly for use as triple therapy with low dose aspirin and clopidogrel in patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who underwent bare-metal or drug-eluting stent placement.[22]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Apixaban (Eliquis®)	Oral anticoagulant	-
Dabigatran etexilate mesylate (Pradaxa®)	Oral anticoagulant	-
Rivaroxaban (Xarelto®)	Oral anticoagulant	-
Warfarin (Coumadin®*, Jantoven®*)	Oral anticoagulant	✔

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-4]

Indication	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement				✔
Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism				✔
Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery	✔		✔	
Reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction				✔
Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation	✔	✔ †	✔ *	
Treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism in patients who have been previously treated		✔	✔ ‡	

*There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.

Apixaban and dabigatran etexilate mesylate has been evaluated for the prevention of venous thromboembolism following arthroplasty of the knee and total hip replacement but are not currently Food and Drug Administration-approved for this indication.[10] Rivaroxaban is currently being evaluated for the treatment acute coronary syndromes. [6,7]

Pharmacokinetics

Table 3. Pharmacokinetics[1-4,6,7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Apixaban	50	27	None	12
Dabigatran etexilate mesylate	3 to 7	80*	Dabigatran (major); 1-, 2-, 3-, 4-O-acylglucuronide (all minor)	12 to 17
Rivaroxaban	80 to 100	66	None	5 to 9
Warfarin	≈100	92	Warfarin alcohols	168

*Intravenous administration.

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the oral anticoagulants in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[12-21,32-64] As it has been the principle oral anticoagulant for more than 60 years, the evidence demonstrating the safety and efficacy of warfarin in FDA-approved indications is well established. Because of this, only meta-analyses and Cochrane Reviews evaluating warfarin are included within this review.

The efficacy of apixaban in patients with nonvalvular atrial fibrillation (AF) was evaluated in the Apixaban vs Acetylsalicylic Acid to Prevent Strokes (AVERROES) trail and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE). AVERROES (N=5,599) was a double-blind, multicenter, randomized controlled trial in which patients were randomized to receive apixaban 5 mg twice daily or aspirin 81 to 324 mg once daily. A dose of 2.5 mg twice daily was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL. Patients were ≥50 years of age with AF for at least six months or documented by 12-lead electrocardiogram (EGG) plus at least one of the following risk factors: prior stroke or transient ischemic attack (TIA), age ≥75, arterial hypertension, diabetes mellitus, heart failure (New York Heart Association [NYHA] Class ≥2), a left ventricular ejection fraction (LVEF) ≤35% or peripheral artery disease. The incidence of stroke or systemic embolism, the primary endpoint, was significantly lower in patients treated with apixaban compared to patients treated with aspirin (1.6 vs 3.7% per year; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.62; *P*<0.001). There was no statistically significant difference in the incidence of major bleeding between the apixaban and aspirin groups (1.4 vs 1.2% per year, respectively; HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57). The incidence of intracranial bleeding (0.4 vs 0.4% per year; *P*=0.69), extracranial bleeding (1.1 vs 0.9% per year; *P*=0.42), gastrointestinal bleeding (0.4 vs 0.4% per year; *P*=0.71), nongastrointestinal bleeding (0.6 vs 0.4% per year; *P*=0.22) or fatal bleeding (0.1 vs 0.2% per year; *P*=0.53) was not significantly different between the apixaban and aspirin groups.[32]

In ARISTOTLE (N=18,201), a large, double-blind, multicenter, randomized controlled trial, patients with AF or flutter and at least one additional risk factor for stroke were randomized to receive apixaban 5 mg twice daily or dose-adjusted warfarin (to target an International Normalized Ratio [INR] of 2.0 to 3.0). A dose of 2.5 mg twice daily was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL. The incidence of stroke or systemic embolism, the primary endpoint, was significantly lower in patients treated with apixaban compared to patients treated with warfarin (1.27 vs 1.60% per year; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority). Apixaban treatment was associated with a significantly lower incidence of major intracranial bleeding (0.33 vs 0.80% per year; HR, 0.42; 95% CI, 0.30 to 0.58; *P*<0.001), and major bleeding at other locations (1.79 vs 2.27% per year; HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin treatment. There was a similar incidence of major gastrointestinal bleeding between treatments (0.76 vs 0.86% per year, respectively; HR, 0.89; 0.70 to 1.15; *P*=0.37). The rate of myocardial infarction (MI) was similar between the apixaban and warfarin groups (0.53 vs 0.61% per year, respectively; HR, 0.88; 95% CI, 0.66 to 1.17; *P*=0.37). Apixaban treatment was associated with a significantly lower incidence of death from any cause (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to

0.998; *P*=0.047) compared to warfarin treatment; a benefit that has not been demonstrated with either dabigatran etexilate mesylate or rivaroxaban.[12] Several subgroup analysis stratifying patients by differences in previous stroke status; different $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores; and previous warfarin use all found no significantly different results among these different patient groups.[35,36,59]

Approval of apixaban for use as prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, was established after being tested in three studies: ADVANCE-1, ADVANCE-2, and ADVANCE-3. They were all large, multi-centered, double-blind, double-dummy randomized controlled trials which compared apixaban 2.5 mg twice daily to enoxaparin. Patients in ADVANCE-1 and ADVANCE-2 evaluated apixaban in knee replacement, while ADVANCE-3 evaluated apixaban in hip replacement.[61-63] In ADVANCE-1, the statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. DVT, non-fatal PE, and all-cause death occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (relative risk [RR], 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2 to 2.4; P<0.001).[62] In ADVANCE-2, apixaban was had statistically significant reduction in risk compared to enoxaparin for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). Absolute risk reduction was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided P<0.0001 for non-inferiority).[63] Also of note, there was a statistically significant increase in major and non-major bleeding for twice daily enoxaparin 30 mg compared to apixaban (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053) as opposed to no difference in major bleeding rates between enoxaparin daily and apixaban (P=0.3014).[62,63] Results from ADVANCE-3 showed that there was a statistically significant reduction in asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause with apixaban 2.5 mg BID compared with enoxaparin 40 mg daily (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The absolute risk reduction with apixaban was 2.5% (95% CI, 1.5% to 3.5%).[64]

Approval of dabigatran etexilate mesylate for use in AF was based on the clinical evidence for safety and efficacy derived from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (N=18,113). The RE-LY trial was a non inferiority, multicenter, randomized, parallel-group trial comparing two blinded doses of dabigatran etexilate mesylate (110 and 150 mg twice daily) with open-label warfarin in patients with nonvalvular, persistent, paroxysmal, or permanent AF. Patients enrolled in the RE-LY trial also had at least one of the following risk factors: previous stroke, TIA or systemic embolism; LVEF <40%; symptomatic heart failure, NYHA Class ≥2; age >75 or age ≥65 plus diabetes, coronary artery disease, or hypertension. For the primary composite endpoint, occurrence of stroke and systemic embolism, both doses of dabigatran etexilate mesylate demonstrated non inferiority to warfarin (*P*<0.001). Specifically, the primary endpoint occurred at a rate of 1.53% per year (RR, 0.91; 95% CI, 0.74 to 1.11; *P*=0.34) and 1.10% per year (RR, 0.66; 95% CI, 0.53 to 0.82; *P*<0.001) for dabigatran etexilate mesylate 110 and 150 mg compared to 1.69% per year with warfarin. The 150 mg dose of dabigatran etexilate mesylate achieved “superiority” over warfarin; however, the 110 mg dose did not. The treatment effect observed with dabigatran etexilate mesylate was primarily a reduction in the incidence of stroke. The rate of major bleeding (life-threatening, non-life-threatening, and gastrointestinal bleeding) was also reduced with dabigatran etexilate mesylate compared to warfarin (dabigatran etexilate mesylate 110 mg: RR, 0.80; 95% CI, 0.69 to 0.93; P=0.003; dabigatran etexilate mesylate 150 mg: RR, 0.93; 95% CI, 0.81 to 1.07; *P*=0.31). No significant differences were observed between dabigatran etexilate mesylate and warfarin in regard to the rate of death from any cause and pulmonary embolism (PE). However, the rate of MI was higher (*P*=0.048 with dabigatran etexilate mesylate 150 mg vs warfarin) and the rate of hospitalization was lower (*P*=0.003 with dabigatran etexilate mesylate 110 mg vs warfarin) with dabigatran etexilate mesylate.[13] Several subgroup analyses of the RE-LY trial have been published.[14,37-39] In one analysis, it was revealed that previous exposure to a vitamin K antagonist does not influence the benefits of dabigatran etexilate mesylate compared to warfarin.[37] Another revealed that the effects of dabigatran etexilate mesylate in patients with a previous stroke or TIA are consistent with those of other patients in the RE-LY trial.[38] A 2012 subgroup analysis demonstrated a nonsignificant increase in MI with dabigatran etexilate mesylate compared to warfarin, but other myocardial ischemic events were not increased. In

addition, results revealed that treatment effects of dabigatran etexilate mesylate were consistent in patients at higher and lower risk of myocardial ischemic events.[14] A meta-analysis published in 2012 demonstrated that dabigatran etexilate mesylate is associated with an increased risk of MI or acute coronary syndrome (ACS) in a broad spectrum of patients (e.g., stroke prophylaxis in AF, acute venous thromboembolism [VTE], ACS, short term prophylaxis of deep venous thrombosis [DVT] compared to different controls (warfarin, enoxaparin or placebo).[56] The RE-COVER study found dabigatran etexilate mesylate to be noninferior to warfarin in preventing recurrent VTE who had presented with acute symptoms of DVT or PE, with the RE-COVER II study also confirming the results.[60,61] Patients who participated in the RE-COVER or RE-COVER II study and received dabigatran etexilate mesylate and had additional risk factors could elect for long term VTE prophylaxis in two follow up studies, RE-MEDY or RE-SONATE. RE-MEDY was and active-control study whereas RE-SONATE was placebo-controlled. Dabigatran etexilate mesylate was found to be noninferior to warfarin and superior to placebo in long-term VTE prophylaxis.[61]

In terms of the evidence demonstrating the efficacy of dabigatran etexilate mesylate for the prevention of stroke and systemic embolization in patients with nonvalvular AF, a phase II, randomized controlled trial was conducted to determine whether a dose-related incidence of bleeding was to be expected with the administration of the agent, and to determine what doses should be used in future clinical trials for further evaluation. This 12-week trial established a dose response for bleeding and an upper limit of tolerability (300 mg twice daily plus aspirin) for dabigatran etexilate mesylate based on the frequency of major and clinically significant bleeding events.[45] Of note, the FDA-approved dosing for dabigatran etexilate mesylate in patients with adequate renal function is 150 mg twice-daily.[2]

Approval of rivaroxaban for use in AF was based on results from the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared to Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) in which 14,264 patients with nonvalvular AF who were considered to be at increased risk for stroke were enrolled. Patients received rivaroxaban 20 mg once daily (or 15 mg once daily in patients with renal impairment) or dose-adjusted warfarin (to target an INR of 2.0 to 3.0). The primary endpoint, a composite of stroke or systemic embolism in the per-protocol population, occurred in 188 patients (1.7% per year) with rivaroxaban and 241 patients (2.2% per year) with warfarin (HR, 0.79; 95% CI, 0.66 to 0.96; $P<0.001$ for non inferiority). The results from the intention-to-treat population did not achieve "superiority" ($P=0.12$).[15] Package labeling for rivaroxaban acknowledges the low percentage of "time in INR range" for patients randomized to warfarin as compared to other clinical trials, and states that is it unknown how rivaroxaban compares to warfarin when patients are well controlled on warfarin.[2] There was no difference in the rate of major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin (14.9 and 14.5% per year, respectively; HR, 1.03; 95% CI, 0.96 to 1.11; $P=0.44$). Rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.5 vs 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; $P=0.02$); however, the rate of major bleeding from a gastrointestinal site was significantly higher with rivaroxaban (3.2 vs 2.2%; $P<0.001$) compared to warfarin.[15] In a subgroup analysis of ROCKET-AF evaluating the efficacy and safety of rivaroxaban among patients with and without previous stroke or TIA, it was revealed that the relative efficacy and safety of rivaroxaban compared to warfarin was not different between these two patient populations. Ultimately, results support the use of rivaroxaban as an alternative to warfarin for the prevention of recurrent as well as initial stroke in patients with AF.[43]

Approval of rivaroxaban for prophylaxis of DVT was based on the results of the Regulation in Orthopedic Surgery to Prevent Deep Vein thrombosis and Pulmonary Embolism (RECORD) trials. The RECORD program consists of four individual trials (RECORD1, 2, 3 and 4) evaluating the safety and efficacy of rivaroxaban for thromboprophylaxis in patients undergoing total elective hip and knee replacement surgeries. Primary and secondary endpoints were similar among the four trials and major bleeding was defined as bleeding that was fatal, involved a critical organ or required reoperation, clinically overt bleeding outside the surgical site that was associated with a decrease in the hemoglobin level of at least 2 g/dL, or a bleed requiring an infusion of two units or more of blood.[16-19]

RECORD1 (N=4,541) and RECORD2 (N=2,509) were two, double-blind, multicenter, randomized controlled trials evaluating rivaroxaban for thromboprophylaxis in patients undergoing hip replacement surgery. Both trials compared rivaroxaban 10 mg once daily to enoxaparin 40 mg once daily. In RECORD1 rivaroxaban and enoxaparin were both administered for 35 days, while in RECORD2 rivaroxaban was administered for 31 to 39 days (extended thromboprophylaxis) and enoxaparin for 10 to 14 days.[16,17] In RECORD1, the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause up to 36 days was significantly reduced with rivaroxaban compared to enoxaparin (1.1 vs 3.7%; absolute risk reduction [ARR], -2.6%; 95% CI, -3.7 to -1.5; *P*<0.001). Treatment with rivaroxaban also significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to -1.0; *P*<0.001).[16] Rivaroxaban had no beneficial effect on all-cause mortality (on-treatment: 0.3 vs 0.3%; *P*=1.00, follow-up: 0.1 vs 0.0%; *P*=1.00). The rate of major bleeding was similar between rivaroxaban and enoxaparin (0.3 vs 0.1%; *P*=0.18). In addition, rivaroxaban and enoxaparin had similar rates of any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and hemorrhagic wound complications (1.5 vs 1.7%; *P* value were not reported).[16] In RECORD2, rivaroxaban significantly reduced the risk of the primary composite endpoint up to 30 to 42 days (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). In this trial, the risk of major VTE was significantly reduced with rivaroxaban (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban demonstrated no beneficial effects on all-cause mortality (0.2 vs 0.7%; *P*=0.29). Similar to RECORD1, there were no differences between rivaroxaban and enoxaparin in the rates of major bleeding, any on-treatment nonmajor bleeding, and hemorrhagic wound complications (*P* values not reported).[17]

Rivaroxaban for thromboprophylaxis in patients undergoing knee replacement surgery was evaluated in RECORD3 (N=2,531) and RECORD4 (N=3,148). Both were double-blind, multicenter, randomized controlled trials. The trials compared rivaroxaban 10 mg once daily to either enoxaparin 40 mg once daily (RECORD3) or 30 mg twice daily (RECORD4) for 10 to 14 days. Again, all primary and secondary endpoints were similar to RECORD1 and RECORD2. Furthermore, results from all four trials were consistent.[18,19] In RECORD3, rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin up to 17 days (9.6 vs 18.9%; absolute risk difference [ARD], -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). Rivaroxaban also significantly reduced the rate of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01) and was not associated with any mortality benefit (*P*=0.21). The rates of major bleeding (*P*=0.77) and any on-treatment bleeding (*P*=0.93) were similar between rivaroxaban and enoxaparin, as well as the rate of hemorrhagic wound complications (*P* value not reported).[14] RECORD4 demonstrated similar results, except in this trial, there was no difference between rivaroxaban and enoxaparin in the rate of major VTE (*P*=0.1237).[19]

The approval of rivaroxaban for the treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE was based on the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis (EINSTEIN-DVT) trial and the Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism (EINSTEIN-PE) trial. In EINSTEIN-DVT, 3,449 patients with an acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily thereafter or enoxaparin 1 mg/kg subcutaneously (SC) twice daily plus warfarin or acenocoumarol adjusted to maintain an INR of 2.0 to 3.0. The occurrence of symptomatic, recurrent VTE was 2.1% in patients receiving rivaroxaban compared to 3.0% of patients receiving standard therapy (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for noninferiority and *P*=0.08 for superiority). The occurrence of clinically relevant (first major or clinically relevant nonmajor) bleeding was similar between the treatment groups (HR, 0.97; 95% CI, 0.76 to 1.22; *P*=0.77). In a 12-month extension study, EINSTEIN-EXT, symptomatic, recurrent VTE occurred in eight patients receiving rivaroxaban and 42 patients receiving placebo (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001).[20] In 4,832 patients with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT (EINSTEIN-PE), there was a symptomatic recurrence of VTE in 50 patients treated with rivaroxaban compared to 44 patients treated with standard therapy (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for noninferiority and *P*=0.57 for superiority). There was no statistically significant difference between the rivaroxaban and standard therapy treatment groups with regard to major or clinically relevant nonmajor bleeding (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23).[21]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Reducing the Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation				
Connolly et al[32] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, MC, PG, RCT Patients ≥50 years of age with AF for at least six months before enrollment or documented by 12-lead ECG on the day of screening and at least one of the following risk factors: prior stroke or TIA, age ≥75, arterial hypertension, diabetes mellitus, heart failure (NYHA Class ≥2), a LVEF ≤35%, or peripheral artery disease Patients could not be receiving VKA therapy because it had already been unsuitable for them or was expected to be unsuitable.	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composite of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients randomized to receive treatment with apixaban compared to treatment with aspirin (1.6 vs 3.7% per year; HR, 0.45; 95% CI, 0.32 to 0.62; *P*<0.001). The incidence of ischemic stroke was significantly lower in the apixaban treatment group (1.1 vs 3.0% per year; HR, 0.37; 95% CI, 0.25 to 0.55; *P*<0.001); however, there was no difference between the groups with regard to hemorrhagic stroke (0.2 vs 0.3% per year, respectively; HR, 0.67; 95% CI, 0.24 to 1.88; *P*=0.45). There was no statistically significant difference in the incidence of major bleeding in the apixaban treatment group compared to the aspirin treatment group (1.4 vs 1.2% per year, respectively; HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57). The incidences of intracranial bleeding (0.4 vs 0.4% per year; *P*=0.69), extracranial bleeding (1.1 vs 0.9% per year; *P*=0.42), gastrointestinal bleeding (0.4 vs 0.4% per year; *P*=0.71), nongastrointestinal bleeding (0.6 vs 0.4% per year; *P*=0.22) and fatal bleeding (0.1 vs 0.2% per year; *P*=0.53) were not significantly different between the apixaban and aspirin treatment groups. Secondary: The incidence of MI was similar between the apixaban and aspirin treatment groups (0.8 vs 0.9% per year, respectively; HR, 0.86; 95% CI, 0.50 to 1.48; *P*=0.59). The incidence of death from vascular causes (2.7 vs 3.1% per year, respectively; HR, 0.87; 95% CI, 0.65 to 1.17; *P*=0.37) or death from any cause (3.5 vs 4.4% per year; HR, 0.79; 95% CI, 0.62 to 1.02; *P*=0.07) was not significantly different between patients receiving apixaban or aspirin. The composite rate of stroke, systemic embolism, MI, death from vascular causes or major bleeding was significantly lower in the apixaban group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to the aspirin group (ITT, 5.3 vs 7.2% per year; HR, 0.74; 95% CI, 0.60 to 0.90; *P*=0.003; on-treatment analysis, 4.0 vs 6.3% per year; HR, 0.64; 95% CI, 0.51 to 0.80; *P*<0.001). Treatment with apixaban significantly reduced the incidence of hospitalization for cardiovascular causes compared to treatment with aspirin (12.6 vs 15.9% per year; HR, 0.79; 95% CI, 0.69 to 0.91; *P*<0.001). The rate of clinically relevant nonmajor bleeding (3.1 vs 2.7% per year; HR, 1.15; 95% CI, 0.86 to 1.54; *P*=0.35) and minor bleeding (6.3 vs 5.0% per year; HR, 1.24; 95% CI, 1.00 to 1.53; *P*=0.50) was similar between the apixaban and aspirin treatment groups.
Diener et al[33] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Suanalysis of AVERROES[32] Patients enrolled in the AVERROES trial stratified based on previous stroke and TIA	N=5,599 1.1 years	Primary: Incidence of stroke (ischemic or hemorrhagic) or systemic embolism and major bleeding Secondary: Rates of MI, death from vascular causes, death from any cause and composites of major vascular events	Primary: The incidence of stroke or systemic embolism was significantly lower in patients with no previous stroke or TIA compared to patients with a history of stroke or TIA (2.36 vs 5.73% per year; HR, 2.38; 95% CI, 1.66 to 3.34; *P*<0.0001). There was a significantly lower incidence of stroke or systemic embolism with apixaban treatment compared to aspirin treatment in those without previous stroke or TIA (HR, 0.51; 95% CI, 0.35 to 0.74) and in those with a previous stroke or TIA (HR; 0.29; 95% CI, 0.15 to 0.60); however, the difference between the groups was not statistically significant (*P*=0.17). The incidence of major bleeding was not significantly different between the apixaban and aspirin treatment groups, regardless of previous stroke or TIA history (*P*=0.73). Secondary: There was no significant difference between apixaban and aspirin treatment with regard to the incidence of MI. Moreover, the difference in MI between patients with a history of stroke or TIA and those without a history of stroke or TIA was not statistically significant (*P*=0.33). There was no significant difference between the apixaban and aspirin treatment groups in the incidence of death from vascular causes, regardless

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of previous stroke history (*P*=0.79). There was no statistically significant difference between the apixaban and aspirin treatment groups with regard to the incidence of stroke (*P*=0.26), ischemic or unspecified stroke (*P*=0.36), hemorrhagic stroke (*P*=0.25), disabling or fatal stroke (*P*=0.32) or death from any cause (*P*=0.89) between patients with and without a prior history of stroke or TIA. Similarly, no significant differences in intracranial bleeding (*P*=0.92), extracranial or unclassified bleeding (*P*=0.49) or gastrointestinal bleeding (*P*=0.89) were observed between the groups with regard to prior stroke or TIA history.
Flaker et al[34] AVERROES Apixaban 5 mg BID vs aspirin 81 to 324 mg QD An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of AVERROES[32] Patients enrolled in the AVERROES trial who experienced bleeding during the treatment period	N=5,599 1.1 years	Primary: Major bleeding and clinically relevant nonmajor bleeding Secondary: Not reported	Primary: There were 44 major hemorrhages in the apixaban group and 39 in the aspirin group. There were 96 clinically relevant nonmajor hemorrhages in the apixaban group and 84 in the aspirin group. Three patients in the apixaban group and seven patients in the aspirin group had both severities of bleeding. There was a similar incidence of major bleeding (HR, 1.13; 95% CI, 0.74 to 1.75; *P*=0.57), clinically relevant nonmajor bleeding (HR, 1.15; 95% CI, 0.86 to 1.54; *P*=0.35) and major or clinically relevant nonmajor bleeding (HR, 1.18; 95% CI, 0.92 to 1.51; *P*=0.19) between the apixaban and aspirin treatment groups. Of patients who experienced bleeding during the treatment with apixaban and aspirin, respectively, the incidence of major intracranial bleeding (0.35 vs 0.41% per year; *P*=0.69), gastrointestinal bleeding (0.35 vs 0.45% per year; *P*=0.56), and surgical or trauma bleeding (0.19 vs 0.16% per year; *P*=0.75) was not significantly different between the groups. With regard to major or clinically relevant nonmajor bleeding, there was no statistically significant difference between apixaban and aspirin at any site of bleeding (*P*>0.05 for all). The independent predictors of major and clinically relevant nonmajor

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				bleeding that were significantly different between those treated with apixaban and aspirin were the use of nonstudy aspirin >50% of the time (*P*=0.02 for both treatments) and a history of daily/occasional nosebleeds (*P*=0.02 and *P*=0.01, respectively). There were no significant differences in major and clinically relevant nonmajor bleeding when patients were stratified by age, sex, body mass index, study dose of aspirin, or estimated glomerular filtration rate (*P* values not reported). Secondary: Not reported
Granger et al[12] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	AC, DB, DD, MC, NI, RCT Patients with AF or flutter at baseline or two or more episodes of AF or flutter, as documented by ECG at least two weeks apart in the 12 months before enrollment and at least one of the following risk factors for stroke age ≥75, previous stroke, TIA, systemic embolism, symptomatic heart failure within previous three months or LVEF ≤40% and	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, rate of MI, composite of stroke, systemic embolism or death from any cause, composite of stroke, systemic embolism, MI or death from any cause, composite of PE or DVT, major bleeding or clinically relevant nonmajor bleeding, any bleeding and adverse events	Primary: Stroke or systemic embolism occurred in 212 patients treated with apixaban and 265 patients treated with warfarin (1.27 vs 1.60% per year, respectively; HR, 0.79; 95% CI, 0.66 to 0.95; *P*<0.001 for non inferiority and *P*=0.01 for superiority. Treatment with apixaban significantly lowered the incidence of hemorrhagic stroke compared to treatment with warfarin (0.24 vs 0.47% per year; HR, 0.51; 95% CI, 0.35 to 0.75; *P*<0.001). There was no statistically significant difference between the apixaban and warfarin treatment groups with regard to a reduction in ischemic or uncertain type of stroke (0.97 vs 1.05% per year, respectively; HR, 0.92; 95% CI, 0.74 to 1.13; *P*=0.42) or systemic embolism (0.09 vs 0.10% per year, respectively; HR, 0.87; 95% CI, 0.44 to 1.75; *P*=0.70). There was a significantly lower incidence of major bleeding associated with apixaban treatment compared to warfarin treatment (2.13 vs 3.09% per year; HR, 0.69; 95% CI, 0.60 to 0.80; *P*<0.001). Apixaban treatment was associated with a significantly lower incidence of major intracranial bleeding (0.33 vs 0.80% per year; HR, 0.42; 95% CI, 0.30 to 0.58; *P*<0.001), and major bleeding at other locations (1.79 vs 2.27% per year; HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin treatment. There was a similar incidence of major gastrointestinal bleeding

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	diabetes mellitus or hypertension requiring treatment			between the treatment groups (0.76 vs 0.86% per year, respectively; HR, 0.89; 0.70 to 1.15; *P*=0.37). Secondary: Patients randomized to receive apixaban had a lower incidence of death from any cause (3.52 vs 3.94% per year; HR, 0.89; 95% CI, 0.80 to 0.998; *P*=0.047) compared to patients randomized to warfarin treatment. There was a similar rate of MI between the apixaban and warfarin treatment groups with regard to incidence of MI (0.53 vs 0.61% per year, respectively; HR, 0.88; 95% CI, 0.66 to 1.17; *P*=0.37). The composite of stroke, systemic embolism, or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.49 vs 5.04% per year; HR, 0.89; 95% CI, 0.81 to 0.98; *P*=0.02). Similarly, the composite of stroke, systemic embolism, MI or death from any cause was significantly lower in the apixaban treatment group compared to the warfarin treatment group (4.85 vs 5.49% per year; HR, 0.88; 95% CI, 0.80 to 0.97; *P*=0.01). The incidence of PE or DVT was similar between the apixaban and warfarin treatment groups (0.04 vs 0.05% per year, respectively; HR, 0.78; 95% CI, 0.29 to 2.10; *P*=0.63). Apixaban treatment was associated with a significantly lower rate of major or clinically relevant nonmajor bleeding compared to warfarin treatment (4.07 vs 6.01% per year; HR, 0.68; 95% CI, 0.61 to 0.75; *P*<0.001). Moreover, apixaban reduced GUSTO severe bleeding, GUSTO moderate or severe bleeding, TIMI major bleeding and TIMI major or minor bleeding compared to warfarin (*P*<0.001 for all). There was a statistically significant reduction in any bleeding in the apixaban treatment group compared to the warfarin treatment group (18.1 vs 25.8% per year; HR, 0.71; 95% CI, 0.68 to 0.75; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events occurred in a similar proportion of patients in the apixaban group and in the warfarin group (81.5 and 83.1%, respectively) as did the proportion of patients who experienced serious adverse events (35.0 and 36.5%, respectively). The rates of liver function abnormalities were similar between the treatment groups.
Easton et al[35] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	Subanalysis of ARISTOTLE[12] Patients enrolled in the ARISTOTLE trial stratified based on previous stroke and TIA	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: Death from any cause, incidence of stroke, hemorrhagic stroke, ischemic or uncertain type of stroke, disabling or fatal stroke, cardiovascular death, intracranial, gastrointestinal and total bleeding	Primary: The relative reduction in the risk of stroke or systemic embolism with apixaban compared to warfarin was not significantly different among patients with a history of previous stroke (HR, 0.76; 95% CI, 0.56 to 1.03) and those without (HR, 0.82; 95% CI, 0.65 to 1.03) a previous history of stroke or TIA (*P*=0.71). Treatment with apixaban significantly reduced the risk of major bleeding compared to warfarin in patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a history of stroke or TIA (HR, 0.68; 95% CI, 0.58 to 0.80); however, the difference between the groups was not statistically significant (*P*=0.69). Secondary: The reduction in death from any cause with apixaban vs warfarin was similar among patients with a history of stroke or TIA (HR, 0.0.89; 95% CI, 0.70 to 1.12) and patients without a stroke or TIA history (HR, 0.90; 95% CI, 0.79 to 1.02; *P*=0.89). The reduction in the risk of stroke was not significantly different between those with a prior history of stroke or TIA (HR, 0.71; 95% CI, 0.52 to 0.98) and those without a history of stroke or TIA (HR, 0.84; 95% CI, 0.67 to 1.06) who were treated apixaban compared to warfarin (*P*=0.40). The reduction in the risk of hemorrhagic stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.40; 95% CI, 0.21 to 0.78) and patients without a history of stroke or TIA (HR, 0.59; 95% CI, 0.37 to 0.94; *P*=0.35). There was no statistically significant difference in the reduction in ischemic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				or unknown type of stroke with apixaban compared to warfarin among patients with a history of stroke or TIA (HR, 0.86; 95% CI, 0.60 to 1.22) and patients without a stroke or TIA history (HR, 0.97; 95% CI, 0.74 to 1.26; *P*=0.61). The reduction in disabling or fatal stroke with apixaban compared to warfarin was similar among patients with a history of stroke or TIA (HR, 0.87; 95% CI, 0.57 to 1.34) and patients without a stroke or TIA history (HR, 0.60; 95% CI, 0.41 to 0.86; *P*=0.18). The significant reduction in death from any cause with apixaban compared to warfarin was consistent among patients with a history of stroke or TIA (HR, 0.73; 95% CI, 0.55 to 0.98) and patients without a stroke or TIA history (HR, 0.68; 95% CI, 0.58 to 0.80; *P*=0.69). There was no significant reduction in the risk of total bleeding (*P*=0.70), intracranial bleeding (*P*=0.60) or gastrointestinal bleeding (*P*=0.87) between patients with a previous history of stroke or TIA who received apixaban compared to warfarin and patients without a history of stroke or TIA.
Lopes et al[36] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80, body weight ≤60 kg or a	Subanalysis of ARISTOTLE[12] Patients enrolled in the ARISTOTLE trial stratified based on $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores	N=18,201 1.8 years	Primary: Incidence of stroke (ischemic, hemorrhagic or uncertain type) or systemic embolism and major bleeding Secondary: MI, death from any cause, intracranial bleeding, TIMI major or minor bleeding, GUSTO moderate or severe bleeding, any bleeding and net clinical events (stroke	Primary: Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke ($CHADS_2$ score; *P*=0.4457, CHA_2DS_2VASc score *P*=0.1210) or bleeding (HAS-BLED score *P*=0.9422). Patients treated with apixaban experienced lower rates of major bleeding compared to patients treated with warfarin, with no difference between score categories ($CHADS_2$; *P*=0.4018, CHA_2DS_2VASc; *P*=0.2059 and HAS-BLED; *P*=0.7127). Secondary: Patients treated with apixaban had significantly lower rates of stroke or systemic embolism (*P*=0.0114), mortality (*P*=0.0465), major bleeding (*P*<0.0001), intracranial bleeding (*P*<0.0001), and any bleeding (*P*<0.0001) compared to patients receiving warfarin, regardless of $CHADS_2$ score. The benefits of apixaban compared to warfarin for all endpoints across CHA_2DS_2VASc categories were similar to those seen across $CHADS_2$ score

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
serum creatinine level ≥1.5 mg/dL.			or systemic embolism, major bleeding and all-cause mortality)	categories. There was no difference in the rate of MI between patients in different risk categories. Regardless of HAS-BLED score, patients receiving treatment with apixaban had lower rates of stroke or systemic embolism (*P*=0.0114), mortality (*P*=0.0465), major bleeding (*P*<0.0001), TIMI major or minor bleeding (*P*<0.0001), GUSTO severe or moderate bleeding (P<0.0001), and any bleeding (*P*<0.0001) compared to patients treated with warfarin. The reduction in intracranial bleeding with apixaban compared to warfarin was greater in patients with a HAS-BLED score of three or higher (HR, 0.22; 95% CI, 0.10 to 0.48) compared to patients with a HAS-BLED score of less than one (HR, 0.66; 95% CI, 0.39 to 1.12); however, the difference was not significant (*P*=0.0604). Irrespective of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score, patients randomized to receive treatment with apixaban experienced lower rates of the composite of stroke, systemic embolism, major bleeding, and all-cause mortality compared to patients randomized to warfarin. These results were driven mainly by reductions in bleeding.
Garcia et al[59] ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg or	Subanalysis of ARISTOTLE[12] Patients enrolled in the ARISTOTLE trial stratified based on previous VKA use	N=18,201 1.8 years	Primary: Composite of all stroke (ischemic or hemorrhagic) and systemic embolism. Secondary: Mortality, major bleeding, intracranial bleeding, and permanent early treatment discontinuation	Primary: Compared with patients in the warfarin arm, patients randomized to receive apixaban had numerically lower rates of stroke/systemic embolism irrespective of prior VKA use. For stroke/systemic embolism, the differences favoring apixaban over warfarin were consistent: the HR was 0.86 (95% CI, 0.67 to 1.11) in the VKA-naive patients and 0.73 (95% CI, 0.57 to 0.95) in the VKA-experienced patients (P=0.39). The treatment effects of apixaban (vs warfarin) were not modified by VKA naivety. Secondary: A similar consistency of treatment effect was seen for other key end points; numerically lower rates of major bleeding and all-cause death were seen in the apixaban treated patients, and there is no evidence that this effect was modified by VKA naivety. Apixaban-treated patients had lower rates of intracranial bleeding overall; the effect of apixaban on intracranial bleeding was less pronounced in patients who were VKA naive (HR, 0.60; 95% CI, 0.38 to 0.93) than in those who were VKA-experienced (HR 0.28; 95% CI,

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a serum creatinine level ≥1.5 mg/dL.				0.17 to 0.46) (P=0.02). Premature permanent study drug discontinuation was numerically less likely in the patients assigned to apixaban whether they were VKA naive (HR, 0.87; 95% CI, 0.79 to 0.95) or VKA experienced (HR, 0.93; 95% CI, 0.85 to 1.02).
Connolly et al[13] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	DB, MC, RCT Patients with AF documented on ECG performed at screening or within six months of enrollment and at least one of the following: previous stroke or TIA, LVEF <40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75 years of age or 65 to 74 years of age plus diabetes, hypertension or CAD	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Both doses of dabigatran were non inferior to warfarin (*P*<0.001). Stroke or systemic embolism occurred in 182 dabigatran 110 mg- (1.53% per year), 134 dabigatran 150 mg (-1.1% per year) and 199 warfarin-treated patients (1.69% per year). The 150 mg dose of dabigatran was "superior" to warfarin (RR, 0.66; 95% CI, 0.53 to 0.82; *P*<0.001), but the 110 mg dose was not (RR, 0.91; 95% CI, 0.74 to 1.11; *P*=0.34). Rates of hemorrhagic stroke were 0.38, 0.12 (RR, 0.31; 95% CI, 0.17 to 0.56; *P*<0.001) and 0.10% (RR, 0.26; 95% CI, 0.14 to 0.49; *P*<0.001) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding (life-threatening, non-life-threatening and gastrointestinal) was 3.36, 2.71 (RR, 0.80; 95% CI, 0.69 to 0.93; *P*=0.003) and 3.11% (RR, 0.93; 95% CI, 0.81 to 1.07; *P*=0.31) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Rates of life-threatening bleeding, intracranial bleeding and major or minor bleeding were higher in warfarin-treated patients (1.80, 0.74 and 18.15%, respectively) compared to either dabigatran 110 (1.22, 0.23 and 14.62%, respectively) or 150 mg-treated patients (1.45, 0.30 and 16.42%, respectively) (*P*<0.05 for all comparisons of dabigatran and warfarin). There was a significantly higher rate of major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients (*P*=0.43 for dabigatran 110 mg vs warfarin and *P*<0.001 for dabigatran 150 mg vs warfarin). The net clinical benefit outcome consisted of major vascular events, major bleeding and death. The rates of this combined outcome were 7.64, 7.09 (RR, 0.92; 95% CI, 0.84 to 1.02; *P*=0.10) and 6.91% (RR, 0.91; 95% CI,

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				0.82 to 1.00; *P*=0.04) per year in warfarin, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Secondary: Rates of death from any cause were 4.13, 3.75 (RR, 0.91; 95% CI, 0.80 to 1.03; *P*=0.13) and 3.64% (RR, 0.88; 95% CI, 0.77 to 1.00; *P*=0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of MI was 0.53, 0.72 (RR, 1.35; 95% CI, 0.98 to 1.87; *P*=0.07) and 0.74% (RR, 1.38; 95%, 1.00 to 1.91; *P*=0.048) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of PE was 0.09, 0.12 (RR, 1.26; 95% CI, 0.57 to 2.78; *P*=0.56) and 0.15% (RR, 1.61; 95% CI, 0.76 to 3.42; *P*=0.21) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Data regarding the incidences of TIA were not reported. The rate of hospitalization was 20.8, 19.4 (RR, 0.92; 95% CI, 0.87 to 0.97; *P*=0.003) and 20.2% (RR, 0.97; 95% CI, 0.92 to 1.03; *P*=0.34) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients.
Ezekowitz et al[37] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[13] Patients enrolled in the RE-LY trial who were naïve to and experienced with VKAs	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: Approximately half of the patients were VKA-naïve (50.4%). Combined stroke and systemic embolism rates were similar in dabigatran 110 mg-treated patients for both the VKA-naïve and -experienced cohorts compared to warfarin-treated patients (RR, 0.93; 95% CI, 0.70 to 1.25; *P*=0.65 and RR, 0.87; 95% CI, 0.66 to 1.15; *P*=0.32). In dabigatran 150 mg-treated patients, both VKA-naïve (RR, 0.63; 95% CI, 0.46 to 0.87; *P*=0.005) and -experienced cohorts (RR, 0.66; 95% CI, 0.49 to 0.89; *P*=0.007) had significantly lower risk of stroke or systemic embolism compared to warfarin-treated patients. Major bleeding rates were lower in the VKA-experienced cohort in dabigatran 110 mg-treated patients compared to warfarin-treated patients (RR, 0.74; 95% CI, 0.60 to 0.90; *P*=0.003). The VKA-naïve cohort in

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				dabigatran 110 mg-treated patients (RR, 0.87; 95% CI, 0.72 to 1.07; *P*=0.19) and the VKA-naïve (RR, 0.94; 95% CI, 0.77 to 1.15; *P*=0.55) and –experienced cohort (RR, 0.92; 95% CI, 0.76 to 1.12; *P*=0.41) in dabigatran 150 mg-treated patients were similar compared to warfarin-treated patients. Intracranial bleeding events were lower in dabigatran 110 VKA-naïve and -experienced cohorts (RR, 0.27; 95% CI, 0.14 to 0.52; *P*<0.001; RR, 0.32; 95% CI, 0.18 to 0.56; *P*<0.001) and in dabigatran 150 mg VKA-naïve and -experienced cohorts (RR, 0.46; 95% CI, 0.27 to 0.78; *P*=0.005; RR, 0.40; 95% CI, 0.24 to 0.67; *P*<0.001) compared to warfarin-treated patients. Secondary: Rates of life threatening bleeding, disabling stroke and death (when combined) were significantly lower in the VKA-experienced patients in both dabigatran 110 mg- (RR, 0.82; 95% CI, 0.70 to 0.96; *P*=0.01) and 150 mg-treated cohort (RR, 0.80; 95% CI, 0.68 to 0.93; *P*=0.004) compared to warfarin-treated patients, but similar for the VKA-naïve cohort. When comparing this combined outcome in VKA-naïve and -experienced cohorts within treatments, the rate was lower in VKA-experienced cohort than in the -naïve cohort (RR, 0.83; 95% CI, 0.71 to 0.98; *P*=0.03), as was the cardiovascular death rate (RR, 0.73; 95% CI, 0.58 to 0.92; *P*=0.007). In dabigatran 150 mg-treated patients, the rate of this combined outcome trended lower in VKA-experienced cohort. There were no differences in the rates of MI among the treatments. Gastrointestinal bleeding rates were similar for dabigatran 110 mg- and warfarin-treated patients, but significantly higher in both dabigatran 150 mg VKA-naïve (RR, 1.56; 95% CI, 1.15 to 2.10; *P*=0.004) and -experienced cohorts (RR, 1.42; 95% CI, 1.06 to 1.89; *P*=0.02) compared to warfarin-treated patients.
Diener et al (abstract)[38] RE-LY Dabigatran 110 mg BID vs	Subanalysis of RE-LY[13] Patients enrolled in the RE-LY trial who had a previous	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary:	Primary: Within the subgroup of patients with previous stroke or TIA, 1,195, 1,233 and 1,195 patients were from the dabigatran 110 mg, dabigatran 150 mg and warfarin groups. Stroke or systemic embolism occurred in 65 warfarin-treated patients (2.78% per year) compared to 55 (2.32% per year) dabigatran 110 mg- (RR, 0.84; 95% CI, 0.58 to 1.20) and 51 (2.07% per

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	stroke or TIA		Death, MI, PE, TIA, hospitalization	year) dabigatran 150 mg-treated patients (RR, 0.75; 95% CI, 0.52 to 1.08). The rate of major bleeding was significantly lower in dabigatran 110 mg-treated patients (RR, 0.66; 95% CI, 0.48 to 0.90), and similar in dabigatran 150 mg-treated patients (RR, 1.01; 95% CI, 0.77 to 1.34) compared to warfarin-treated patients. Secondary: The effects of both doses of dabigatran compared to warfarin were not different between patients with previous stroke or TIA and those without for any of the outcomes from RE-LY apart from vascular death (dabigatran 110 mg vs warfarin; *P*=0.038).
Wallentin et al[39] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The cTTR was estimated by averaging the TTR for individual warfarin-treated patients.	Subanalysis of RE-LY[13] Patients enrolled in the RE-LY trial across the three treatment groups within four groups defined by quartiles of cTTR (<57.1, 57.1 to 65.5, 65.5 to 72.6 and >72.6%)	N=18,113 2 years	Primary: Composite of stroke or systemic embolism, major hemorrhage Secondary: Death, MI, PE, TIA, hospitalization	Primary: In the total population, the rate of the primary outcome of stroke and systemic embolism was reduced from 1.71% per year in warfarin-treated patients, to 1.54% per year in dabigatran 110 mg-treated patients (non inferiority; *P*<0.001) and to 11.1% per year in dabigatran 150 mg-treated patients ("superiority"; *P*<0.001). Event rates seemed to decrease with higher cTTR in warfarin-treated patients; however, there were no significant interactions between cTTR and stroke and systemic embolism in dabigatran- vs warfarin-treated patients. The rate of nonhemorrhagic stroke and systemic embolism seemed to be lower with higher cTTR in warfarin-treated patients (*P*=0.08). In the total population, the rate of major bleeding was 3.57% per year in warfarin-treated patients compared to 2.87 ("superiority"; *P*=0.003) and 3.32% ("superiority"; *P*=0.31) per year in dabigatran 110 mg- and dabigatran 150 mg-treated patients. The rate of major bleeding, as well as major gastrointestinal bleeding, was numerically lower at higher cTTR quartiles in warfarin-treated patients. When comparing major bleedings between dabigatran 150 mg- and warfarin-treated patients, there were benefits at lower cTTR but similar results at higher cTTR (*P*=0.03). The rates of intracranial bleeding in warfarin-treated patients were associated with the cTTR and were consistently lower in dabigatran-treated patients than warfarin-treated patients irrespective of cTTR. There was a higher rate of

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				major gastrointestinal bleeding in dabigatran 150 mg-treated patients compared to warfarin-treated patients at higher cTTR (*P*=0.019). There was an increase in total bleeding rate with increasing cTTR with all three treatments, without any significant interactions between them. Secondary: Mortality rates were 4.13, 3.75 ("superiority"; *P*<0.13) and 3.64% ("superiority"; *P*<0.051) per year in warfarin-, dabigatran 110 mg- and dabigatran 150 mg-treated patients. Total mortality was lower at higher cTTR in warfarin-treated patients; the interaction *P* value was 0.052 for the interaction between cTTR and the effects of dabigatran 110 mg and 0.066 for the effects of dabigatran 150 mg, with differences in mortality at lower cTTR but similar rates at higher cTTR. For all cardiovascular events, including total mortality and major bleeding, there were significantly lower event rates at higher cTTR in warfarin-treated patients. There was a significant interaction between cTTR and the composite of all cardiovascular events when comparing dabigatran 150 mg- and warfarin-treated patients (*P*=0.0006), and dabigatran 110 mg- and warfarin-treated patients (*P*=0.036). These interactions were mainly attributable to significant differences between treatments in the rates of nonhemorrhagic events (*P*=0.017 for dabigatran 110 mg vs warfarin and *P*=0.0046 for dabigatran 150 mg vs warfarin), with advantages at lower cTTR, whereas rates were greater at higher cTTR.
Hohnloser et al[14] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg;	Subanalysis of RE-LY[13] Patients with AF documented on ECG performed at screening or within six months of enrolment and at least one of the following: previous stroke or TIA,	N=18,113 2 years	Primary: Myocardial and ischemic events Secondary: Not reported	Primary: The annual rates of MI with dabigatran 110 and 150 mg were 0.82 (HR, 1.29; 95% CI, 0.96 to 1.75; *P*=0.09) and 0.81% per year (HR, 1.27; 95% CI, 0.94 to 1.71; *P*=0.12) compared to 0.64% per year with warfarin. When both doses of dabigatran were compared to warfarin results were similar to those obtained when the two doses were compared separately. With regards to the composite outcome of MI, unstable angina, cardiac arrest, and cardiac death, annual rates were 3.16 (HR, 0.93; 95% CI, 0.80 to 1.06; *P*=0.28) and 33.3% per year (HR, 0.98; 95% CI, 0.85 to 1.12; *P*=0.77) with dabigatran 110 and 150 mg compared to 3.41% per year with warfarin. When revascularization events were included, again no significant

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dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	LVEF<40%, heart failure (NYHA Class ≥2) symptoms within six months before screening and ≥75 years of age or 65 to 74 years of age plus diabetes, hypertension or CAD			differences emerged among the three treatments. With regards to the composite outcome of MI, unstable angina, cardiac arrest, cardiac death, revascularization events, and stroke and systemic embolic events, annual rates were 4.76 (HR, 0.93; 95% CI, 0.83 to 1.05; *P*=0.24) and 4.47% per year (HR, 0.88; 95% CI, 0.78 to 0.98; *P*=0.03) with dabigatran 110 and 150 mg compared to 5.10% per year with warfarin. Events prespecified in the net clinical benefit analysis occurred at annual rates of 7.34 (HR, 0.92; 95% CI, 0.84 to 1.01; *P*=0.09) and 7.11% per year (HR, 0.90; 95% CI, 0.82 to 0.99; *P*=0.02) with dabigatran 110 and 150 mg compared to 7.91% per year with warfarin. Patients who had at least one myocardial ischemic event were older and had more coronary risk factors compared to the remainder of the population. Across all treatments, these patients received more antiplatelet medications, β-blockers, and statins at baseline, and they also more often had a $CHADS_2$ score >2. Fifty-six of 87 clinical MIs with dabigatran 110 mg, 59/89 with dabigatran 150 mg, and 46/66 with warfarin occurred on the study drug treatment. MIs that occurred greater than six days after study drug discontinuation were observed in 17, 20, and 12 patients in all three treatment groups. Accordingly, 33, 34, and 30% of all clinical MIs were diagnosed when patients were not taking the study drug in the respective treatment arms. There were 1,886 (31%) CAD/MI patients receiving dabigatran 110 mg, 1,915 (31%) receiving dabigatran 150 mg, and 1,849 (31%) receiving warfarin. The effects of dabigatran compared to warfarin were highly consistent between patients with prior CAD/MI compared to those without. Secondary: Not reported
Hart et al[40] RE-LY	Subanalysis of RE-LY[13]	N=18,113 2 years	Primary: Intracranial hemorrhages	Primary: There were 154 intracranial hemorrhages, with an overall 30-day mortality of 36%. Intracranial hemorrhages included intracerebral hemorrhages (46%,

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Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Patients enrolled in the RE-LY trial who experienced an intracranial hemorrhage while on treatment		occurring during anticoagulation, including sites, rates, risk factors, associated trauma and outcomes Secondary: Not reported	with 49% mortality), subdural hematomas (45%, with 24% mortality) and subarachnoid hemorrhages (8%, with 31% mortality). Patients with an intracranial hemorrhage were older (*P*<0.001), had a history of stroke or TIA (*P*=0.001), more often took aspirin during follow-up (*P*=0.001), had lower incidence of heart failure (*P*=0.02) lower estimated creatinine clearances (*P*<0.001) compared to patients without intracranial hemorrhage. The rate of intracranial hemorrhage was higher with warfarin treatment (0.76% per year) compared to patients receiving dabigatran 150 mg (0.31% per year, RR, 0.40; 95% CI, 0.27 to 0.59) and dabigatran 110 mg (0.23% per year, RR, 0.30; 95% CI, 0.19 to 0.45). Intracranial hemorrhage-related mortality was similar between the treatments. Age was predictive of intracranial hemorrhage among patients treated with dabigatran (RR, 1.06 per year; *P*=0.002). The independent predictors of developing spontaneous intracerebral bleeding were the assignment to warfarin (RR, 4.1; *P*<0.001), previous stroke or TIA (RR, 2.7; *P*<0.001), aspirin use (RR, 1.8; *P*=0.02) and age (1.04 per year; *P*=0.02). The rate of spontaneous intracerebral hemorrhage was significantly higher among those assigned to warfarin (0.36% per year) compared to 0.09% per year with dabigatran 150 mg (RR, 0.26; 95% CI, 0.13 to 0.50) and 0.08% with dabigatran 110 mg (RR, 0.23; 95% CI, 0.12 to 0.47). There was no significant difference in mortality associated with spontaneous intracerebral hemorrhage between treatments. Patients with spontaneous intracerebral bleeding in the basal ganglia/thalamus were, on average, younger (*P*=0.04) and more likely to have diabetes (*P*=0.02) compared to those with lobar bleeding. The rate of subdural hematoma was 0.31% per year in the warfarin group compared to 0.20% per year in the dabigatran 150 mg group (RR, 0.65; *P*=0.10) and 0.08% per year in the dabigatran 110 mg group (RR, 0.27; *P*<0.001). The rate of subdural hematomas was significantly higher with

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				dabigatran 150 mg compared to the 110 mg dosage (RR, 2.4; *P*=0.02). Fatal subdural bleeding occurred in 10 patients receiving warfarin compared to five and two patients receiving dabigatran 150 mg and 110 mg, respectively (*P*<0.05 the 110 mg group). Secondary: Not reported
Healey et al[41] RE-LY Dabigatran 110 mg BID vs dabigatran 150 mg BID vs warfarin 1, 3, or 5 mg; dose adjusted to maintain an INR of 2.0 to 3.0 (OL)	Subanalysis of RE-LY[13] Patients enrolled in the RE-LY trial who required surgery, dental procedures, cardiac catheterization, or invasive diagnostic procedures (including percutaneous biopsy, peripheral angiography, and similar procedures)	N=4,591 2 years	Primary: Perioperative major bleeding, fatal bleeding, bleeding requiring surgery and thrombotic events Secondary: Not reported	Primary: The incidence of perioperative major bleeding was not significantly different between patients receiving dabigatran 110 mg (3.8%) or dabigatran 150 mg (5.1%) compared to patients receiving warfarin (4.6%; *P*>0.05 for both). Perioperative fatal bleeding was similar in the dabigatran 110 mg (RR, 1.57; 95% CI, 0.26 to 9.39; *P*=0.62) or 150 mg treatment groups (RR, 1.01; 95% CI, 0.14 to 7.15; *P*=0.99) compared to the warfarin group. Bleeding requiring surgery was not significantly different in the dabigatran 110 mg (RR, 0.59; 95% CI, 0.26 to 1.33; *P*=0.20) or 150 mg treatment groups (RR, 1.39; 95% CI, 0.73 to 2.63; *P*=0.32) compared to the warfarin group. The incidences cardiovascular death, stroke (all-cause), ischemic stroke, hemorrhagic stroke, systemic embolism, MI, or PE, were low and not significantly different between patients receiving dabigatran 110 mg, 150 mg or warfarin (*P*>0.05 for all). Secondary: Not reported
Connolly et al[58] (RELY-ABLE) Dabigatran 110 mg BID vs dabigatran 150 mg BID	Subanalysis of RE-LY[13] Patients enrolled in the RE-LY trial who received dabigatran who were not discontinued	N=5,891 28 months	Primary: Stroke (ischemic or hemorrhagic), systemic embolism, Secondary: Myocardial infarction, PE,	Primary: During RELY-ABLE, the annual rates of stroke or systemic embolism were 1.46% and 1.60% per year on dabigatran 150 and 110 mg, respectively (HR, 0.91; 95% CI, 0.69 to 1.20). Annual rates of ischemic stroke (including stroke of uncertain cause) were 1.15% and 1.24% per year on dabigatran 150 and 110 mg, respectively (HR, 0.92; 95% CI, 0.67 to 1.27). Annual rates of hemorrhagic stroke were similar in the two treatment arms and were very low at 0.13% and 0.14% per year on dabigatran 150 and 110 mg,

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	medication at the time of the final RE-LY study visit and have AF and at least one risk factor for stroke		vascular death, and total mortality	respectively. Secondary: Annual rates of myocardial infarction were also low and similar between the two groups at 0.69% and 0.72% per year. PE occurred in 0.13% and 0.11% per year on dabigatran 150 and 110 mg, respectively (HR, 1.14; 95% CI, 0.41 to 3.15). Vascular death and total mortality were not reported.
Ezekowitz et al[42] Dabigatran 50, 150, and 300 mg BID vs warfarin, dose adjusted to maintain an INR of 2.0 to 3.0 (OL) The three doses of dabigatran were combined in a 3x3 factorial fashion with no aspirin or 81 to 325 mg of aspirin QD.	AC, DB, MC, RCT Patients with documented AF with CAD and at least one of the following: hypertension requiring medical treatment, diabetes, symptomatic heart failure (LVEF <40%), previous stroke or TIA or age >75	N=502 12 weeks	Primary: Incidence of bleeding Secondary: Suppression of D-dimer	Primary: Major bleeding events were limited to dabigatran 300 mg plus aspirin-treated patients (four patients out of 64); being statistically different compared to dabigatran 300 mg with no aspirin-treated patients (zero patients out of 150; *P*<0.02). There was a significant difference in major plus clinically relevant bleeding episodes (11 out of 64 vs six out of 105; *P*=0.03) and total bleeding episodes (25 out of 64 vs 14 out of 105; *P*=0.0003) between dabigatran 300 mg plus aspirin- and dabigatran 300 mg with no aspirin-treated patients. The frequency of bleeding in both dabigatran 50 mg treatment groups was significantly lower than that within the warfarin treatment group (seven out of 107 vs 12 out of 70; *P*=0.044). When the doses of dabigatran were compared to each other, irrespective of aspirin use, there were differences in total bleeding episodes in 300 and 150 mg- vs 50 mg-treated patients (37 out of 169 and 30 out of 169 vs seven out of 107; *P*=0.0002 and *P*=0.01, respectively). Secondary: Generally, at 12 weeks, a 13% relative increase of D-dimer plasma measurements was observed in dabigatran 50 mg-treated patients (*P*=0.0008) and a 3% relative increase in dabigatran 150 mg-treated patients (*P*=0.027) was observed. No significant changes in 300 mg dabigatran- (0%; *P*=0.413) or warfarin-treated patients (-1%; *P*=0.267) were seen. Aspirin treatment had no effect on any of these analyses. There were significantly fewer traumatic intracranial hemorrhages in patients receiving either dosage of dabigatran (11 patients for both) compared to

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				patients receiving warfarin (24 patients; (*P*<0.05 for both dabigatran dosages vs warfarin). Fatal traumatic intracranial hemorrhages occurred in five, three and three patients receiving warfarin, dabigatran 150 mg, and 110 mg, respectively.
Patel et al[15] ROCKET-AF Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	AC, DB, DD, MC, PRO, RCT Patients with nonvalvular AF, as documented on ECG, at moderate- to high-risk for stroke, indicated by a history of stroke, TIA, or systemic embolism or at least two of the following risk factors: heart failure or LVEF ≤35%, hypertension, age ≥75 years, or diabetes mellitus The proportion of patients who had not had a previous ischemic stroke, TIA, or systemic embolism and who had less than two risk factors was limited to 10% of the cohort for each region; the	N=14,264 590 days (median duration of treatment; 707 days median follow-up)	Primary: Composite of stroke (ischemic or hemorrhagic) and systemic embolism Secondary: Composite of stroke, systemic embolism, or death from cardiovascular causes; composite of stroke, systemic embolism, death from cardiovascular causes, or MI; individual components of composite outcomes; major and nonmajor clinically relevant bleeding events	Primary: In the PP population, stroke or systemic embolism occurred in 188 rivaroxaban-treated patients (1.7% per year) compared to 241 warfarin-treated patients (2.2% per year). Rivaroxaban was non inferior to warfarin in regard to the primary outcome (HR, 0.79; 95% CI, 0.66 to 0.96; *P*<0.001 for non inferiority). In the as-treated safety population, the primary outcome occurred in 189 (1.7% per year) and 243 (2.2% per year) rivaroxaban- and warfarin-treated patients (HR, 0.79; 95% CI, 0.65 to 0.95; *P*=0.01 for superiority). In the ITT population, the primary end point occurred in 269 rivaroxaban-treated patients (2.1% per year) compared to 306 patients in warfarin-treated patients (2.4% per year; HR, 0.88; 95% CI, 0.74 to 1.03; *P*<0.001 for non inferiority; *P*=0.12 for superiority). Secondary: In the on-treatment population, the composite of stroke, systemic embolism, or vascular death occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.11 vs 5.79% per year, respectively; HR, 0.86; 95% CI 0.74 to 0.99; *P*=0.034). In the on-treatment population, the composite of stroke, systemic embolism, vascular death or MI occurred in significantly fewer rivaroxaban-treated patients compared to warfarin treated patients (3.91 vs 4.62% per year, respectively; HR, 0.85; 95% CI 0.74 to 0.96; *P*=0.010). In the on-treatment population, stroke occurred in 184 (2.61%) and 221 (3.12%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.65 vs 1.96% per year; HR, 0.85; 95% CI, 0.70 to 1.03; *P*=0.092).

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	remainder of patients were required to have had either previous thromboembolism or at least three risk factors			In the on-treatment population, non-central nervous system systemic embolism occurred in five (0.07%) and 22 (0.31%) rivaroxaban- and warfarin-treated patients; the event rate was significantly lower with rivaroxaban (0.04 vs 0.19% per year; HR, 0.23; 95% CI, 0.09 to 0.61; *P*=0.003). In the on-treatment population, vascular death occurred in 170 (2.41%) and 193 (2.73%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (1.53 vs 1.71% per year; HR, 0.89; 95% CI, 0.73 to 1.10; *P*=0.289). In the on-treatment population, MI occurred in 101 (1.43%) and 126 (1.78%) rivaroxaban- and warfarin-treated patients; there was no difference in event rates between the two treatments (0.91 vs 1.12% per year; HR, 0.81; 95% CI, 0.63 to 1.06; *P*=0.121). There was no difference in major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin. Bleeding occurred in 1,475 and 1,449 rivaroxaban- and warfarin-treated patients (14.9 and 14.5% per year, respectively; HR, 1.03; 95% CI, 0.96 to 1.11; *P*=0.44). The incidence of major bleeding was similar with rivaroxaban and warfarin (3.6 and 3.4%, respectively; *P*=0.58). Decreases in hemoglobin levels ≥2 g/dL and transfusions were more common among rivaroxaban-treated patients, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent compared to warfarin treated patients. Rates of intracranial hemorrhage were significantly lower with rivaroxaban compared to warfarin (0.5 vs 0.7% per year; HR, 0.67; 95% CI, 0.47 to 0.93; *P*=0.02). Major bleeding from a gastrointestinal site was more common with rivaroxaban, with 224 bleeding events (3.2%), compared to 154 events (2.2%) with warfarin (*P*<0.001).
Hankey et al[43] ROCKET-AF	Subanalysis of ROCKET-AF[15]	N=14,264 (previous	Primary: Composite of stroke	Primary: The number of events per 100 person-years for the primary endpoint in

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Rivaroxaban 20 mg QD (15 mg QD in patients with a creatinine clearance 30 to 49 mL/min) vs warfarin (INR of 2.0 to 3.0)	Patients enrolled in the ROCKET-AF trial stratified based on previous stroke and TIA	stroke or TIA; n=7,468) 590 days (median duration of treatment; 707 days median follow-up)	(ischemic or hemorrhagic) and systemic embolism Secondary: Safety, major and nonmajor clinically relevant bleeding events	patients receiving rivaroxaban compared to patients receiving warfarin was consistent among patients with previous stroke or TIA (2.79 vs 2.96%; HR, 0.94; 95% CI, 0.77 to 1.16) and those without (1.44 vs 1.88%; HR, 0.77; 95% CI, 0.58 to 1.01; *P*=0.23). Secondary: The overall number of adverse events per 100 person-years was similar with both treatments and in patients with and without previous stroke or TIA. The number of major and nonmajor clinically relevant bleeding events per 100 person-years in patients receiving rivaroxaban and warfarin was consistent among patients with previous stroke or TIA (13.31 vs 13.87%; HR, 0.96; 95% CI, 0.87 to 1.07) and those without (16.69 vs 15.19%; HR, 1.10; 95% CI, 0.99 to 1.21; *P*=0.08). The number of major bleeding events per 100 person-years among patients who received at least one dose of study drug was significantly lower among those with previous stroke or TIA (n=318, 3.18%) compared to those without (n=420, 3.89%; HR, 0.81; 95% CI, 0.70 to 0.93; *P*=0.0037), but the safety of rivaroxaban compared to warfarin with respect to major bleeding showed no interaction among patients with (HR, 0.97; 95% CI, 0.79 to 1.19) and without previous stroke or TIA (HR, 1.11; 95% CI, 0.92 to 1.34; *P*=0.36). The effect of rivaroxaban compared to warfarin on intracerebral hemorrhage was consistent among patients with (HR, 0.84; 95% CI, 0.50 to 1.41) and without previous stroke or TIA (HR, 0.46; 95% CI, 0.24 to 0.89; *P*=0.16).
Anderson et al[44] Warfarin (INR ≥2.0) vs placebo, antiplatelet agents (aspirin, aspirin plus clopidogrel, indobufen*), low dose warfarin and low dose warfarin plus aspirin	MA (15 RCTs) Patients ≥18 years of age with AF or atrial flutter	N=16,058 ≥3 months	Primary: Incidence of systemic embolism and major bleeding Secondary: Not reported	Primary: *Warfarin vs placebo* Four trials compared the efficacy of warfarin vs placebo for prevention of thromboembolic events (n=1,909). Eleven systemic embolic events were observed; two and nine in warfarin- and placebo-treated patients (OR, 0.29; 95% CI, 0.08 to 1.07; *P*=0.06). The rates of major bleeding were higher in warfarin-treated patients in three trials. The combined OR for major bleeding was higher in warfarin-treated patients (OR, 3.01; 95% CI, 1.31 to 6.92; *P*=0.01). *Warfarin vs antiplatelet agents* Nine trials compared the efficacy of warfarin and antiplatelet agents for the

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Results for aspirin plus clopidogrel and indobufen were not reported.				prevention of systemic embolism (n=11,756). Thirty four and 71 systemic embolism events occurred in warfarin- and antiplatelet-treated patients (OR, 0.50; 95% CI, 0.33 to 0.75; *P*<0.001). Pooled analysis for the risk of major bleeding showed no evidence of increased risk with warfarin treatment (OR, 1.07; 95% CI, 0.85 to 1.34; *P*=0.59). *Warfarin vs low dose warfarin or a combination of low dose warfarin and aspirin* Five trials compared warfarin vs low dose warfarin or the combination of low dose warfarin and aspirin for the prevention of thromboembolic events. Four trials compared warfarin directly with low dose warfarin (n=1,008), and five and three patients had an embolic event (OR, 1.52; 95% CI, 0.40 to 5.81; *P*=0.54). Two trials compared warfarin to low dose warfarin and aspirin (n=1,385); two patients in each group had a systemic embolic event (OR, 1.00; 95% CI, 0.17 to 5.81; *P*=1.00). The risk of major bleeding was higher in warfarin-treated patients compared to low dose warfarin-treated patients (OR, 2.88; 95% CI, 1.09 to 7.60; *P*=0.03), but there was no difference when comparing warfarin-treated patients to low dose warfarin and aspirin-treated patients (OR, 1.14; 95% CI, 0.55 to 2.36; *P*=0.72). All trials were stopped early owing to the "superiority" of warfarin treatment in stroke prevention seen in other trials. Secondary: Not reported
Agarwal et al[45] Warfarin vs alternative thromboprophylaxis (ximelagatran*, idraparinux*, aspirin, aspirin plus clopidogrel, dabigatran, rivaroxaban,	MA (8 RCTs) Patients with nonvalvular AF	N=32,053 (55,789 patient-years) Duration not specified	Primary: Ischemic or hemorrhagic stroke or non-central nervous system embolism Secondary: MI, all-cause mortality, composite adverse vascular events (stroke, non-central nervous system	Primary: The rate of stroke or non-central nervous system embolism varied from 1.2 to 2.3% per year. The pooled event rate for stroke or non-central nervous system embolism was calculated to be 1.66% (95% CI, 1.41 to 1.91) per year. There was a significantly higher incidence of stroke and non-central nervous system embolism in patients ≥75 years (2.27% per year) compared to those <75 years of age (1.62% per year; *P*<0.001). A significantly higher pooled incidence of stroke or non-central nervous system embolism in females compared to males (*P*<0.01) and in patients with a history of stroke or TIA compared to patients without previous events (*P*=0.001). Patients with no history of exposure to VKA had a significantly higher incidence of stroke and non-central nervous system embolism compared to patients who

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
apixaban)			embolism, MI, and death), major bleeding, intracranial hemorrhage, clinically relevant nonmajor bleeding, minor bleeding	reported use of VKA at the time of enrollment (RR, 1.16; 95% CI, 1.01 to 1.33). Pooled analysis stratified by $CHADS_2$ score yielded pooled annual event rates of 0.89% (95% CI, 0.66 to 1.13) per year for scores ≤1, 1.43% (95% CI, 1.19 to 1.66) per year for scores of 2, and 2.50% (95% CI, 2.17 to 2.82) per year for scores ≥3. Compared to with the lowest risk $CHADS_2$ category, the RR of stroke or non-central nervous system embolism was significantly higher with intermediate risk category (RR, 1.46; 95% CI, 1.13 to 1.89; *P*=0.004) and in the high risk category (RR, 2.89; 95% CI, 2.28 to 3.66; *P*<0.001). Secondary: Rates of MI, all-cause mortality, and composite vascular events varied from 0.53 to 1.40% per year, 2.21 to 8.00% per year, and 3.93 to 5.90% per year, respectively. Pooled event rates for MI, all-cause mortality, and composite vascular events were calculated to be 0.76% (95% CI, 0.57 to 0.96) per year, 3.83% (95% CI, 3.07 to 4.58) per year, and 4.80% (95% CI, 4.22 to 5.38) per year, respectively. The incidence of major bleeding episodes ranged from 1.40 to 3.40% per year. The annual rate of intracranial hemorrhage in patients with AF taking warfarin ranged from 0.33 to 0.80% per year. MA of intracranial hemorrhage yielded a pooled event rate of 0.61% (95% CI, 0.48 to 0.73) per year. The cumulative adverse event rate, defined as major vascular events reported or death or major bleedings episodes, was observed to range from 3.00% per year in one trial to 7.64% per year in another.
Saxena et al[46] Oral anticoagulants (warfarin) vs placebo Target INR ranges in patients receiving oral	SR (2 RCTs) Patients with nonrheumatic AF and a previous TIA or minor ischemic stroke	N=485 1.7 to 2.3 years	Primary: Fatal or non-fatal recurrent stroke, all major vascular events (vascular death, recurrent stroke, MI, and systemic embolism), any intracranial bleed, major extracranial bleed	Primary: In one RCT, the annual rate of all vascular events was eight vs 17% in oral anticoagulation and placebo-treated patients. The risk of stroke was reduced from 12 to four percent per year. In absolute terms, 90 vascular events (mainly strokes) were prevented per 1,000 patients treated with oral anticoagulation per year. There were eleven out of 225 nonvascular deaths in oral anticoagulation-treated patients compared to nine out of 214 nonvascular deaths in placebo-treated patients, and 30 out of 225 and 35 out of 214 vascular deaths. In the same trial, the incidence of all bleeding events while receiving oral anticoagulation was low (2.8 vs 0.7% per year). The absolute annual excess of major bleeds was 21 per 1,000 patients

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anticoagulants were 2.5 to 4.0 and 1.4 to 2.8 in the two RCTs included in the review.			Secondary: Not reported	treated, with no documented intracerebral bleeding. In the second RCT, four and two placebo- and oral anticoagulation-treated patients had a recurrent stroke. The number of all vascular events was eight out of 21 in warfarin-treated patients compared to eleven out of 25 in placebo-treated patients (OR, 0.78; 95% CI, 0.20 to 2.9). In the same trial, no intracranial bleeds occurred. Combined results demonstrate that oral anticoagulation is highly effective; it reduces the odds of recurrent stroke (disabling and non-disabling) by two-thirds (OR, 0.36; 95% CI, 0.22 to 0.58) and it almost halves the odds of all vascular events (OR, 0.55; 95% CI, 0.37 to 0.82). The benefit is not negated by an unacceptable increase of major bleeding complications (OR, 4.32; 95% CI, 1.55 to 12.10). In both trials, no intracranial bleeds were reported in oral anticoagulation-treated patients (OR, 0.13; 95% CI, 0.00 to 6.49). Secondary: Not reported
Aguilar et al[47] Oral anticoagulants (warfarin [and congeners*] and orally active DTIs) vs control or placebo	SR (5 RCTs) Patients with AF without prior stroke or TIA	N=2,313 1.5 years (mean follow-up; range, 1.2 to 2.3 years)	Primary: All strokes Secondary: Ischemic strokes, all disabling or fatal stroke, MI, systemic emboli, all intracranial hemorrhage, major extracranial hemorrhage, vascular death, composite of all stroke, MI or vascular death, all-cause mortality	Primary: Consistent reductions were likewise evident in all trials, with an overall OR of 0.39 (95% CI, 0.26 to 0.59). About 25 strokes would be prevented yearly per 1,000 patients given oral anticoagulants. Secondary: Warfarin was associated with a reduction in ischemic stroke in all five trials, which was significant in four (pooled analysis vs control: OR, 0.34; 95% CI, 0.23 to 0.52). With the annualized rate of ischemic stroke in the control group of about four percent per year, the absolute reduction by oral anticoagulants was about 2.6% per year for patients without prior stroke or TIA, or about 25 ischemic strokes saved yearly per 1,000 patients given warfarin. Consistent reductions in all disabling or fatal strokes were seen in all trials, not reaching statistical significance in individual trials but with a significant reduction in pooled analysis (OR, 0.47; 95% CI, 0.28 to 0.80). About 12 of these serious strokes would be prevented yearly for every 1,000 participants

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				given warfarin. Fifteen MIs occurred in three trials; therefore, no meaningful estimate of the effect of oral anticoagulants on this outcome could be made (OR, 0.87; 95% CI, 0.32 to 2.42). Ten systemic emboli occurred in the five trials; therefore, no meaningful estimate of the effect of oral anticoagulants could be made, but with the trend similar to that for ischemic stroke (OR, 0.45; 95% CI, 0.13 to 1.57). Seven intracranial hemorrhages occurred, with a nonsignificant trend toward the expected increase (OR, 2.38; 95% CI, 0.54 to 10.50). Major extracranial hemorrhage was similar in warfarin-treated patients, but with wide CIs due to the relatively small number of events (OR, 1.07; 95% CI, 0.53 to 2.12). A nonsignificant trend favoring treatment with warfarin was seen (OR, 0.84; 95% CI, 0.56 to 1.30) for vascular death. For the composite of stroke, MI or vascular death, the OR with oral anticoagulants was 0.57 (95% CI, 0.42 to 0.76). About 25 of these events would be prevented per year for every 1,000 patients given warfarin. Sixty nine and 99 deaths occurred in warfarin- and control-treated patients (OR, 0.69; 95% CI, 0.50 to 0.94). The mortality rate averaged 5% per year in the control group. About 17 deaths would be prevented per year for every 1,000 AF patients given warfarin.
Ezekowitz et al[48] Warfarin vs aspirin	MA (10 trials) Patients with AF	N=not reported 1.2 to 2.3 years (average follow-up)	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Pooled analysis from the five PC, primary prevention trials demonstrate the value of warfarin for reducing the risk of stroke was consistent among trials

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vs warfarin plus aspirin A total of 10 trials were included: five primary prevention PC trials, one secondary prevention trial, one trial comparing warfarin to aspirin, and three trials of warfarin plus aspirin.				and decreased the risk by 68% (4.5 to 1.4% per year) with virtually no increase in the frequency of major bleeding (rates: 1.2, 1.0 and 1.0% per year for warfarin, aspirin and placebo, respectively). Two of these trials evaluated aspirin for the primary prevention of stroke. In one trial, aspirin use was associated with a 42% reduction in stroke and in the other; the reduction of stroke with aspirin compared to placebo was 36%. The primary prevention trials demonstrate that warfarin is "superior" to both aspirin and placebo, with aspirin being more effective than placebo for preventing stroke. The annual rate of the main outcome measures of death due to vascular disease, any stroke, MI or systemic embolism in the secondary prevention trial was 8% per year in warfarin-treated patients and 17% per year in placebo-treated patients. Treatment with warfarin reduced the risk of stroke from 12 to 4% per year (66% reduction). Among the aspirin-treated patients, the incidence of outcome events was 15% per year compared to 19% per year among placebo-treated patients. The incidence of major bleeding was low in this trial: 2.8, 0.9 and 0.7% per year for warfarin, aspirin and placebo. In the trial comparing warfarin to aspirin for the primary prevention of stroke, the primary event rate was 1.3 and 1.9% per year in warfarin- and aspirin-treated patients (RR, 0.67; *P*=0.24), and by ITT analysis there was no benefit from treatment with warfarin. Of note, the trial was not adequately powered to show a difference between the two treatments. Patients >75 years of age had a substantial risk of thromboembolism during treatment with aspirin (4.8% per year); treatment with warfarin reduced the risk to 3.6% per year (RR, 0.73; *P*=0.39). The trial evaluating warfarin in combination with aspirin to warfarin monotherapy in AF patients with at least one prespecified risk factor for thromboembolic disease was terminated after a mean follow-up of 1.1 years because the rate of ischemic stroke and systemic embolization in combination-treated patients was 7.9% per year compared to 1.9% per year in warfarin-treated patients (*P*<0.001). The rates of major bleeding were similar in both treatments.
Garcia et al[59]	Subanalysis of	N=18,201	Primary:	Primary:

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ARISTOTLE Apixaban 5 mg BID vs warfarin 2 mg; dose adjusted to maintain an INR of 2.0 to 3.0 An apixaban dose of 2.5 mg BID was used in patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg or a serum creatinine level ≥1.5 mg/dL.	ARISTOTLE[12] Patients enrolled in the ARISTOTLE trial stratified based on previous VKA use	1.8 years	Composite of all stroke (ischemic or hemorrhagic) and systemic embolism. Secondary: Mortality, major bleeding, intracranial bleeding, and permanent early treatment discontinuation	Compared with patients in the warfarin arm, patients randomized to receive apixaban had numerically lower rates of stroke/systemic embolism irrespective of prior VKA use. For stroke/systemic embolism, the differences favoring apixaban over warfarin were consistent: the HR was 0.86 (95% CI, 0.67 to 1.11) in the VKA-naive patients and 0.73 (95% CI, 0.57 to 0.95) in the VKA-experienced patients (P=0.39). The treatment effects of apixaban (vs warfarin) were not modified by VKA naivety. Secondary: A similar consistency of treatment effect was seen for other key end points; numerically lower rates of major bleeding and all-cause death were seen in the apixaban treated patients, and there is no evidence that this effect was modified by VKA naivety. Apixaban-treated patients had lower rates of intracranial bleeding overall; the effect of apixaban on intracranial bleeding was less pronounced in patients who were VKA naive (HR, 0.60; 95% CI, 0.38 to 0.93) than in those who were VKA-experienced (HR 0.28; 95% CI, 0.17 to 0.46) (P=0.02). Premature permanent study drug discontinuation was numerically less likely in the patients assigned to apixaban whether they were VKA naive (HR, 0.87; 95% CI, 0.79 to 0.95) or VKA experienced (HR, 0.93; 95% CI, 0.85 to 1.02).
Reduce the Risk of Death, Recurrent Myocardial Infarction and Thromboembolic Events Such as Stroke or Systemic Embolization After Myocardial Infarction				
Rothberg et al[49] Warfarin (high intensity) plus aspirin vs aspirin	MA (10 RCTs) Patients with ACS who were not stented	N=5,938 3 months to 4 years (follow-up)	Primary: MI, stroke, revascularization Secondary: Not reported	Primary: The annualized rate of MI in aspirin-treated patients ranged from 0.03 to 0.93. Nine of the ten trials found a risk reduction attributable to treatment with warfarin, but only two trials were sufficiently powered for the reduction to reach statistical significance. Reductions in RR ranged from 29 to 100%, with an overall RR of 44%. The annualized risk for ischemic stroke in aspirin-treated patients ranged from 0.000 to 0.080, with a weighted average of 0.008. In the five trials in which at least one stroke was reported, a risk reduction for warfarin plus aspirin-treated patients was found, but only one risk reduction was statistically significant. Reductions in the RR ranged from 50 to 100%, with

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				an overall RR of 54% (CI, 23 to 73). Oversall, four hemorrhagic strokes occurred in warfarin-treated patients and one in aspirin-treated patients, translating to one additional intracranial hemorrhage per 1,800 patient-years of combined anticoagulation. The annualized risk for revascularization ranged from 0.076 to 1.300. Five of the seven trials showed decreased rates of percutaneous transluminal coronary angioplasty or CABG for warfarin-treated patients, but only one rate reached statistical significance. HRs ranged from 0.51 to 1.70, with an overall RR reduction of 20% (95% CI, 5 to 33). No trial showed a significant difference in mortality. The combined trials showed a four percent decrease in overall mortality in warfarin-treated patients, but this did not reach significance (*P* value not reported). Nine trials showed an increased risk for major bleeding associated warfarin treatment. The annualized risk for major bleeding in warfarin-treated patients ranged from 0.6 to 18.0%, with an overall risk of 1.5%. The RR for major bleeding with warfarin treatment compared to aspirin was 2.5 (95% CI, 1.7 to 3.7). The RR for minor bleeding was 2.6 (95% CI, 2.0 to 3.3). Secondary: Not reported
Prophylaxis and/or Treatment of Venous Thromboembolism				
Eriksson et al[16] RECORD1 Rivaroxaban 10 mg QD for 35 days vs enoxaparin 40 mg SC QD in the evening for 35 days	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total hip replacement	N=4,541 70 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to 36 days; incidence of major bleeding beginning after the first dose of the study drug and up to two days after the last dose of the study drug	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint (1.1 vs 3.7%; ARR, -2.6%; 95% CI, -3.7 to -1.5; *P*<0.001). There was no difference between rivaroxaban and enoxaparin for major bleeding events (0.3 vs 0.1%; *P*=0.18). Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.2 vs 2.0%; ARR, -1.7%; 95% CI, -2.5 to 1.0; *P*<0.001). Rivaroxaban significantly reduced the risk of DVT (0.8 vs 3.4%; ARR, -2.7;

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Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and then reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events and death	95% CI, -3.7 to -1.7; *P*<0.001). Rivaroxaban and enoxaparin had similar rates of symptomatic VTE during treatment (0.3 vs 0.5%; ARR, -0.2%; 95% CI, -0.6 to 0.1; *P*=0.22) and follow-up (<0.1 vs 0.0%; ARR, -0.1%; 95% CI, -0.4 to 0.1; *P*=0.37). Both treatments had <0.1% cases of death occurring during follow-up (*P* value not reported). Rivaroxaban and enoxaparin had similar rates for any on-treatment bleeding (6.0 vs 5.9%; *P*=0.94) and any on-treatment nonmajor bleeding events (5.8 vs 5.8%; *P* value not reported). The rate of hemorrhagic wound complications was also similar (1.5 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after the first dose of rivaroxaban or placebo were also similar (5.5 vs 5.0%; *P* value not reported). Rivaroxaban and enoxaparin had similar rates of any on-treatment adverse event (64.0 vs 64.7%; *P* value not reported). The incidence of death during the on-treatment period was similar between the two treatments (0.3 vs 0.3%; ARR, 0%; 95% CI, -0.4 to 0.4; *P*=1.00). Of the four deaths that occurred with rivaroxaban, two were possibly related to VTE. Of the four deaths that occurred with enoxaparin, one was related to VTE.
Kakkar et al[17] RECORD2 Rivaroxaban 10 mg QD for 31 to 39 days vs enoxaparin 40 mg SC	DB, DD, MC, RCT Patients ≥18 years of age undergoing complete hip replacement	N=2,509 75 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause up to day 30 to 42; incidence of major bleeding beginning after the first dose of the study drug and up	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (2.0 vs 9.3%; ARR, 7.3%; 95% CI, 5.2 to 9.4; *P*<0.0001). Major bleeding occurred at a rate <0.1% with both rivaroxaban and enoxaparin (*P* value not reported). The one major bleeding event with enoxaparin was deemed unrelated to the treatment drug by the adjudication committee.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was administered 12 hours prior to surgery and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			to two days after the last dose of the study drug Secondary: Major VTE, (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow-up, death during the follow-up period, any on-treatment bleeding, any on-treatment nonmajor bleeding, hemorrhagic wound complications, any postoperative bleeding that started after the first dose and up to two days after the last dose of the study drug, adverse events and death	Secondary: Rivaroxaban significantly reduced the risk of major VTE (0.6 vs 5.1%; ARR, 4.5%; 95% CI, 3.0 to 6.0; *P*<0.0001). Rivaroxaban significantly reduced the risk of DVT (1.6 vs 8.2%; ARR, 6.5%; 95% CI, 4.5 to 8.5; *P*<0.0001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.2 vs 1.2%; ARR, 1.0%; 95% CI, 0.3 to 1.8; *P*=0.004); however, the rates during follow-up were similar (0.1 vs 0.2%; ARR, 0.1%; 95% CI, -0.2 to 0.4; *P*=0.62). The incidence of death during the follow-up period was similar between the two treatments (0.0 vs 0.2%; ARR, 0.2%; 95% CI, -0.1 to 0.6; *P*=0.50). Rates of any on-treatment bleeding (6.6 vs 5.5%; *P* value not reported) and any on-treatment nonmajor bleeding (6.5 vs 5.5%; *P* value not reported) were similar between the two treatments. Hemorrhagic wound complications also occurred at similar rates (1.6 vs 1.7%; *P* value not reported). The rate of any bleeding beginning after initiation of rivaroxaban or placebo was also similar (4.7 vs 4.1%; *P* value not reported). Adverse events from any cause were similar between the two treatments (62.5 vs 65.7%; *P* values not reported). The incidence of on-treatment death was similar between the two treatments (0.2 vs 0.7%; ARR, 0.5%; 95% CI, -0.2 to 1.1; *P*=0.29).
Lassen et al[18] RECORD3 Rivaroxaban 10 mg QD for 10 to 14 days vs	DB, DD, MC, RCT Patients ≥18 years of age undergoing elective total knee replacement	N=2,531 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause within 13 to 17 days post surgery; incidence of major bleeding beginning	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (9.6 vs 18.9%; ARD, -9.2%; 95% CI, -12.4 to -5.9; *P*<0.001). The rate of major bleeding was similar between the two treatments (0.6 vs 0.5%; *P*=0.77).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 40 mg SC QD for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin as administered 12 hour preoperatively and reinitiated six to eight hours after wound closure. All patients received either placebo tablets or placebo injection.			after the first dose of the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow up period, any on-treatment bleeding or any major bleeding occurring between intake of the first dose of the study medication and two days after the last dose, nonmajor bleeding, adverse events and death	Secondary: Rivaroxaban significantly reduced the risk of major VTE (1.0 vs 2.6%; ARD, -1.6%; 95% CI, -2.8 to -0.4; *P*=0.01). Rivaroxaban significantly reduced the risk of DVT (9.6 vs 18.2%; ARD, -8.4; 95% CI, -11.7 to -5.2; *P*<0.001). Rivaroxaban significantly reduced the risk of on-treatment symptomatic VTE (0.7 vs 2.0%; ARD, -1.3%; 95% CI, -2.2 to -0.4; *P*=0.005); however, during follow-up the rates were similar (0.4 vs 0.2%; ARD, 0.2%; 95% CI, -0.3 to 0.6; *P*=0.44). The incidence of death during follow-up was similar between the two treatments (ARD, -0.2%; 95% CI, -0.6 to 0.2; *P*=0.21). Rates of any on-treatment bleeding (4.9 vs 4.8%; *P*=0.93) or any major bleeding between the start of treatment and two days after the last dose (0.6 vs 0.5%; *P*=0.77) were similar between the two treatments. The rate of nonmajor bleeding was also similar (4.3 vs 4.4%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (12 vs 13%; *P* value not reported). The incidence of death during treatment was similar between the two treatments (0.0 vs 0.2%; ARD, -0.2%; 95% CI, -0.8 to 0.2; *P*=0.23)
Turpie et al[21] RECORD4 Rivaroxaban 10 mg QD for 10 to 14 days vs	DB, DD, MC, RCT Patients ≥18 years of age undergoing total knee replacement	N=3,148 49 days	Primary: The composite of any DVT, nonfatal PE, or death from any cause 17 days after surgery; incidence of major bleeding beginning after the first dose of	Primary: Rivaroxaban significantly reduced the risk of the primary composite endpoint compared to enoxaparin (6.9 vs 10.1%; ARD, -3.19%; 95% CI, -5.67 to -0.71; *P*=0.0118). There was no difference in the rate of major bleeding between the two treatments (0.7 vs 0.3%; *P*=0.1096).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enoxaparin 30 mg SC BID for 10 to 14 days Rivaroxaban was initiated six to eight hours after wound closure. Enoxaparin was initiated 12 to 24 hours after wound closure. All patients received either placebo tablets or placebo injection.			the study drug and up to two days after the last dose of the study drug Secondary: Major VTE (composite of proximal DVT, nonfatal PE, or death from VTE), incidence of asymptomatic DVT (any thrombosis, including both proximal and distal), incidence of symptomatic VTE during treatment and follow up, death during the follow-up period, clinically relevant nonmajor bleeding, any on-treatment bleeding, any nonmajor bleeding, hemorrhagic wound complications, adverse events and death	Secondary: Rivaroxaban did not reduce the risk of major VTE compared to enoxaparin (1.2 vs 2.0%; ARD, -0.80; 95% CI, -1.34 to 0.60; *P*=0.1237). The rates of asymptomatic DVT were similar between the two treatments (*P* value not reported). Rivaroxaban did not reduce the risk of symptomatic VTE on-treatment (0.7 vs 1.2%; ARD, -0.47; 95% CI, -1.16 to 0.23; *P*=0.1868) or during follow-up (0.2 vs 0.2%; ARD, 0.00%; 95% CI, -0.32 to 0.32; *P*=0.9979). The incidence of death during follow-up was similar between the two treatments (0.3 vs 0.2%; ARD, 0.06%; 95% CI, -0.35 to 0.50; *P*=0.8044). The rates of clinically relevant nonmajor bleeding (10.2 vs 9.2%; *P* value not reported) and any on-treatment bleeding (10.5 vs 9.4%; *P*=0.3287) were similar between the two treatments. The rate of hemorrhagic wound complications was also similar (1.4 vs 1.5%; *P* value not reported). The rates of drug-related adverse events were similar between the two treatments (20.3 vs 19.6%; *P* value not reported). The rates of on-treatment death were similar between the two treatments (0.1 vs 0.2%; *P*=0.7449).
Hutten et al[50] Oral anticoagulants (dicoumarol*, warfarin) Trials were included if different durations of treatment with a VKA were compared.	SR (8 trials) Patients with symptomatic VTE	N=2,994 Duration varied	Primary: Recurrent VTE Secondary: Major bleeding, mortality	Primary: All trials reported on the occurrence of symptomatic VTE during the period from cessation in VKA-treated patients in the short duration arm until cessation of treatment in the long duration arm. Four trials demonstrated a significant protection from recurrent VTE complications during prolonged treatment with VKAs, while the others revealed a clear trend. In the combined analysis of all eight trials, a significant reduction in thromboembolic events during prolonged treatment was observed (116 out of 1,495 short duration vs 14 out of 1,499 long duration; OR, 0.18; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
The eight trials compared seven different periods of treatment with VKAs: four weeks vs three months, six vs 12 weeks, six weeks vs six months, three vs six months, three months vs one year, three vs 27 months, and six months vs four years.				0.13 to 0.26). Six trials evaluated the incidence of recurrent VTE in the period after cessation of study medication. No trial demonstrated a significant increase in VTE events among participants in the long arm after cessation of treatment, and combined analysis demonstrated similar results (96 out of 1,304 long duration vs 78 out of 1,301 short duration; OR, 1.24; 95% CI, 0.91 to 1.69). Analyses of pooled data demonstrated a significant reduction in recurrent VTE for the following comparisons: four weeks vs three months (OR, 0.23; 95% CI, 0.06 to 0.70), three vs six months (OR, 0.13; 95% CI, 0.05 to 0.33) and three vs 12 months (OR, 0.22; 95% CI, 0.11 to 0.44). Secondary: Four trials reported the incidence of major bleeding during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. No trial demonstrated a significant increase in bleeding complications during prolonged treatment, but combined results demonstrated a significant increase in major bleeding complications during this period (one out of 405 short duration vs eight out of 403 long duration; OR, 4.87; 95% CI, 1.31 to 18.15). Only one trial reported the incidence of major bleeding in the period after cessation of study medication. All trials reported on the occurrence of major bleeding complications for the entire period after randomization until the end of follow-up. No trial demonstrated a significant increase during prolonged treatment, but combined results demonstrated a significant increase during this period (36 out of 1,499 long duration vs 13 out of 1,495 short duration; OR, 2.61; 95% CI, 1.48 to 4.61). Three trials reported mortality during the period from cessation of treatment with VKAs in the short duration arm until cessation of treatment in the long duration arm. One trial demonstrated a non-significant decrease in mortality during prolonged treatment, while the others showed no trends. Combined results demonstrated a non-significant reduction in mortality favoring

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				prolonged treatment (12 out of 188 short duration vs 10 out of 188 long duration; OR, 0.80; 95% CI, 0.34 to 1.91). All trials reported on mortality for the entire period after randomization, with none demonstrating a significant reduction in morality. When the results were combined, a nonsignificant reduction in mortality during the entire study period was observed (71 out of 1,498 long duration vs 75 out of 1,496 short duration; OR, 0.93; 95% CI, 0.67 to 1.30).
van der Heijden et al[51] VKAs vs LMWH	SR (7 RCTs) Patients with symptomatic DVT receiving long-term treatment	N=1,137 3 to 9 months	Primary: Recurrent symptomatic VTE, major bleeding complications, mortality Secondary: Not reported	Primary: All seven trials reported the occurrence of recurrent symptomatic VTE during the first three to six months after randomization. Six trials showed no differences between treatment with LMWH and VKAs, and one trial found a significant OR of 0.38 (95% CI, 0.17 to 0.86) in favor of treatment with LMWH. When the seven trials are combined, the rate of recurrent symptomatic VTE was 6.7 vs 4.8% in VKA- and LMWH-treated patients, corresponding to a nonsignificant reduction in favor of LMWH (OR, 0.70; 95% CI, 0.42 to 1.16). Six trials evaluated the occurrence of recurrent symptomatic VTE during a period of six to nine months after cessation of the allocated treatment. The rate of recurrent symptomatic VTE was 3.5 vs 5.0% of VKA- and LMWH-treated patients, corresponding to nonsignificant difference in favor of VKA treatment (OR, 1.46; 95% CI, 0.80 to 2.69). All seven trials reported the incidence of major bleeding during allocated treatment, with six trials finding no difference between the two treatments and one finding a significant difference in favor of treatment with LMWH (OR, 0.12; 95% CI, 0.02 to 0.89). When the trials were combined, 2.5 vs 0.9% VKA- and LMWH-treated patients had a major bleed; a significant difference in favor of treatment with LMWH (OR, 0.38; 95% CI, 0.15 to 0.94). No major bleeding occurred in the additional nine months of follow-up. All seven trials reported on mortality during the allocated treatment, with the individual trials not finding a significant difference between the two treatments. In the combined analysis, 2.5 vs 3.7% of VKA- and LMWH-treated patients died (OR, 1.51; 95% CI, 0.77 to 2.97). Six trials extended

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the follow-up period for an additional six to nine months and found that the rate of death was 3.5 vs 3.9% (OR, 1.11; 95% CI, 0.58 to 2.15). Secondary: Not reported
Salazar et al[52] DTI (dabigatran†, desirudin, ximelagatran*) vs warfarin or LMWH (dalteparin, enoxaparin)	SR (12 RCTs) Patients who have undergone total hip replacement or total knee replacement	N=21,642 (efficacy) N=27,360 (safety) Duration varied	Primary: Mortality associated with VTE, incidence of proximal VTE, mortality associated with treatment, appearance of serious hepatopathy, appearance of other serious adverse effects associated with treatment Secondary: Incidence of distal VTE, presence of hepatopathy after treatment, morbidity associated with treatment	Primary and Secondary end points are reported together in the groupings below. *Major, total and symptomatic VTE* Combined analysis from two trials comparing DTIs to LMWH demonstrated that when evaluating the combination of both surgery groups, no difference was observed between the two treatments (557 out of 10,736 vs 392 out of 6,692 events/patients; OR, 0.91; 95% CI, 0.69 to 1.19). Evaluation of the individual surgery groups had similar results. No difference was observed between the two treatments for total VTE (data not reported) or symptomatic VTE (234 out of 12,056 vs 143 out of 7,563; OR, 1.04; 95% CI, 0.84 to 1.29). Combined analysis from three trials comparing ximelagatran to warfarin demonstrated no statistical difference between the two treatments (95 out of 2,498 vs 83 out of 1,829 events/patients; OR, 0.85; 95% CI, 0.63 to 1.15). There were fewer total VTE events in DTI-treated patients (555 out of 2,514 vs 543 out of 1,840; OR, 0.68; 95% CI, 0.59 to 0.78). No difference between the two treatments were observed for symptomatic VTE (47 out of 3,022 vs 48 out of 2,237; OR, 0.80; 95% CI, 0.53 to 1.21). *Major/significant and total bleeding events* Combined analysis from eleven trials comparing DTIs to LMWH demonstrated a nonsignificant higher number of major significant bleeding events in DTI-treated patients (334 out of 13,753 vs 138 out of 8,356 events/patients; OR, 1.17; 95% CI, 0.87 to 1.58). In the comparison of each independent dose, only dabigatran 225 mg BID showed more bleeding events in the DTI group (OR, 1.90; 95% CI, 1.05 to 3.44) in the combination of both surgeries and specifically in total hip replacement (26 out of 270 vs 13 out of 270; OR, 2.11; 95% CI, 1.06 to 4.19). Combined analysis from ten trials demonstrated no difference between the two treatments in terms of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				total bleeding events; however, more events were observed in DTI-treated patients undergoing total hip replacement (2,370 out of 5,949 vs 1,374 out of 4,378; OR, 1.40; 95% CI, 1.06 to 1.85). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated more major/significant bleeding events with ximelagatran, but the difference was not statistically significant (30 out of 3,022 vs 13 out of 2,237 events/patients; OR, 1.76; 95% CI, 0.91 to 3.38). Partial and total bleeding events were very similar to major bleeding events. *All-cause mortality* Combined analysis of eleven trials comparing DTIs to LWMH demonstrated a nonsignificant higher all-cause mortality event rate with DTI treatment (15 out of 13,730 vs four out of 8,335 events/patients; OR, 1.72; 95% CI, 0.68 to 4.35). When including follow-up events the difference met statistical significance (41 out of 13,730 vs 11 out of 8,335; OR, 2.06; 95% CI, 1.10 to 3.87). Combined analysis of three trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (six out of 3,013 vs four out of 2,230 events/patients; OR, 1.19; 95% CI, 0.36 to 4.01), even when follow-up events were included (10 out of 3,013 vs five out of 2,230; OR, 1.62; 95% CI, 0.57 to 4.58). *ALT greater than three times the upper normal limit* The seven trials comparing DTIs to LMWH had high heterogeneity; therefore, results could not be combined. Fewer events were observed in DTI-treated patients, but with high heterogeneity, in the ximelagatran trials. No difference was noted when treatment with dabigatran was compared to treatment with LMWH, but these trials had very high heterogeneity. Combined analysis of two trials comparing ximelagatran to warfarin demonstrated no significant difference between the two treatments (18 out of 2,493 vs 21 out of 1,768 events/patients; OR, 0.52; 95% CI, 0.27 to 0.97), even when follow-up events were included (11 out of 2,484 vs one out of 1,783; OR, 5.61; 95% CI, 1.00 to 31.64).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Volume of blood loss No difference was observed between treatment with DTIs and LMWH in the combined analysis of five trials (n=8,782; WMD, 5.12; 95% CI, -33.81 to 44.04), but these trials had high heterogeneity. No difference was observed between ximelagatran and warfarin in the combined analysis of three trials (n=5,259; WMD, -7.12; 95% CI, -17.08 to 2.84), with no heterogeneity. *Time effect of the beginning of anticoagulation* Trials comparing DTIs to LMWH that began anticoagulation before surgery demonstrated fewer major (OR, 0.54; 95% CI, 0.35 to 0.83) and total (OR, 0.72; 95% CI, 0.63 to 0.82) VTE in DTI-treated patients in both surgery groups. There was also no difference regarding symptomatic VTE. Trials that began anticoagulation after surgery demonstrated more major (OR, 1.68; 95%, 1.12 to 2.52) and total (OR, 1.29; 95% CI, 0.69 to 2.39) VTE events in DTI-treated patients in both surgery groups. Again, there was no difference regarding symptomatic VTE. Trials that began anticoagulation before surgery demonstrated a non-significant greater incidence of major (OR, 1.64; 95% CI, 0.85 to 3.15) and total (OR, 1.45; 95% CI, 0.93 to 2.28) bleeding events in DTI-treated patients in both combined surgeries and in the individual analysis of each surgery. There was no significant difference regarding mortality. *Extended prophylactic anticoagulation vs standard prophylactic anticoagulation* No difference was found in major or total VTE between DTI- and LMWH-treated patients. Symptomatic VTE events in extended anticoagulation occurred more with dabigatran in comparison to LMWH, but the difference was not statistically significant (25 out of 2,293 vs five out of 1,142 events/patients; OR, 2.51; 95% CI, 0.96 to 5.67). In standard anticoagulation, no difference between DTI- and LMWH-treated patients was noted (76 out of 3,351 vs 37 out of 1,542; OR, 0.99; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.67 to 1.48). Regarding safety, no difference in major or total bleeding events was noted. All-cause mortality, transaminase levels and blood loss were not evaluated.
Brookenthal et al[53] Thromboprophylaxis (aspirin, dextran, heparin [with or without antithrombin III], LMWH [ardeparin*, enoxaparin, tinzaparin], lower extremity pneumatic compression stockings, or warfarin) vs placebo A prophylactic agent of interest was compared to another method of interest or placebo.	MA (14 trials) Patients receiving prophylaxis for ≥7 days for an elective total knee arthroplasty	N=3,482 Duration varied	Primary: Total DVT, proximal DVT, distal DVT, symptomatic PE, fatal PE, minor bleeding, major bleeding, total bleeding, intracranial hemorrhage, non-PE mortality, all-cause mortality Secondary: Not reported	Primary: For total DVT, all treatments, except dextran and aspirin, protected significantly better than placebo (*P*<0.0001). For proximal DVT, no comparison against placebo was available, and rates ranged from 1.7 (aspirin) to 12.8% (SC heparin/antithrombin III). The only significant difference was between treatment with LMWH and warfarin (5.9 vs 10.2%; *P*=0.0002). There was a strong trend that aspirin protected better than warfarin (1.7 vs 10.2%; *P*=0.0106). For distal DVT, no comparison against placebo was available. LMWH (24.4%) protected significantly better than dextran (71.1%; *P*=0.0001), warfarin (35.6%; *P*=0.0001) and aspirin (55.2%; *P*=0.0001). Warfarin (35.6%) protected significantly better than aspirin (55.2%; *P*=0.0045) but worse than SC heparin (21.5%; *P*=0.0029). Aspirin (55.2%) protected significantly less than SC heparin (21.5%; *P*=0.0001) and pneumatic compression stockings (29.5%; *P*=0.0051). Rates of symptomatic PE ranged from 0.0 (aspirin, pneumatic compression stockings and placebo) to 0.4% (warfarin, SC heparin); there was no significant detectable difference among the agents. No fatal PE occurred with any treatment. The rate of total bleeding ranged from 8.6 (aspirin) to 18.9% (SC heparin). No comparison with placebo was available. The rate of minor bleeding ranged from 8.6 (aspirin) to 18.3% (SC heparin). Rates of major bleeding ranged from 0.0 (aspirin, pneumatic compression stockings) to 2.4% (LWMH), but no difference between treatments were noted.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no observed intracranial hemorrhages. Rates for overall and non-PE mortality ranged from 0.0 (aspirin, SC heparin, pneumatic compression stockings, placebo, SC heparin/antithrombin III and dextran) to 0.3% (warfarin), but no difference among the treatments were noted. Secondary: Not reported
Cundiff et al[54] Anticoagulants (heparin, phenprocoumon*, warfarin) vs NSAIDs (phenylbutazone*) or placebo	SR (2 RCTs) Patients with DVT or PE	N=113 3 months	Primary: Mortality due to PE, PE, DVT and extension of DVT or both Secondary: All-cause mortality, major hemorrhagic events, fatal hemorrhagic events, morbidity and mortality due to HIT with thrombosis	Data were not pooled because of heterogeneity between the trials, and the trials were too small to determine any difference in mortality, occurrence of PE, and progression or return of DVT between patients receiving anticoagulation and those who were not. Primary: In one trial (n=23), no deaths due to PE were reported and in the other trial (n=90), there was no significant difference in deaths due to PE between anticoagulant- and NSAID-treated patients (one vs zero; RR, 2.63; 95% CI, 0.11 to 62.95). In one trial (n=23), there was no difference in the combined outcome PE, DVT progression or return in anticoagulation-treated patients compared to those who did not receive anticoagulation (five vs five; RR, 1.09; 95% CI, 0.43 to 2.77). In one trial (n=90), there was no difference in the combined outcome recurrent DVT or DVT (18 vs 22; RR, 0.72; 95% CI, 0.45 to 1.14). Secondary: There was no difference in the secondary outcomes of all-cause mortality and major hemorrhage in either trial between the two treatments. Neither trial reported morbidity or mortality due to HIT with thrombosis, or VKA necrosis.
Di Nisio et al[55] Any oral or parenteral	SR (9 RCTs) Ambulatory	N=3,538 Duration varied	Primary: Symptomatic VTE, major bleeding	Primary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that when compared to placebo,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
anticoagulant (UFH, LMWH, VKA, direct thrombin or factor Xa inhibitors), or both vs inactive control (placebo, no treatment, standard care) or active control	outpatients of any age with either a solid or hematological cancer, at any stage, and receiving chemotherapy, without a positive history of VTE		Secondary: Symptomatic PE, symptomatic DVT, asymptomatic VTE, overall VTE, minor bleeding, one year overall mortality, arterial thromboembolic events, superficial thrombophlebitis, quality of life, number of patients experiencing any serious adverse event	LMWH was associated with a significant reduction symptomatic VTE (RR, 0.62; 95% CI, 0.41 to 0.93), corresponding to a NNT of 60. Pooled analysis of six RCTs suggested a 60% increased risk of a major bleeding (RR, 1.57; 95% CI, 0.69 to 3.60). *LMWH vs active control* In one trial, LMWH was associated with a 67% reduction in symptomatic VTE relative to warfarin (RR, 0.33; 95% CI, 0.14 to 0.83) while the difference with aspirin was not significant (RR, 0.50; 95% CI, 0.19 to 1.31). In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of major bleeding. *VKA vs inactive control* In one trial, a trend for a reduction in symptomatic VTE (RR, 0.15; 95% CI, 0.02 to 1.20) was reported. There was no significant effect on major bleeding (RR, 0.52; 95% CI, 0.05 to 5.71). *VKA vs active control* One trial reported a nonsignificant difference between VKA and aspirin (RR, 1.50; 95% CI, 0.74 to 3.04). *Antithrombin vs inactive control* In one trial, the effects of antithrombin on symptomatic VTE (RR, 0.84; 95% CI, 0.41 to 1.73) and major bleeding (RR, 0.78; 95% CI, 0.03 to 18.57) were not significant. Secondary: *LMWH vs inactive control* Pooled analysis of six RCTs demonstrated that there was no significant effect on symptomatic PE (RR, 0.63; 95% CI, 0.21 to 1.91) or DVT (RR, 0.60; 95% CO. 0.33 to 1.07). In pooled data from six RCTs, the risk of overall VTE was reduced by 45% with LMWH (RR, 0.55; 95% CI, 0.34 to 0.88) whereas there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant benefit or harm for asymptomatic VTE, minor bleeding, one-year mortality, symptomatic arterial thromboembolism, superficial thrombophlebitis, or serious adverse events. None of the six trials considered quality of life, heparin-induced thrombocytopenia, or the incidence of osteoporosis as study incomes. Three trials reported on symptomatic VTE and major bleeding in patient with non-small cell or small cell lung cancer, or both. Pooled analysis showed a nonsignificant 46% reduction in symptomatic VTE (RR, 0.54; 95% CI, 0.27 to 1.09) and a nonsignificant 73% higher risk of major bleeding with LMWH compared to control (RR, 1.73; 95% CI, 0.65 to 4.57). *LMWH vs active control* In one trial, there were no differences between LMWH, aspirin, and warfarin regarding the incidence of symptomatic PE or DVT, minor bleeding, and symptomatic arterial thromboembolism. *VKA vs inactive control* In one trial, there was no significant effect on symptomatic PE (RR, 1.05; 95% CI, 0.07 to 16.58), symptomatic DVT (RR, 0.08; 95% CI, 0.00 to 1.42), or minor bleeding (RR, 2.44; 95% CI, 0.64 to 9.27). No symptomatic arterial thromboembolic events were observed in the VKA or placebo groups. *VKA vs active control and antithrombin vs inactive control* Secondary outcomes were not reported for these comparisons.
Schulman et al[57] RE-COVER Dabigatran 150 mg BID vs Warfarin dose adjusted QD	DB, DD, MC, RCT Patients ≥ 18 years of age with acute symptomatic, objectively verified proximal DVT thrombosis of the legs or PE and for	N= 2,539 6 months	Primary: Time to the first occurrence of symptomatic VTE or death associated with VTE Secondary: Symptomatic DVT,	Primary: After central adjudication, the primary outcome for efficacy was confirmed in 30 patients in the dabigatran group (2.4%) and 27 patients in the warfarin group (2.1%). The difference in risk was 0.4% (95% CI; −0.8 to 1.5; HR, 1.10; 95% CI, 0.65 to 1.84). As compared with warfarin, dabigatran was noninferior with regard to the prevention of recurrent or fatal VTE (P<0.001 for the criteria of both HR and the difference in risk). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received parenteral anticoagulation for a mean of 10 days	who six months of anticoagulant therapy was considered to be an appropriate treatment		symptomatic nonfatal PE, death related to VTE, all deaths	Symptomatic DVT occurred in 16 patients in the dabigatran group (1.3%) and 18 patients in the warfarin group (2.1%), HR 0.87 (95% CI; 0.44 to 1.71). Symptomatic nonfatal PE occurred in 13 patients in the dabigatran group (1.0%) and 7 patients in the warfarin group (0.6%), HR 1.85 (95% CI; 0.74 to 4.64). Death related to VTE occurred in one patient in the dabigatran group (0.1%) and three patients in the warfarin group (0.3%), HR 0.33 (95% CI; 0.03 to 3.15). All deaths occurred in 21 patients in the dabigatran group (1.6%) and 21 patients in the warfarin group (1.7%), HR 0.98 (95% CI; 0.53 to 1.79).
Schulman et al[60] RE-COVER II Dabigatran 150 mg BID vs warfarin dose adjusted QD All patients received five to 11 days of therapy with LMWH or unfractionated heparin	DB, DD, MC, RCT Patients ≥ 18 years of age with acute symptomatic, objectively verified proximal DVT thrombosis of the legs or PE and for who six months of anticoagulant therapy was considered to be an appropriate treatment	N=2,589 6 months	Primary: Recurrent symptomatic, objectively confirmed VTE and related deaths during six months of treatment. Secondary: Symptomatic DVT, symptomatic non-fatal PE, death related to PE, and all death	Primary: Recurrent non-fatal or fatal VTE was confirmed after central adjudication in 30 patients in the dabigatran group (2.3%) and in 28 patients in the warfarin group (2.2%) (HR, 1.08; 95% CI, 0.64 to 1.80). The difference in risk was 0.2% (95% CI, −1.0 to 1.3) in favor of warfarin. Dabigatran was non-inferior to warfarin for the prevention of recurrent or fatal VTE (P<0.001 for both HR and difference in absolute risk criteria). Efficacy results were consistent in all the predefined subgroups (data not shown). Secondary: Symptomatic DVT occurred in 25 patients (2.0%) in the dabigatran group and 2.2 patients (1.3%) in the warfarin group (HR, 1.08; 95% CI, 0.80 to 2.74). Symptomatic nonfatal PE occurred in seven patients (0.5%) in the dabigatran group and 13 (1.0%) patients in the warfarin group (HR, 0.54; 95% CI, 0.21 to 1.35). There occurred that were related to PE in the dabigatran group with zero in the warfarin group. There were 25 deaths (2.0%) in the dabigatran group and 25 deaths (1.9%) in the warfarin group (HR, 0.98; 95% CI, 0.56 to 1.71)
Schulman et al[61] Study 1: RE-MEDY Dabigatran 150 mg BID Vs	Study 1: AC, DB, MC, NI, RCT Study 2: PC, DB, MC, RCT	N= 4,199 6 to 36 months	Primary: Recurrent symptomatic and objectively verified VTE or death associated with VTE (or unexplained death	Primary: In the active-control study, recurrent VTE occurred in 26 of 1,430 patients in the dabigatran group (1.8%) and 18 of 1426 patients in the warfarin group (1.3%) (HR, 1.44; 95% CI, 0.78 to 2.64; P=0.01 for noninferiority). Major bleeding occurred in 13 patients in the dabigatran group (0.9%) and 25 patients in the warfarin group (1.8%) (HR, 0.52; 95% CI, 0.27 to 1.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
warfarin (dose adjusted) QD Study 2: RE-SONATE Dabigatran 150 mg BID vs placebo	Patients ≥18 years of age diagnosed with VTE who completed at least the first three months of therapy (six months for the second study)		in the placebo-control study), major bleeding and clinically relevant non-major bleeding Secondary: Not reported	Major or clinically relevant bleeding was less frequent with dabigatran (HR, 0.54; 95% CI, 0.41 to 0.71). Acute coronary syndromes occurred in 13 patients in the dabigatran group (0.9%) and three patients in the warfarin group (0.2%) (P=0.02). In the placebo-control study, recurrent venous thromboembolism occurred in 3 of 681 patients in the dabigatran group (0.4%) and 37 of 662 patients in the placebo group (5.6%) (HR, 0.08; 95% CI, 0.02 to 0.25; P<0.001). Major bleeding occurred in two patients in the dabigatran group (0.3%) and 0 patients in the placebo group. Major or clinically relevant bleeding occurred in 36 patients in the dabigatran group (5.3%) and 12 patients in the placebo group (1.8%) (HR, 2.92; 95% CI, 1.52 to 5.60). Acute coronary syndromes occurred in one patient each in the dabigatran and placebo groups. Secondary: Not reported
Lassen et al[62] ADVANCE-1 Apixaban 2.5 mg BID and matching placebo injection vs enoxaparin 30 mg SC every 12 hours and matching placebo tablets BID Patients received the first doses of the study medications 12 to 24	AC, DB, DD, MC, RCT Patients who were to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint	N=3,195 10 to 14 days of treatment (plus 60 days follow-up)	Primary: Composite of asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause during the intended treatment period Secondary: Composite of major thromboembolism and death from any cause, and symptomatic thromboembolism during the intended	Primary: The statistical criterion for the noninferiority of apixaban as compared with twice-daily administration of enoxaparin was not met. The primary efficacy outcome occurred in 104 of 1157 patients (9.0%) in the apixaban group, as compared with 100 of 1130 patients (8.8%) in the enoxaparin group (RR, 1.02; 95% CI, 0.78 to 1.32; P=0.06 for noninferiority; difference in risk, 0.1%; 95% CI, –2.2% to 2.4%; P<0.001). Secondary: Composite major thromboembolism and death from any cause occurred in 26 of 1269 patients (2.1%) in the apixaban group and in 20 of 1216 patients (1.6%) in the enoxaparin group (RR, 1.25; 95% CI, 0.70 to 2.23; difference in risk, 0.36%; 95% CI, –0.68% to 1.40%). Symptomatic thromboembolism and death from any cause occurred in 26 of 1269 patients (2.1%) in the apixaban group and in 20 of 1216 patients(1.6%) in the enoxaparin group (RR, 1.25; 95% CI, 0.70 to 2.23; difference in risk, 0.36%; 95% CI, –0.68% to 1.40%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hours after surgery in order to be consistent with FDA label for enoxaparin.			treatment period	Follow-up for 60 days after the last dose of study medication was completed in 1562 of the 1599 patients (97.7%) assigned to apixaban and in 1554 of the 1596 patients (97.4%) assigned to enoxaparin. During the 60-day follow-up period, symptomatic venous thromboembolism occurred in 4 of 1562 patients (0.3%) in the apixaban group and in 7 of 1554 patients (0.5%) in the enoxaparin group. Major bleeding events occurred in 11 of 1596 patients (0.7%) who received apixaban and in 22 of 1588 patients (1.4%) who received enoxaparin (adjusted difference in event rates according to type of surgery, -0.81%; 95% CI, -1.49% to −0.14%; P=0.053). The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 46 patients (2.9%) in the apixaban group and 68 patients (4.3%) in the enoxaparin group (adjusted difference in event rates according to type of surgery, −1.46%; 95% CI, −2.75% to −0.17%; P=0.03).
Lassen et al[63] ADVANCE-2 Apixaban 2.5 mg BID and matching placebo injection QD vs enoxaparin 40 mg SC QD and matching placebo tablets BID The first subcutaneous injection of study drug was given 12 hours (within three hours) before operation, and injections were	AC, DB, DD, MC, RCT Patients who were scheduled to have unilateral elective total knee replacement or same-day bilateral knee replacement, including revision	N=3,057 10 to 14 days of treatment (plus 60 days follow-up)	Primary: Composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death during the intended treatment period or within two days of last dose of study drug, whichever was longer Secondary: Composite major VTE; composite of symptomatic DVT, non-fatal PE and VTE-	Primary: Apixaban was had statistically significant reduction in risk compared to enoxaparin for prevention of all VTE and all-cause death (RR, 0.62; 95% CI, 0.51 to 0.74, one-sided P<0.0001 when tested for non-inferiority and for superiority). ARR was 9.3% (95% CI, 5.8% to 12.7%) in favor of apixaban (one-sided p<0·0001 for non-inferiority). Secondary: Apixaban was also provided a statistically significant risk reduction compared with enoxaparin for major VTE prevention (RR, 0.50; 95% CI, 0.26 to 0.97, one-sided P=0.0186 for superiority; ARR, 1.04%; 95% CI, 0.05% to 2.03%). Rates of symptomatic VTE and VTE-related death did not differ between study groups (RR, 1.00; 0.35 to 2.85; ARR, 0.00%; (95% CI, −0.48% to 0.48%). One apixaban patient died of pulmonary embolism during. 1458 (95%) of 1528 apixaban patients and 1469 (96%) of 1529 enoxaparin patients completed 60 days of follow-up after last dose of study drug. Symptomatic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
resumed after surgery according to investigators' standard of care. The first dose of oral study drug was given 12 to 24 h after wound closure.			related death; composite of all DVTs (including asymptomatic); components of all DVT, including symptomatic DVT, proximal DVT, non-fatal PE, and VTE-related death; composite of PE and VTE-related death; VTE-related death	venous thromboembolism developed during follow-up in five (<1%) of 1458 apixaban patients and two (<1%) of 1469 enoxaparin patients. There were no statistically significant differences between treatments for the remaining secondary outcomes. Frequency of major bleeding events did not differ between treatment groups (P=0.3014).
Lassen et al[64] ADVANCE-3 Apixaban 2.5 mg BID plus matching placebo injection vs enoxaparin 40 mg SC QD plus matching placebo tablets BID The first subcutaneous injection of study drug was given 12 hours (within three hours) before operation, and injections were resumed after surgery according to	AC, DB, DD, MC, RCT Patients who were scheduled to undergo elective total hip replacement or revision of a previously inserted hip prosthesis	N=5,407 32 to 38 days of treatment (plus 95 day follow-up)	Primary: Composite of adjudicated asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the intended treatment period Secondary: Major VTE (composite of adjudicated symptomatic or asymptomatic proximal DVT [popliteal, femoral, or iliac-vein thrombosis]), nonfatal PE, or death related to VTE during the intended treatment period	Primary: The primary efficacy outcome occurred in 27 of the 1949 patients in the apixaban group who could be evaluated for that outcome (1.4%) and in 74 of the 1917 patients in the enoxaparin group who could be evaluated (3.9%) (RR with apixaban, 0.36; 95% CI, 0.22 to 0.54; one-sided P<0.001 for noninferiority and two-sided P<0.001 for superiority). The ARR with apixaban was 2.5% (95% CI, 1.5% to 3.5%). Secondary: Major VTE occurred in 10 of the 2199 patients (0.5%) in the apixaban group who could be evaluated for that outcome and in 25 of the 2195 (1.1%) in the enoxaparin group (RR, 0.40; 95% CI, 0.15 to 0.80; one-sided P<0.001 for noninferiority and two-sided P=0.01 for superiority). The ARR with apixaban was 0.7% (95% CI, 0.2% to 1.3%). With this reduction in risk, one additional episode of VTE would be prevented for every 147 patients treated with apixaban rather than enoxaparin. Major bleeding during the treatment period occurred in 22 of the 2673 patients who received apixaban (0.8%) and 18 of the 2659 patients who received enoxaparin (0.7%) with an absolute difference in risk of 0.1% (95% CI, −0.3% to 0.6%). Thirteen of the 22 major bleeding events in the apixaban group occurred before the first dose was administered; therefore, major

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
investigators' standard of care. The first dose of oral study drug was given 12 to 24 h after wound closure.				bleeding with an onset after the first dose of apixaban occurred in 9 of 2673 patients (0.3%; 95% CI, 0.2% to 0.7%). No bleeding event in either group was related to spinal or epidural anesthesia. The composite of major and clinically relevant non-major bleeding occurred in 129 patients who received apixaban (4.8%) and in 134 patients who received enoxaparin (5.0%) with an absolute difference in risk of −0.2% (95% CI, −1.4% to 1.0%). Of the 129 events that occurred in the apixaban group, 33 occurred before the first dose was administered. Thus, major or clinically relevant non-major bleeding with onset after the first dose of apixaban occurred in 96 of the 2673 patients (3.6%; 95% CI, 3.0% to 4.4%).
Treatment of DVT and PE, and for the reduction in the risk of recurrence of DVT and of PE				
EINSTEIN Investigators et al[20] EINSTEIN-DVT and EINSTEIN-EXT Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or acenocoumarol started within 48 hours of randomization and adjusted to maintain an INR of 2.0 to 3.0 Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had	AC, MC, OL, NI, RCT (EINSTEIN-DVT) DB, MC, PC, RCT (EINSTEIN-EXT) Patients with acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE; for enrollment into the extension phase, patients had objectively confirmed symptomatic DVT or PE and had been treated for six to 12 months with rivaroxaban or acenocoumarol	N=3,449 Up to 12 months (both studies)	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE), clinically relevant bleeding (EINSTEIN-DVT) or major bleeding (EINSTEIN-EXT) Secondary: All-cause mortality, vascular events (ACS, ischemic stroke, TIA, or systemic embolism), and net clinical benefit (composite of the primary efficacy outcome or major bleeding)	Primary: *EINSTEIN-DVT* A symptomatic, recurrent VTE occurred in 2.1% of patients treated with rivaroxaban and 3.0% of patients receiving standard therapy with enoxaparin (HR, 0.68; 95% CI, 0.44 to 1.04; *P*<0.001 for non inferiority, and *P*=0.08 for superiority). There was no statistically significant difference in the occurrence of clinically relevant (first major or clinically relevant nonmajor) bleeding between patients receiving rivaroxaban or standard therapy with enoxaparin (8.1% for both, HR, 0.97; 95% CI, 0.76 to 1.22; *P*=0.77). *EINSTEIN-EXT* Symptomatic, recurrent VTE occurred in eight patients in the rivaroxaban group and 42 patients in the placebo group (1.3 vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; *P*<0.001). Major bleeding occurred in four patients in the rivaroxaban group and zero patients in the placebo group (*P*=0.11). Secondary: *EINSTEIN-DVT* All-cause mortality was similar between patients treated with rivaroxaban or standard therapy with enoxaparin (2.2 vs 2.9%, respectively; HR, 0.67; 95% CI, 0.44 to 1.02; *P*=0.06).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
received at least five days of enoxaparin treatment. In the EINSTEIN-EXT trial, patients were randomized to receive rivaroxaban 20 mg QD or placebo for six to 12 months.	or warfarin (in the EINSTEIN studies or from routine care)			There was no statistically significant difference in vascular events between patients receiving rivaroxaban or standard therapy with enoxaparin (0.7 vs 0.8%, respectively; HR, 0.79; 95% CI, 0.36 to 1.71; *P*=0.55). There was a significantly greater net clinical benefit with rivaroxaban compared to standard therapy with enoxaparin (2.9 vs 4.2%; HR, 0.67; 95% CI, 0.47 to 0.95; *P*=0.03). *EINSTEIN-EXT* There was one death in the rivaroxaban treatment group and two deaths in the placebo group during follow up (*P* value not reported). There was no statistically significant difference in vascular events between patients receiving treatment with rivaroxaban or placebo (0.5 vs 0.7%, respectively; HR, 0.74; 95% CI, 0.17 to 3.3; *P*=0.69). There was a significantly greater net clinical benefit in patients who received rivaroxaban compared to placebo (2.0 vs 7.1%; HR, 0.28; 95% CI, 0.15 to 0.53; *P*<0.001).
EINSTEIN PE Investigators et al[21] EINSTEIN-PE Rivaroxaban 15 mg BID for three weeks followed by 20 mg QD vs enoxaparin 1 mg/kg SC BID plus warfarin or acenocoumarol started within 48 hours of randomization and adjusted to maintain an INR of 2.0 to 3.0	AC, MC, NI, OL, RCT Patients with an acute, symptomatic PE with objective confirmation, with or without symptomatic DVT Patients were ineligible if they had received a therapeutic dose of LMWH, fondaparinux, or UFH for more than	N=4,832 Up to 12 months	Primary: Symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) and clinically relevant bleeding Secondary: Major bleeding, death from any cause, vascular events (ACS, ischemic stroke, TIA, or systemic embolism) and net clinical benefit (composite of the	Primary: Symptomatic, recurrent VTE occurred in 50 patients (2.1%) receiving rivaroxaban and 44 patients (1.8%) receiving standard therapy with enoxaparin (HR, 1.12; 95% CI, 0.75 to 1.68; *P*=0.003 for non inferiority and *P*=0.57 for superiority). Recurrent, nonfatal VTE was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard therapy group. Major or clinically relevant nonmajor bleeding occurred in 249 patients (10.3%) receiving rivaroxaban and 274 patients (11.4%) receiving standard therapy with enoxaparin (HR, 0.90; 95% CI, 0.76 to 1.07; *P*=0.23). Secondary: Major bleeding occurred in 26 patients (1.1%) receiving rivaroxaban treatment compared to 52 patients (2.2%) receiving standard therapy with enoxaparin (HR, 0.49; 95% CI, 0.31 to 0.79, *P*=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Enoxaparin was discontinued when the INR was ≥2.0 for two consecutive days and the patient had received at least five days of enoxaparin treatment.	48 hours or if they had received more than a single dose of a VKA before randomization.		primary efficacy outcome and major bleeding)	There was no statistically significant difference in death from any cause between patients receiving rivaroxaban or standard therapy (2.4 vs 2.1%, respectively, HR, 1.13; 95% CI, 0.77 to 1.65; *P*=0.53). Fifteen patients in the rivaroxaban group and 21 patients in the standard therapy group experienced an acute coronary event (*P* value not reported). A cerebrovascular event was reported in 12 and 13 patients receiving rivaroxaban or standard therapy with enoxaparin, respectively (*P* value not reported). A systemic embolism occurred in five patients receiving rivaroxaban and three patients receiving standard therapy (*P* value not reported). A net clinical benefit was reported in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the standard therapy group (HR, 0.85; 95% CI, 0.63 to 1.14; *P*=0.28).
Safety				
Uchino et al[56] Dabigatran vs control (warfarin, enoxaparin, or placebo)	MA (7 RCTs; 2 trials of stroke prophylaxis in AF, 1 trial in acute VTE, 1 in ACS, and 3 of short term prophylaxis in DVT) Patient population not specified	N=30,514 Duration not specified	Primary: Acute coronary events (MI or ACS) Secondary: Overall mortality	Primary: Dabigatran was significantly associated with a higher risk of MI or ACS compared to control (237/20,000 [1.19%] vs 83/10,514 [0.79%]; OR, 1.33; 95% CI, 1.03 to 1.71; *P*=0.03). The risk of MI or ACS was similar when using revised RE-LY trial results (OR, 1.27; 95% CI, 1.00 to 1.61; *P*=0.05) or after exclusion of short term trials (OR, 1.33; 95% CI, 1.03 to 1.72; *P*=0.03). No relationship between the baseline risk of acute coronary events and the OR for acute coronary events associated with dabigatran use (*P*=0.61). Secondary: Six trials reported on overall mortality. Dabigatran was significantly associated with lower mortality compared to control (945/19,555 [4.83%] vs 524/10,444 [5.02%]; OR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.04).

*Not available in the United States.
†Not Food and Drug Administration approved for this indication.
Drug regimen abbreviations: BID=twice daily, SC=subcutaneous, QD=once daily
Study abbreviations: AC=active control, ARD=absolute risk difference, ARR=absolute risk reduction, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta analysis, MC=multicenter, NI=non inferiority, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PP=per-protocol, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference

Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, ALT=alanine transaminase, CABG=coronary artery bypass graft surgery, CAD=coronary artery disease, cTTR=center's mean time in therapeutic range, DTI=direct thrombin inhibitor, DVT=deep vein thrombosis, ECG=electrocardiogram, FDA=Food and Drug Administration, GUSTO= Global Utilization Of Streptokinase and Tpa For Occluded Arteries, HIT=heparin induced thrombocytopenia, INR=International Normalized Ratio, LMWH=low molecular weight heparin, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NSAID=nonsteroidal anti-inflammatory drug, NYHA=New York Heart Association, PE=pulmonary embolism, TIA=transient ischemic attack, TIMI=Thrombolysis in Myocardial Infarction, TTR=time in therapeutic range, UFH=unfractionated heparin, VKA=vitamin k antagonist, VTE=venous thromboembolism

Special Populations

Table 5. Special Populations[1-4,6,7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Apixaban	Dose adjustment is required; a dose of 2.5 mg and a dosing frequency of twice daily are recommended for subjects with any two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for a serum creatinine ≥1.5 mg/dL, a dose of 2.5 mg and a dosing frequency of twice daily are recommended.	No dosage adjustment required in mild hepatic impairment. Not recommended for use in patients with severe hepatic impairment.	B	Unknown
Dabigatran etexilate mesylate	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances 15 to 30 mL/minute, a dose of 75 mg and a dosing frequency of twice daily are recommended. Dosing recommendations for patients with creatinine clearance <15 mL/minute or on dialysis cannot be provided. Avoid concomitant P-gp inhibitors in patients with creatinine clearance l<50 mL/min. Discontinue in patients who develop acute renal	Not reported	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		failure while receiving therapy and consider alternative anticoagulant therapy.			
Rivaroxaban	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances 30 to 50 mL/minute, a dose of 15 mg is recommended. Creatinine clearance of 15 to 30 was not studied, but it is expected to be similar to creatinine clearance of 30 to 50 (atrial fibrillation only). Avoid use in patients with severe renal dysfunction (creatinine clearance <30 mL/minute).*	No dosage adjustment required. Avoid use in patients with moderate or severe hepatic dysfunction or with any hepatic disease associated with coagulopathy.	C	Unknown
Warfarin	Caution should be observed with administration to elderly patients in any situation or physical condition where added risk of hemorrhage is present. Safety and efficacy in children have not been established.†	No dose adjustment required.	No dosage adjustment required. Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.	X	Not detected in milk. Monitor infants for bruising or bleeding if administered to a nursing mother.

*Restriction does not apply when being used for the management of nonvalvular atrial fibrillation.
†The use of warfarin in pediatric patients is well documented for the prevention and treatment of thromboembolic events.

Adverse Drug Events

Table 6. Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE[1]

Bleeding Event	Reported Frequency	
	Apixaban n (%/year), N=9,088	Warfarin n (%/year), N=9,052
Clinically relevant nonmajor bleeding	318 (2.08)	444 (3.00)
Fatal bleeding*	10 (0.06)	37 (0.24)
Gastrointestinal bleeding†	128 (0.83)	141 (0.93)
Intracranial bleeding	52 (0.33)	123 (0.82)
Intraocular bleeding‡	32 (0.21)	22 (0.14)
Major bleeding§	327 (2.13)	462 (3.09)

* Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.
†Gastrointestinal bleed includes upper gastrointestinal, lower gastrointestinal and rectal bleeding.
‡Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).
§International Society on Thrombosis and Hemostasis major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

Table 8. Bleeding Events in the ADVANCE-1, ADVANCE-2, and ADVANCE-3 Trials[1]

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCD-1 Knee Replacement Surgery	
	Apixaban 2.5 mg BID for 35 ± 3 days	Enoxaparin 40 mg SC QD for 35 ± 3 days	Apixaban 2.5 mg BID for 12 ± 2 days	Enoxaparin 40 mg SC QD for 12 ± 2 days	Apixaban 2.5 mg BID for 12 ± 2 days	Enoxaparin 30 mg SC q12h for 12 ± 2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post
All Treated (N)	2673	2659	1501	1508	1596	1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.93%)
Fatal	0	0	0	0	0	1 (1.39%)
Bleed at critical site§	1 (0.04%)	2 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + clinically relevant nonmajor	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

q12h=every 12 hours
*All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeds that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery)
‡ Includes 5 subjects with major bleeds that occurred before the first dose of apixaban (administered 12 to 24 hours post- surgery)
§Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

Table 8. Bleeding Events in the RE-LY Trial (per 100 Patient Years)*[2]

Bleeding Event	Reported Frequency	
	Dabigatran Etexilate Mesylate, 150 mg Twice Daily; n (%), N=6,067	Warfarin; n (%), N=6,022
Any bleed	1,993 (16.6)	2,166 (18.4)
Intracranial hemorrhage	38 (0.3)	90 (0.8)
Life-threatening bleed	179 (1.5)	218 (1.9)
Major bleed	399 (3.3)	421 (3.6)

*Patients contributed multiple events and events were counted in multiple categories.

Table 9. Bleeding Events in the ROCKET-AF Trial (per 100 Patient Years)*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban, n (%), N=7,111	Warfarin n (%), N=7,125
Bleeding into critical organ*	91 (0.8)	133 (1.2)
Bleeding requiring ≥2 units of whole or packed red blood cells	183 (1.7)	149 (1.3)
Fatal bleeding	27 (0.2)	55 (0.5)
Gastrointestinal bleeding	221 (2)	140 (1.2)
Major bleeding†	395 (3.6)	386 (3.5)

*The majority of the events were intracranial, but also included intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome or retroperitoneal.
†Defined as clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL, transfusion of at least two units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding events excluding strokes are 3.3 per 100 patient years for rivaroxaban vs 2.9 per 100 patient years for warfarin.

Table 10. Bleeding Events in the RECORD1, RECORD2 and RECORD3 Trials* (%)[3]

Bleeding Event(s)	Rivaroxaban n (%)	Enoxaparin† n (%)
Total Patients	**N=4,487**	**N=4,524**
Any bleeding event‡	261 (5.8)	251 (5.6)
Major bleeding event	14 (0.3)	9 (0.2)
• Bleeding into a critical organ	2 (<0.1)	3 (0.1)
• Bleeding that required re-operation	7 (0.2)	5 (0.1)
• Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
• Fatal bleeding	1 (<0.1)	0
Hip Surgery	**N=3,281**	**N=3,298**
Any bleeding event‡	201 (6.1)	191 (5.8)
Major bleeding event	7 (0.2)	3 (0.1)
• Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
• Bleeding that required re-operation	2 (0.1)	1 (<0.1)
• Extra-surgical site bleeding required transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
• Fatal bleeding	1 (<0.1)	0
Knee Surgery	**N=1,206**	**N=1,226**
Any bleeding event‡	60 (5)	60 (4.9)
Major bleeding event	7 (0.6)	6 (0.5)
• Bleeding into a critical organ	1 (0.1)	2 (0.2)
• Bleeding that required reoperation	5 (0.4)	4 (0.3)
• Extra-surgical site bleeding required transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
• Fatal bleeding	0	0

*Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of the double-blind study medication. Patients may have more than one event.
†Includes the placebo-controlled period for RECORD2, enoxaparin dosing was 40 mg once daily (RECORD1 to 3).
‡Includes major bleeding events.

Table 11. Bleeding Events in the Pooled Analysis of EINSTEIN-DVT and EINSTEIN-PE Trials*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban† n (%), N=4,130	Enoxaparin/Vitamin K Antagonist n (%), N=4,416
Major bleeding	40 (1.0)	72 (1.7)
• Fatal bleeding	3 (<0.1)	8 (0.2)
o Intracranial	2 (<0.1)	4 (<0.1)
• Nonfatal critical organ bleeding	10 (0.2)	29 (0.7)
o Intraarticular‡	0	4 (<0.1)
o Intracranial‡	3 (<0.1)	10 (0.2)
o Intraocular‡	3 (<0.1)	2 (<0.1)
o Retroperitoneal‡	1 (<0.1)	8 (0.2)
• Nonfatal critical organ bleeding§	27 (0.7)	37 (0.9)
• Decreased hemoglobin ≥2g/dL	28 (0.7)	42 (1.0)
• Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant nonmajor bleeding	357 (8.6)	359 (8.7)
Any bleeding	1,169 (28.3)	1,153 (28)

*Bleeding event occurred after randomization and up to two days after the last dose of study drug. Although a patient may have had two or more events, the patient is counted only once in a category.
†Patients in the EINSTEIN DVT and EINSTEIN PE trials received rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily or enoxaparin 1 mg/kg twice daily then vitamin K antagonist titrated doses to achieve a target International Normalized Ratio of 2.5.
‡Treatment-emergent major bleeding events with at least two subjects in any pooled treatment group.
§Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in hemoglobin of at least 2 g/dL and/or transfusion of two or more units of whole blood or packed red blood cells.

Table 12. Bleeding Events in EINSTEIN-EXT Trial*[3]

Bleeding Event	Reported Frequency	
	Rivaroxaban† n (%), N=598	Placebo† n (%), N=590
Any bleeding	104 (17.4)	63 (10.7)
Clinically relevant nonmajor bleeding	32 (5.4)	7 (1.2)
Major bleeding‡	4 (0.7)	0
• Decreased hemoglobin ≥2g/dL	4 (0.7)	0
• Gastrointestinal	3 (0.5)	0
• Menorrhagia	1 (0.2)	0
• Transfusion of ≥2 units of whole blood or packed red blood cells	2 (0.2)	0

*Bleeding event occurred after randomization and up to two days after the last dose of study drug. Although a patient may have had two or more events, the patient is counted only once in a category.
† Patients in the EINSTEIN extension trial received rivaroxaban 20 mg once daily or placebo.
‡ There were no fatal or critical organ bleeding events.

Table 13. Adverse Events[4,6,7]

Adverse Event	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Abdominal pain	✔	-	✔	1.7
Alopecia	✔	-	-	-
Anemia	-	2.6	-	-

Adverse Event	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Back pain	-	-	-	3.7
Bloating	✔	-	-	-
Chills	✔	-	-	-
Cholestatic hepatitis	✔	-	-	-
Cholesterol microemboli	✔	-	-	-
Confusion	-	1.4	-	-
Dermatitis	✔	-	-	-
Diarrhea	✔	-	-	-
Elevated liver enzymes	✔	0.6 to 0.8	-	-
Flatulence	✔	-	-	-
GERD	-	-	✔	1.3
Hemorrhage	✔	1.1	✔	✔
Hepatitis	✔	-	-	-
Hypersensitivity/allergic reactions	✔	✔	<0.1	-
Infection, sinusitis or urinary tract infection	-	-	-	✔
Myocardial infarction, fatal and non-fatal	-	-	✔	-
Nausea	✔	2.6	-	-
Necrosis of the skin	✔	-	-	-
Oropharyngeal pain	-	-	-	1.0
Osteoarthritis	-	-	-	1.7
Pruritus	✔	-	-	-
Rash	✔	-	-	-
Systemic atheroemboli	✔	-	-	-
Taste perversion	✔	-	-	-
Toothache	-	-	-	1
Tracheal or tracheobronchial calcification	✔	-	-	-
Ulcer, gastrointestinal	-	-	✔	-
Vomiting	✔	-	-	-

✔ Percent not specified.
- Not reported or percent less than threshold for reporting

The risk of major bleeds was similar with dabigatran etexilate mesylate 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on dabigatran etexilate mesylate (hazard ratio [HR], 1.2; 95% confidence interval [CI], 1.0 to 1.4) for patients ≥75 years of age. There was a higher rate of major gastrointestinal bleeds and any gastrointestinal bleeds in patients receiving dabigatran etexilate mesylate 150 mg than in patients receiving warfarin (1.6 vs 1.1%, respectively; HR, 1.5; 95% CI, 1.2 to 1.9; and 6.1 vs 4.0%, respectively). In addition, patients receiving dabigatran etexilate mesylate 150 mg had an increased incidence of gastrointestinal adverse reactions compared to patients receiving warfarin (35 vs 24%).[1]

Adverse events occurring more often with rivaroxaban compared to placebo include abdominal pain, dyspepsia, fatigue, sinusitis, toothache and urinary tract infection. Compared to patients treated with enoxaparin, patients treated with rivaroxaban reported a higher incidence of blisters, muscle spasms, pain in extremities, pruritus, and syncope and wound secretions.[3,6,7]

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, (ARISTOTLE), the incidence of major bleeding was consistent across most major subgroups including age, weight, $CHADS_2$ score, prior warfarin use, geographic region and aspirin use at randomization. Patients with diabetes who received apixaban had a higher incidence of bleeding compared to patients

without diabetes (3.0 vs 1.9% per year). In the Apixaban Vs Acetylsalicylic acid (ASA) to Prevent Strokes (AVERROES) trial, there was no difference in the incidence of major bleeding between patients randomized to receive apixaban or ASA (*P*=0.07). Moreover, the incidence of fatal (HR, 0.99; 95% CI, 0.23 to 4.29) or intracranial bleeds (HR, 0.99; 95% CI, 0.39 to 2.51) did not differ significantly between the treatments. Hypersensitivity reactions (hypersensitivity, skin rash and anaphylactic reactions) and syncope have been reported in <1% of patients treated with apixaban.

Contraindications

Table 14. Contraindications[1-4,6,7]

Contraindication	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Active pathological bleeds	✔	✔	✔	-
Bleeding tendencies	-	-	-	✔
Hemorrhagic tendencies or blood dyscrasias	-	-	-	✔
Hypersensitivity to any component of the product	✔	✔	✔	✔
Major regional or lumbar block anesthesia	-	-	-	✔
Malignant hypertension	-	-	-	✔
Mechanical prosthetic heart valves	-	✔	-	-
Pregnancy	-	-	-	✔
Recent or contemplated surgery of the central nervous system or eye, or traumatic surgery resulting in large open surfaces	-	-	-	✔
Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding	-	-	-	✔
Threatened abortion, eclampsia and preeclampsia	-	-	-	✔
Unsupervised patients with conditions associated with potential high level of non-compliance	-	-	-	✔

Black Box Warning for Apixaban (Eliquis®), Rivaroxaban (Xarelto®) and Dabigatran (Pradaxa®)[1-3]

WARNING
(A) Premature discontinuation of any oral anticoagulant, including Pradaxa, Xarelto and Eliquis increases the risk of thrombotic events. If anticoagulation is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant. (B) Epidural or spinal hematomas may occur in patients treated with oral anticoagulatns who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: - Use of indwelling epidural catheters - Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants

WARNING
- History of traumatic or repeated epidural or spinal punctures - History of spinal deformity or spinal surgery - Optimal timing between the administration of oral anticoagulants and neuraxial procedures is not known Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

Black Box Warning for warfarin (Coumadin®, Jantoven®)[4]

WARNING
Bleeding risk: Warfarin can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher international normalized ratio [INR]). Risk factors for bleeding include high intensity of anticoagulation (INR >4), ≥65 years of age, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal function impairment, concomitant drugs and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to health care provider signs and symptoms of bleeding.

Warnings/Precautions

Table 15. Warnings and Precautions[1-4,6,7]

Warning/Precaution	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Acute pulmonary embolism in hemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy; avoid use	-	-	✔	-
Avoid strong P-glycoprotein and CYP3A4 inducers or inhibitors	-	-	✔	-
Deficiency in protein C-mediated anticoagulant response	-	-	-	✔
Diabetes mellitus; risk of therapy may be increased	-	-	-	✔
Eye surgery; minor complications of sharp needle and local anesthesia block have been reported	-	-	-	✔
Heparin-induced thrombocytopenia; treatment may be considered after platelet count has normalized	-	-	-	✔

Warning/Precaution	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
Females of reproductive potential; may cause pregnancy loss, birth defects or fetal death	-	-	-	✔
Increased risk of stroke after discontinuing treatment in nonvalvular atrial fibrillation	✔	✔	✔	-
Increased risk of bleeding and may cause serious or fatal bleeding	✔	✔	✔	✔
Infectious diseases or disturbances of intestinal flora	-	-	-	✔
Moderate to severe hepatic impairment; risk of therapy may be increased	-	-	✔	✔
Moderate to severe hypertension; risk of therapy may be increased	-	-	-	✔
Patients with renal impairment (creatinine clearance of <30 or <15 mL/minute [atrial fibrillation only])	-	-	✔	-
Polycythemia vera; risk of therapy may be increased	-	-	-	✔
Pregnant women; risk of pregnancy-related hemorrhage has not been evaluated	-	-	✔	-
Prosthetic heart valves; not evaluated in this population	✔	-	✔	-
Risk of epidural or spinal hematoma when neuraxial anesthesia or spinal puncture is employed in anticoagulated patients	-	-	✔	-
Spinal/epidural anesthesia or puncture; increased risk for developing hematoma	✔	✔	✔	-
Strong P-glycoprotein inducers reduce drug exposure	-	✔		-
Thromboembolic and bleeding events in patients with prosthetic heart valves	-	✔	-	-
Tissue necrosis or gangrene of the skin has been reported	-	-	-	✔
Systemic atheroemboli and cholesterol microemboli; discontinue treatment if such phenomena is observed	-	-	-	✔
Use of an indwelling catheter; risk of therapy may be increased	-	-	-	✔
Use in pregnant women with	-	-	-	✔

Warning/Precaution	Apixaban	Dabigatran Etexilate Mesylate	Rivaroxaban	Warfarin
mechanical heart valves; potential benefits may outweigh the risks for pregnant women with mechanical heart valves at high risk of thromboembolism				
Vasculitis; risk of therapy may be increased	-	-	-	✔

Drug Interactions

Table 16. Drug Interactions[1-4,6,7]

Generic Name	Interacting Medication or Disease	Potential Result
Oral anticoagulants (apixaban, dabigatran etexilate mesylate, rivaroxaban)	P-glycoprotein inducers (i.e., rifampin)	The exposure of the oral anticoagulant may be decreased, resulting in decreased therapeutic effects.
Oral anticoagulants (apixaban, rivaroxaban, warfarin)	Salicylates	The risk of bleeding may be increased. The adverse reactions of aspirin on gastric mucosa and platelet function also may enhance the possibility of hemorrhage.
Oral anticoagulants (apixaban, rivaroxaban)	Clopidogrel	The risk of bleeding may be increased, and bleeding time may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	Dabigatran etexilate mesylate	The risk of bleeding may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	Heparins	Additive effects on anti-factor Xa activity and the risk of bleeding may be increased.
Oral anticoagulants (apixaban, rivaroxaban)	P-glycoprotein inhibitors (i.e., clarithromycin)	The exposure of the oral anticoagulant may be increased, resulting in increased therapeutic effects and risk of bleeding.
Oral anticoagulants (apixaban, rivaroxaban)	Strong cytochrome P450 3A4 inhibitors (i.e., ketoconazole)	The exposure of the oral anticoagulant may be increased, resulting in increased therapeutic effects and risk of bleeding.
Oral anticoagulants (apixaban, rivaroxaban)	Warfarin	The risk of bleeding may be increased.
Oral anticoagulants (apixaban, warfarin)	Alteplase	The risk of serious bleeding may be increased.
Oral anticoagulants (apixaban)	Strong cytochrome P450 3A4 inducers (i.e., ketoconazole)	The exposure of the oral anticoagulant may be decreased, resulting in decreased therapeutic effects.
Oral anticoagulants (rivaroxaban)	Nonsteroidal anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs are known to increase bleeding, and bleeding risk may be increased when rivaroxaban is given concomitantly.
Oral anticoagulants (warfarin)	Acetaminophen	Acetaminophen appears to increase the antithrombotic effect of warfarin in a dose-dependent

Generic Name	Interacting Medication or Disease	Potential Result
		manner.
Oral anticoagulants (warfarin)	Aminoglutethimide	Warfarin's action to decrease prothrombin levels may be reduced.
Oral anticoagulants (warfarin)	Amiodarone	The hypoprothrombinemic effect of warfarin is augmented.
Oral anticoagulants (warfarin)	Androgens (17-alkyl derivatives)	The hypoprothrombinemic effect of warfarin is potentiated.
Oral anticoagulants (warfarin)	Antineoplastic agents	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Argatroban	The risk of bleeding may be increased due to abnormal prolongation of the prothrombin time and International Normalized Ratio.
Oral anticoagulants (warfarin)	Azole antifungals	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Barbiturates	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Bosentan	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Carbamazepine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Cephalosporins	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Chloramphenicol	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Cholestyramine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Corticosteroids	The anticoagulant dose requirements may be reduced. Corticosteroids may induce hypercoagulation that could oppose warfarin actions.
Oral anticoagulants (warfarin)	Dextrothyroxine	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants (warfarin)	Disulfiram	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Ethchlorvynol	The hypoprothrombinemic effect of warfarin is decreased.
Oral anticoagulants (warfarin)	Fibric acids	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants (warfarin)	Gefitinib	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Glutethimide	Inadequate therapeutic response to warfarin may occur.
Oral anticoagulants (warfarin)	Griseofulvin	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Histamine H_2 antagonists	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Hydroxymethylglutaryl coenzyme A reductase inhibitors	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Hydantoins	Hydantoin serum concentrations may be increased, resulting in possible toxicity. Prothrombin time may be increased, increasing the risk of bleeding.

Generic Name	Interacting Medication or Disease	Potential Result
Oral anticoagulants (warfarin)	Macrolides	The anticoagulant effect of warfarin may be increased.
Oral anticoagulants (warfarin)	Metronidazole	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Nevirapine	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Penicillins	Large intravenous doses of penicillins can increase the bleeding risks of warfarin by prolonging bleeding time.
Oral anticoagulants (warfarin)	Quinidine derivatives	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Quinolones	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Rifamycins	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Sulfinpyrazone	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Sulfonamides	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Tamoxifen	The hypoprothrombinemic effect of warfarin is increased.
Oral anticoagulants (warfarin)	Tetracyclines	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Thioamides	The effects of warfarin may be augmented.
Oral anticoagulants (warfarin)	Thiopurines	The effects of warfarin may be decreased.
Oral anticoagulants (warfarin)	Thyroid hormones	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Tramadol	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Trazodone	The hypoprothrombinemic effect of warfarin is decreased.
Oral anticoagulants (warfarin)	Vitamin E	The effects of warfarin may be increased.
Oral anticoagulants (warfarin)	Vitamin K	The effects of warfarin is attenuated or reversed, leading to possible thrombus formation.

Dosing and Administration

When converting patients from warfarin to apixaban or dabigatran etexilate mesylate, warfarin should be discontinued and apixaban or dabigatran etexilate mesylate should be started when the International Normalized Ratio (INR) is <2.0. When converting from warfarin, rivaroxaban should be started when the INR is <3.0. When switching between apixaban and anticoagulants other than warfarin, discontinue the treatment being taken and start the other treatment at the next scheduled dose. For patients currently receiving a parenteral anticoagulant, dabigatran etexilate mesylate or rivaroxaban should be started zero to two hours before the time that the next dose of the parenteral medication was to have been administered, or at the time of discontinuation of a continuously administered parenteral medication.[1-4,6,7]

Apixaban should be discontinued at least 48 hours prior to an elective surgery or invasive procedure that carries a moderate or high risk of unacceptable or clinically significant bleeding. For elective surgeries or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled, discontinue apixaban at least 24 hours prior to the procedure. If possible, dabigatran

etexilate mesylate should be discontinued one to five days before invasive or surgical procedures because of the increased risk of bleeding. A longer time should be considered for patients undergoing major surgery, spinal surgery, or placement of a spinal or epidural catheter or part, in whom complete hemostasis may be required. If surgery cannot be delayed, there is an increased risk of bleeding.[1] If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, rivaroxaban should be stopped at least 24 hours before the procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban, the increased risk of bleeding should be weighed against the urgency of intervention. Rivaroxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. If oral medication cannot be taken after surgical intervention consider administering a parenteral anticoagulant.[1,6,7]

The recommended dose and duration of rivaroxaban and apixaban vary depending on indication. The recommended treatment durations for these anticoagulants in patients undergoing hip or knee replacement surgery are 35 (hip) or 12 (knee) days. Rivaroxaban may be administered independently of meals when used for prophylaxis of deep vein thrombosis. When used in atrial fibrillation or the treatment and prevention of recurrence of deep vein thrombosis and pulmonary embolism, administration with the evening meal is recommended.[3,6,7]

The dosage and administration of warfarin must be individualized for each patient according to the patient's prothrombin time/INR response to the drug, with the dosage adjusted based on this measurement. The selected starting dose of warfarin should be based on the expected maintenance dose. The initial dose of warfarin is usually 2 to 5 mg/day; however, this dose should be modified based on consideration of patient-specific clinical factors. Lower initial doses should be considered for elderly and/or debilitated patients. Regarding maintenance treatment, most patients are satisfactorily maintained at a dose of 2 to 10 mg/day. Flexibility of dosage is provided by breaking scored tablets in half, and the individual dose and interval should be gauged by the patient's prothrombin response. The duration of therapy in each patient is also individualized. In general, treatment with warfarin should be continued until the danger of thrombosis and embolism has passed.[4,6,7]

Table 17. Dosing and Administration[1-4,6,7]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Apixaban	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Tablet: 5 mg BID Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery: Tablet: 2.5 mg BID for 12 days (knee) or 35 days (hip)	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg
Dabigatran etexilate mesylate	Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation:[†] Capsule: 150 mg BID Treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism in patients who have been previously treated:	Safety and efficacy in children have not been established.	Capsule: 75 mg 150 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule: 150 mg BID		
Rivaroxaban	Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery: Tablet: 10 mg QD for 12 days (knee) or 35 days (hip) Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation*: Tablet: 20 mg QD Treatment of deep vein thrombosis and pulmonary embolism, and for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism in patients who have been previously treated‡: Tablet: initial, 15 mg BID for the first 21 days; maintenance, 20 mg QD	Safety and efficacy in children have not been established.	Tablet: 10 mg 15 mg 20 mg
Warfarin	Prophylaxis and treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 2.0 to 3.0 Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; treat for six to 12 months or indefinitely Reduce the risk of death, recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction: Tablet: initial, 2 to 5 mg QD; maintenance, 2 to 10 mg QD; maintain an INR of 3.0 to 4.0 (high intensity) or of 2.0 to 3.0 (moderate intensity)	Safety and efficacy in children have not been established.*	Tablet: 1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 6 mg 7.5 mg 10 mg

BID=twice-daily, INR=International Normalized Ratio, QD=once-daily
*There is limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
†Indicated for treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for five to 10 days.
‡Indicated to reduce the risk of recurrent DVT or PE following initial six months of treatment for DVT/PE.

Clinical Guidelines

Table 18. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[22]	Management of anticoagulant therapy • For outpatients, vitamin K antagonist (VKA) therapy with warfarin 10 mg/day for the first two days, followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose is suggested. • Routine use of pharmacogenetic testing for guiding doses of VKA therapy is not recommended. • For acute venous thromboembolism (VTE), it is suggested that VKA therapy be started on day one or two of low molecular weight heparin (LMWH) or low dose unfractionated heparin (UFH) therapy rather than waiting for several days to start. • For VKA therapy with stable INRs, INR testing frequency of up to 12 weeks is suggested rather than every four weeks. • For patients receiving previously stable VKA therapy who present with a single out-of-range INR ≤0.5 below or above therapeutic, it is suggested to continue the current dose and test the INR within one to two weeks. • For patients receiving stable VKA therapy presenting with a single subtherapeutic INR value, routine administering of bridging heparin is not recommended. • Routine use of vitamin K supplementation is suggested against with VKA therapy. • For patients receiving VKA therapy who are motivated and can demonstrate competency in self-management strategies, it is suggested that patient self-management be utilized rather than usual outpatient INR monitoring. • For maintenance VKA dosing, it is suggested that validated decision support tools be utilized rather than no decision support. • Concomitant use of nonsteroidal anti-inflammatory drugs and certain antibiotics should be avoided in patients receiving VKA therapy. • Concomitant use of platelet inhibitors should be avoided in patients receiving VKA therapy, except in situations where benefit is known or is highly likely to be greater than harm from bleeding. • With VKA therapy, a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended rather than a lower (<2.0) or higher (range, 3.0 to 5.0) range. • In patients with antiphospholipid syndrome with previous arterial or VTE, VKA therapy should be titrated to a moderate intensity INR (range, 2.0 to 3.0) rather than higher intensity (range, 3.0 to 4.5). • For discontinuations of VKA therapy, it is suggested that discontinuation be done abruptly rather than gradual tapering of the dose. • For initiation of intravenous (IV) UFH, the initial bolus and rate of continuous infusion should be weight adjusted or fixed-dose rather than alternative regimens. • In outpatients with VTE receiving subcutaneous (SC) UFH, dosing should be weight-based without monitoring rather than fixed or weight-adjusted dosing with monitoring. • A reduction in therapeutic LMWH dose is suggested in patients with severe renal insufficiency rather than using standard doses. • In patients with VTE and body weight >100 kg, the treatment dose of

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	fondaparinux should be increased from 7.5 to 10 mg/day SC. • For INRs between 4.5 and 10.0 with VKA therapy and no evidence of bleeding, routine use of vitamin K is not recommended. • For INRs >10.0 with VKA therapy and no evidence of bleeding, it is suggested that oral vitamin K be administered. • In patients initiating VKA therapy, routine use of clinical prediction rules for bleeding as the sole criterion to withhold VKA therapy is not recommended. • For VKA-associated major bleeding, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate is suggested over plasma. Additional use of vitamin K 5 to 10 mg administered by slow IV injection is recommended rather than reversal with coagulation factors alone. <u>Prevention of VTE in nonsurgical patients</u> • Acutely ill hospitalized medical patients at increased risk of thrombosis: anticoagulant thromboprophylaxis with LMWH, low dose UFH (two or three times daily), or fondaparinux is recommended. Choice should be based on patient preference, compliance, and ease of administration, as well as on local factors affecting acquisition costs. • Acutely ill hospitalized patients at low risk of thrombosis: pharmacologic or mechanical prophylaxis is not recommended. • Acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding: anticoagulant thromboprophylaxis is not recommended. • Acutely ill hospitalized medical patients at increased risk for thrombosis who are bleeding or at high risk of major bleeding: optimal use of mechanical thromboprophylaxis is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, it is suggested that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis. • Acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis: extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay is suggested against. • Critically ill patients: routine ultrasound screening for deep vein thrombosis (DVT) is suggested against. • Critically ill patients: use of LMWH or low dose UFH thromboprophylaxis is suggested over no prophylaxis. • Critically ill patients who are bleeding or are at high risk for major bleeding: use of mechanical thromboprophylaxis until the bleeding risk decreases is suggested rather than no mechanical thromboprophylaxis. When bleeding risk decreases, pharmacologic thromboprophylaxis is suggested to be substituted for mechanical thromboprophylaxis. • Outpatients with cancer who have no additional risk factors for VTE: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is not recommended. • Outpatients with solid tumors who have additional risk factors for VTE with low risk of bleeding: prophylaxis with LMWH or low dose UFH is suggested over no prophylaxis. • Outpatients with cancer and indwelling central venous catheters: routine prophylaxis with LMWH or low dose UFH is suggested against, and prophylactic use of VKAs is suggested against. • Chronically immobilized patients residing at home or at a nursing home:

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	routine thromboprophylaxis is suggested against. • Long distance travelers at increased risk of VTE: frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible is suggested. • Long distance travelers at increased risk of VTE: use of properly fitted, below-knee graduated compression stockings during travel is suggested. For all other long distance travelers, use of graduated compression stockings is suggested against. • Long distance travelers: use of aspirin or anticoagulants to prevent VTE is suggested against. • Patients with asymptomatic thrombophilia: long term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE is not recommended. <u>Prevention of VTE in nonorthopedic surgical patients</u> • General and abdominal-pelvic surgery patients at very low risk for VTE: no specific pharmacologic or mechanical prophylaxis is recommended for use other than early ambulation. • General and abdominal-pelvic surgery patients at low risk for VTE: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are not at high risk major bleeding complications: LMWH, low dose UFH, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at moderate risk for VTE who are at high risk for major bleeding complication or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients at high risk for VTE who are not at high risk for major bleeding complications: LMWH or low dose UFH is recommended over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • High-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications: extended duration (four weeks) of LMWH prophylaxis is recommended over limited duration prophylaxis. • High-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe: mechanical prophylaxis is suggested over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • General and abdominal-pelvic surgery patients at high risk for VTE in whom both LMWH and UFH are contraindicated or unavailable and who are not at high risk for major bleeding complications: low dose aspirin, fondaparinux, or mechanical prophylaxis is suggested over no prophylaxis. • General and abdominal-pelvic surgery patients: it is suggested that an inferior vena cava filter not be used for primary VTE prevention. • General and abdominal-pelvic surgery patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. • Cardiac surgery patients with an uncomplicated postoperative course: mechanical prophylaxis is suggested over either no prophylaxis or pharmacologic prophylaxis.

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	• Cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications: adding pharmacologic prophylaxis with low dose UFH or LMWH to mechanical prophylaxis is suggested. • Thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding: low dose UFH or LWMH is suggested over no prophylaxis. It is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis. • Thoracic surgery patients who are at high risk for major bleeding: mechanical prophylaxis over no prophylaxis is suggested until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. • Craniotomy patients: mechanical prophylaxis is suggested over no prophylaxis or pharmacologic prophylaxis. • Craniotomy patients at very high risk for VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Patients undergoing spinal surgery: mechanical prophylaxis is suggested over no prophylaxis, UFH, or LMWH. • Patients undergoing spinal surgery at high risk of VTE: it is suggested that pharmacologic prophylaxis be added to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases. • Major trauma patients: low dose UFH, LMWH, or mechanical prophylaxis is suggested over no prophylaxis. • Major trauma patients at high risk for VTE: it is suggested that mechanical prophylaxis be added to pharmacologic prophylaxis when not contraindicated by lower extremity injury. • Major trauma patients in whom LMWH and low dose UFH are contraindicated: mechanical prophylaxis is suggested over no prophylaxis when not contraindicated by lower extremity injury. It is suggested that either LMWH or low dose UFH be added when the risk of bleeding diminishes or the contraindication to heparin resolves. • Major trauma patients: it is suggested that an interior vena cava filter not be used for primary VTE prevention. • Major trauma patients: it is suggested that periodic surveillance with venous compression ultrasound not be performed. <u>Prevention of VTE in orthopedic surgery patients</u> • Total hip arthroplasty or total knee arthroplasty: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, aspirin, or an intermittent pneumatic compression device. • Hip fracture surgery: use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis is recommended: LMWH, fondaparinux, low dose UFH, adjusted-dose VKA, aspirin, or intermittent pneumatic compression device. • Patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, hip fracture surgery) and receiving LMWH as thromboprophylaxis: it is recommended to start either 12 hours or more

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	preoperatively or postoperatively rather than within four hours or less preoperatively or postoperatively. • Total hip or knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low dose UFH, adjusted-dose VKA, or aspirin. • Hip replacement surgery, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment: LMWH is suggested in preference to other agents recommended as alternatives: fondaparinux, low dose UFH, adjusted-dose VKA, or aspirin. • Major orthopedic surgery: it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days. • Major orthopedic surgery: it is suggested to use dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay. • Major orthopedic surgery in patients at an increased risk of bleeding: intermittent pneumatic compression device or no prophylaxis is suggested over pharmacologic prophylaxis. • Major orthopedic surgery in patients who decline or are uncooperative with injections or intermittent pneumatic compression device: apixaban or dabigatran etexilate mesylate (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran etexilate mesylate are unavailable) is recommended over alternative forms of prophylaxis. • Major orthopedic surgery in patients with an increased bleeding risk or contraindications to both pharmacologic and mechanical prophylaxis: inferior vena cava filter placement for primary prevention of VTE is suggested against over no thromboprophylaxis. • Asymptomatic patients following major orthopedic surgery: doppler ultrasound screening before hospital discharge is not recommended. • Patients with lower leg injuries requiring leg immobilization: no prophylaxis is suggested rather than pharmacologic thromboprophylaxis. • Knee arthroscopy in patients without a history of prior VTE: no thromboprophylaxis is suggested rather than prophylaxis. <u>Antithrombotic therapy for VTE disease</u> • Acute DVT of the leg or pulmonary embolism (PE) treated with VKA therapy: initial treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) is recommended over no such initial treatment. • High clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment while awaiting the results of diagnostic tests. • Intermediate clinical suspicion of acute VTE or PE: treatment with parenteral anticoagulation is suggested over no treatment if the results of diagnostic tests are expected to be delayed for more than four hours. • Low clinical suspicion of acute VTE or PE: it is suggested to not treat with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 hours. • Acute isolated distal DVT of the leg without severe symptoms or risk factors for extension: serial imaging of the deep veins for two weeks is suggested over initial anticoagulation.

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	• Acute isolated distal DVT of the leg and severe symptoms or risk factors for extension: initial anticoagulation is suggested over serial imaging of the deep veins. • Acute isolated distal DVT of the leg in patients managed with initial anticoagulation: using the same approach as for patients with acute proximal DVT is recommended. • Acute isolated distal DVT of the leg who are managed with serial imaging: no anticoagulation if the thrombus does not extend is recommended; anticoagulation is suggested if the thrombus extends but remains confined to the distal veins; and anticoagulation is recommended if the thrombus extends into the proximal veins. • Acute DVT of the leg or PE: early initiation of VKA therapy is recommended over delayed initiation, and continuation of parenteral anticoagulation for a minimum on five days and until the INR is 2.0 or above for at least 24 hours. • Acute DVT of the leg or PE: LMWH or fondaparinux is suggested over IV or SC UFH. • Patients with acute DVT of the leg or PE receiving LMWH: once daily LMWH administration is suggested over twice daily administration. • Acute DVT of the leg and home circumstances are adequate: initial treatment at home is recommended over treatment in hospital. • Low risk PE and home circumstances are adequate: early discharge is suggested over standard discharge. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over catheter-directed thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over systemic thrombolysis. • Acute proximal DVT of the leg: anticoagulation therapy alone is suggested over venous thrombectomy. • Acute DVT of the leg in patients who undergo thrombosis removal: the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal is recommended. • Acute DVT of the leg: use of an inferior vena cava filter in addition to anticoagulants is not recommended. • Acute proximal DVT of the leg in patients with contraindication to anticoagulation: use of an inferior vena cava filter is recommended. • Acute proximal DVT of the leg in patients with an inferior vena cava filter inserted as an alternative to anticoagulation: a conventional course of anticoagulant therapy is suggested if the risk of bleeding resolves. • Acute DVT of the leg: early ambulation is suggested over initial bed rest. • Acute VTE in patients receiving anticoagulant therapy: long term therapy is recommended over stopping anticoagulant therapy after about one week of initial therapy. • Acute symptomatic DVT of the leg: compression stockings are suggested. • Acute PE associated with hypotension in patients who do not have a high bleeding risk: systemically administered thrombolytic therapy is suggested over no such therapy. • In most patients with acute PE not associated with hypotension: systemically administered thrombolytic therapy is not recommended. • In selected patients with acute PE not associated with hypotension and with a low bleeding risk who initial clinical presentation or clinical course after starting anticoagulant therapy, suggests a high risk of developing

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	hypotension: administration of thrombolytic therapy is suggested. • Proximal DVT of the leg or PE provoked by surgery: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment of a longer time limited period, or extended therapy. • Proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor: treatment with anticoagulation for three months is recommended over treatment for a shorter period, treatment for a longer time limited period, extended therapy if there is high bleeding risk. Anticoagulation treatment for three months is suggested over extended therapy if there is a low or moderate bleeding risk. • Isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor: treatment with anticoagulation for three months is suggested over treatment for a shorter period, and anticoagulation treatment for three months is recommended over treatment of longer time limited period or extended therapy. • Unprovoked DVT of the leg or PE: treatment with anticoagulation for three months is recommended over treatment of a shorter duration. After three months, patients should be evaluated for the risk-benefit ratio of extended therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a low or moderate bleeding risk: extended anticoagulant therapy is suggested over three months of therapy. • First VTE that is an unprovoked proximal DVT of the leg or PE in patients who have a high bleeding risk: three months of anticoagulant therapy is recommended over extended therapy. • First VTE that is an unprovoked isolated distal DVT of the leg: three months of anticoagulation therapy is suggested over extended therapy in those with a low or moderate bleeding risk, and three months of anticoagulant treatment is recommended in those with a high bleeding risk. • Second unprovoked VTE or PE: extended anticoagulant therapy is recommended over three months of therapy in those who have a low bleeding risk, and extended anticoagulant therapy is suggested in patients with a moderate bleeding risk. • Second unprovoked VTE or PE in patients with a high bleeding risk: three months of anticoagulant therapy is suggested over extended therapy. • DVT of the leg or PE and active cancer: if the risk of bleeding is not high, extended anticoagulation therapy is recommended over three months of therapy, and if there is a high bleeding risk, extended anticoagulant therapy is suggested. • DVT of the leg or PE in patients treated with VKA: a therapeutic INR range of 2.0 to 3.0 (target, 2.5) is recommended over a lower (<2.0) or higher (range, 3.0 to 5.0) range for all treatment durations. • DVT of the leg or PE in patients with no cancer: VKA therapy is suggested over LMWH for long-term therapy. For patients with DVT or PE and no cancer who are not treated with VKA therapy, LMWH is suggested over dabigatran etexilate mesylate or rivaroxaban for long term therapy. • DVT of the leg or PE and cancer: LMWH is suggested over VKA therapy. In patients with DVT of the leg or PE and cancer who are not treated with LMWH, VKA is suggested over dabigatran etexilate mesylate or rivaroxaban for long-term therapy.

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	• DVT of the leg or PE in patients who receive extended therapy: treatment with the same anticoagulant chosen for the first three months is suggested. • Patients incidentally found to have asymptomatic DVT of the leg or PE: treatment with the same anticoagulant is suggested as for comparable patients with symptomatic DVT or PE. • In patients with chronic thromboembolic pulmonary hypertension, extended anticoagulation is recommended over stopping therapy. • Superficial vein thrombosis of the lower limb of at least 5 cm in length: use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation. • Superficial vein thrombosis in patients treated with anticoagulation: fondaparinux 2.5 mg/day is suggested over a prophylactic dose of LMWH. • Upper-extremity DVT that involves the axillary or more proximal veins: acute treatment with parenteral anticoagulation (LMWH, fondaparinux, or IV or SC UFH) over no such acute treatment. • Acute upper-extremity DVT that involves the axillary or more proximal veins: LMWH or fondaparinux is suggested over IV or SC UFH, and anticoagulation therapy alone is suggested over thrombolysis. • Upper-extremity DVT in patients undergoing thrombolysis: the same intensity and duration of anticoagulant therapy as in similar patients who do not undergo thrombolysis is recommended. • In most patients with upper-extremity DVT that is associated with a central venous catheter: it is suggested that the catheter not be removed if it is functional and there is an ongoing need for the catheter. • Upper-extremity DVT that involves the axillary or more proximal veins: a minimum duration of anticoagulation of three months is suggested over a shorter duration. • Upper-extremity DVT that is associated with a central venous catheter that is removed: three months of anticoagulation is recommended over a longer duration of therapy in patients with no cancer, and this is suggested in patients with cancer. • Upper-extremity DVT that is associated with a central venous catheter that is not removed: it is recommended that anticoagulation is continued as long as the central venous catheter remains over stopping after three months of treatment in patients with cancer, and this is suggested in patients with no cancer. • Upper-extremity DVT that is not associated with a central venous catheter or with cancer: three months of anticoagulation is recommended over a longer duration of therapy. • Acute symptomatic upper-extremity DVT: use of compression sleeves or venoactive medications is suggested against. • Symptomatic splanchnic vein thrombosis: anticoagulation is recommended over no anticoagulation. • Symptomatic hepatic vein thrombosis: anticoagulation is suggested over no anticoagulation. • In patients with incidentally detected splanchnic vein thrombosis or hepatic vein thrombosis: no anticoagulation is suggested over anticoagulation. <u>Antithrombotic therapy for atrial fibrillation (AF)</u>

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	• Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran etexilate mesylate 150 mg twice daily is suggested over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0). • Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone. • Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin. • Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. • Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm.

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	• Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior myocardial infarction (MI) and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet

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	therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations.
American Heart Association/American Stroke Association: **Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: A Science Advisory for Healthcare Professionals (2012)**[31]	<u>Prevention of stroke in nonvalvular AF</u> • Apixaban, dabigatran etexilate mesylate, rivaroxaban and warfarin are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF. • The choice of antithrombotic treatment should be individualized based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin. • Dabigatran etexilate mesylate 150 mg twice daily is an efficacious alternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF who have at least one additional risk factor and a creatinine clearance (CrCl) >30 mL/min. • The use of dabigatran etexilate mesylate 75 mg twice daily in patients with AF and at least one additional risk factor who have a low CrCl (15 to 30 mL/min) may be considered, but its safety and efficacy have not been established. The use of dabigatran etexilate mesylate in patients with

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	more severe renal failure is not recommended in patients with a CrCl <15 mL/min. • Apixaban 5 mg twice daily is an effective alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy with one or more additional risk factor and no more than one of the following characteristics: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Although safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for VKA therapy who have one or more additional risk factor and two or more of the following criteria: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. • Apixaban 5 mg twice daily is a relatively safe and efficacious alternative to warfarin in patients with nonvalvular AF deemed appropriate for VKA therapy that have one or more risk factors and no more than one of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. • Apixaban should not be used if the CrCl is <25 mL/min. • In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of transient ischemic attack [TIA], stroke, or systemic embolization or have two additional risk factors), rivaroxaban 20 mg daily is a reasonable alternative to warfarin. • In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or two or more additional risk factors), with a CrCl 15 to 50 mL/min, rivaroxaban 15 mg daily may be considered; however, its safety and efficacy have not been established. • Rivaroxaban should not be used if the CrCl is <15 mL/min. • The safety and efficacy of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established.
American Heart Association/American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary (2014)**[9]	Recommendations for Risk-Based Antithrombotic Therapy: Class I • In patients with AF, antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). • Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). • In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). • For patients with AF who have mechanical heart valves, warfarin is recommended and the target INR should be based on type and location of the prosthesis (Level of Evidence: B). • For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). • Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) • For patients with nonvalvular AF unable to maintain a therapeutic INR

Clinical Guideline	Recommendations
	level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended (Level of Evidence: C). • Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). • Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). • For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). • Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). • For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). • For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb • For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). • For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). • In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). • Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit • The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm • The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B).

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	Recommendations for Thromboembolism Prevention: Class I • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). • For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated (Level of Evidence: C). • For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). • Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa • For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). • For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb • For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C).
The American Heart Association: **Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific**	Recommendations for initial anticoagulation for acute PE • Therapeutic anticoagulation with SC LMWH, IV or SC UFH with monitoring, unmonitored weight-based SC UFH, or SC fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation. • Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation. Fibrinolysis is not recommended for undifferentiated cardiac arrest. Recommendations for initial anticoagulation for patients with iliofemoral DVT • In the absence of suspected or proven heparin induced thrombocytopenia, patients with iliofemoral DVT should receive therapeutic anticoagulation with IV UFH, SC UFH, a LMWH agent, or

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Statement From the American Heart Association (2011)[25]	fondaparinux. • Patients with iliofemoral DVT who have suspected or proven heparin-induced thrombocytopenia should receive a direct thrombin inhibitor. <u>Recommendations for long-term anticoagulation therapy for patients with iliofemoral DVT</u> • Adult patients with iliofemoral DVT who receive oral warfarin as first-line long-term anticoagulation therapy should have warfarin overlapped with initial anticoagulation therapy for a minimum of five days and until the INR is >2.0 for at least 24 hours, and then targeted to an INR 2.0 to 3.0. • Patients with first episode iliofemoral DVT related to a major reversible risk factor should have anticoagulation stopped after three months. • Patients with recurrent or unprovoked iliofemoral DVT should have at least six months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation. • Cancer patients with iliofemoral DVT should receive LMWH monotherapy for at least three to six months, or as long as the cancer or its treatment (e.g., chemotherapy) is ongoing. • In children with DVT, the use of LMWH monotherapy may be reasonable.
American College of Cardiology/American Heart Association and American College of Cardiology/American Heart Association: **Guideline for the Management of Patients with ST-Segment Elevation Myocardial Infarction (2012)**[23]	<u>Complications after ST-elevation MI (STEMI): anticoagulation</u> • Anticoagulant therapy with a VKA should be provided to patients with ST-elevation myocardial infarction and AF with $CHADS_2$ score of two or more, mechanical heart valves, VTE, or hypercoagulable disorder. • The duration of triple-antithrombotic therapy with a VKA, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding. • Anticoagulant therapy with a VKA is reasonable for patients with STEMI and asymptomatic left ventricle mural thrombi. • Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis. • Targeting VKA therapy to a lower INR (e.g., 2.0 to 2.5) might be considered in patients with STEMI who are receiving dual antiplatelet therapy.
American College of Cardiology/American Heart Association: **2012 Focused Update Replacing the 2011 Focused Update and Updating the 2007 Guidelines for the Management of Patients with Unstable Angina/ Non-ST-Elevation Myocardial Infarction (2012)**[26]	<u>Recommendations for warfarin therapy</u> • Use of warfarin in conjunction with aspirin and/or a $P2Y_{12}$ receptor inhibitor is associated with an increased risk of bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal, and seek medical evaluation for evidence of bleeding. • Warfarin with or without low-dose aspirin (75 to 81 mg/day; INR, 2.0 to 2.5) may be reasonable for patients at high coronary artery disease risk and low bleeding risk who do not require or are intolerant of a $P2Y_{12}$ receptor inhibitor. • Targeting an oral anticoagulant therapy to lower INR (e.g., 2.0 to 2.5) might be reasonable in patients with unstable angina/non-ST-elevation myocardial infarction managed with aspirin and a $P2Y_{12}$ receptor inhibitor.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary**	• These guidelines provide no formal recommendations for the use of oral anticoagulants.

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Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2011)[29]	
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[28]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.
The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2011)**[29]	<u>Exercise and lower extremity peripheral artery disease (PAD) rehabilitation</u> • A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication. • Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks. • The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication. <u>Smoking cessation</u> • Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking. • Patients should be provided with counseling and assistance with developing a plan for smoking cessation. • One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy. <u>Antiplatelet and antithrombotic drugs</u> • Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99. • Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin. • Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding. • The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding. <u>Medical and pharmacological treatment for claudication</u> • Cilostazol (100 mg orally twice daily) is indicated as an effective therapy

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	to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure). • Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication. • The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established. • The effectiveness of L-arginine for patients with intermittent claudication is not well established. • The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established. • The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established. • Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication. • Vitamin E is not recommended as a treatment for patients with intermittent claudication. • Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2014)**[30]	<u>Recommendations for Nonvalvular Atrial Fibrillation:</u> • For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event (Level of Evidence: C). • VKA therapy (Level of Evidence: A), apixaban, dabigatran and rivaroxaban (Level of Evidence: B) are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. o Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR therapeutic range if the patient has been taking VKA therapy. • Target INR for patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0) (Level of Evidence: A). • Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA. o Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement (Level of Evidence: C). • For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended (Level of Evidence: A). o Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (Level of Evidence: B). • For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Level of Evidence: B).

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	• In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Level of Evidence: B). • For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding (Level of Evidence: C). • The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain (Level of Evidence: B). <u>Recommendations for Acute MI and LV Thrombus:</u> • Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting (Level of Evidence: C). o Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians. • Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging (Level of Evidence: C). • In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for three months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA (Level of Evidence: C). <u>Recommendations for Cardiomyopathy:</u> • In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months (Level of Evidence: C). • In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) is reasonable in the absence of major contraindications (Level of Evidence: C). • In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized (Level of Evidence: B). • In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke (Level of Evidence: C). <u>Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease</u>:

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	• For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended (Level of Evidence: A). • For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy (Level of Evidence: C). • For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added (Level of Evidence: C). • For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered (Level of Evidence: C). • For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended (Level of Evidence: C). • For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification (Level of Evidence: C). • For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse (Level of Evidence: C). <u>Recommendations for Prosthetic Heart Valves:</u> • For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0) (Level of Evidence: B). • For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5) (Level of Evidence: B). • For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended (Level of Evidence: B). • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk (Level of Evidence: C). • For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation (Level of Evidence: C). • For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered (Level of Evidence: C).

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	Recommendations for Noncardioembolic Stroke or TIA: • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level of Evidence: A). • Aspirin (50 to 325 mg/day) monotherapy (Level of Evidence: A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Level of Evidence: B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Level of Evidence: B). This recommendation also applies to patients who are allergic to aspirin. • The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Level of Evidence: C). • The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stork or TIA and for continuation for 90 days (Level of Evidence: B). • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA (Level of Evidence: A). • For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin (Level of Evidence: C). • For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events (Level of Evidence: C). Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or VKA therapy. • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Level of Evidence: A).

*Agent not available in the United States.

Conclusions

The oral anticoagulants consist of apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), rivaroxaban (Xarelto®) and warfarin (Coumadin®, Jantoven®). Apixaban, dabigatran etexilate mesylate and rivaroxaban are Food and Drug Administration (FDA)-approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[1-3] Rivaroxaban and apixaban are also approved for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. Rivaroxaban and dabigatran etexilate mesylate also have the additional indication to treat DVT and PE and to reduce risk of recurrent DVT and PE in patients who have been previously treated.[1,3] Warfarin has various indications, including

prophylaxis and/or treatment of PE; prophylaxis and/or treatment of thromboembolic complications associated with AF and/or cardiac valve replacement prophylaxis and/or treatment of venous thrombosis and its extension; and reduce the risk of death, recurrent myocardial infarction (MI) and thromboembolic events such as stroke or systemic embolization after MI.[4] Warfarin, along with aspirin, has been the principle oral anticoagulant for the past 60 years in high-risk AF patients.[5] Warfarin is a generically available vitamin K antagonist (VKA), and the evidence from clinical trials and recommendations from current clinical guidelines support the use of warfarin in FDA-approved indications.[9,22-31] Warfarin and rivaroxaban are approved for once-daily dosing, while apixaban and dabigatran etexilate mesylate are administered twice-daily. Apixaban, dabigatran etexilate mesylate and rivaroxaban require a dose adjustment in patients with renal impairment and are only available as branded products. Furthermore, apixaban requires a dosage adjustment when two or more of the following factors are present: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL.[1-4]

The available oral anticoagulants have different mechanisms of action and affect different parts of the coagulation cascade.[1-4] Dabigatran etexilate mesylate is a direct thrombin inhibitor that prevents conversion of fibrinogen into fibrin, while apixaban and rivaroxaban selectively block the active site of factor Xa, preventing the production of thrombin and ultimately preventing platelet activation and the formation of fibrin clots.[1-3] The major advancement with apixaban, dabigatran etexilate mesylate and rivaroxaban is that they do not require the routine monitoring required with warfarin therapy; however, it may be difficult for physicians to objectively assess adherence to therapy. Moreover, apixaban, dabigatran etexilate mesylate and rivaroxaban are not associated with the food and drug interactions that are associated with warfarin.[1-4]

In a large head-to-head trial, apixaban was superior to warfarin in preventing stroke or systemic embolism, with less major bleeding and intracranial bleeding compared to warfarin, and a similar incidence of gastrointestinal bleeding. Notably, apixaban also reduced death from any cause compared to warfarin.[12] In two studies apixaban was shown to reduce the risk of DVT and PE after hip or knee surgery, with similar bleeding rates compared to once daily enoxaparin.[63,64] Dabigatran etexilate mesylate demonstrated non inferiority for reducing the risk of stroke and systemic embolism, with a dose of 150 mg twice-daily achieving “superiority” over warfarin. In this trial, the incidence of major bleeding was also reduced with dabigatran etexilate mesylate compared to warfarin. In general, evidence suggests that the two agents are comparable in terms of overall bleeding, with more intracranial bleeding being associated with warfarin and more gastrointestinal bleeding being associated with dabigatran etexilate mesylate.[14] Several studies have also show that dabigatran etexilate mesylate is superior to placebo and noninferior to warfarin for the short- and long-term therapy after VTE to prevent recurrent VTE.[57,60,61] Rivaroxaban was compared to warfarin in a large, double-blind trial including over 14,000 patients at risk for stroke. Rivaroxaban demonstrated non inferiority to warfarin in regard to the primary endpoint, a composite of stroke or systemic embolism; however, “superiority” compared to warfarin was not achieved. The incidence of major and clinically relevant nonmajor bleeding between rivaroxaban and warfarin was similar. The rate of intracranial bleeding was significantly lower with rivaroxaban compared to warfarin, but major bleeding from a gastrointestinal site was more common with rivaroxaban.[15] For the prophylaxis of DVT, rivaroxaban was evaluated in four trials compared to enoxaparin, a low molecular weight heparin agent (LMWH), for use as thromboprophylaxis in patients undergoing hip and knee replacement surgeries. In all four trials, rivaroxaban significantly reduced the risk of the primary composite endpoint of any DVT, nonfatal PE, or death from any cause compared to enoxaparin. In addition, there were similar rates of major bleeding and hemorrhagic wound complications between rivaroxaban and enoxaparin. These trials evaluated both short (10 to 14 days) and extended (31 to 30 days) thromboprophylaxis with rivaroxaban.[16-19] In patients with an acute, symptomatic, proximal DVT without symptomatic PE, and acute, symptomatic PE with or without symptomatic DVT, treatment with rivaroxaban was associated with a reduction in symptomatic, recurrent VTE (composite of DVT or nonfatal or fatal PE) compared to standard therapy, without an increase in bleeding events.[20,21]

In 2014, the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society released an updated guideline on the management of AF. The guidelines state that dabigatran etexilate mesylate, apixaban, and rivaroxaban are useful as an alternative to warfarin in nonvalvular AF,

and patients already receiving warfarin with excellent International Normalized Ratio (INR) control may have little to gain by switching to a newer agent.[9] The 2012 American College of Chest Physicians guidelines regarding antithrombotic therapy and prevention of thrombosis, state that oral anticoagulation is recommended in patients with AF at intermediate to high risk of stroke, with dabigatran etexilate mesylate suggested over adjusted-dose VKA therapy.[22] A Science Advisory by the American Heart Association and American Stroke Association states that apixaban, dabigatran etexilate mesylate and rivaroxaban are recommended as alternatives to warfarin in patients with AF who have at least one additional risk factor for stroke.[31] All of the oral anticoagulants are recommended as potential options for thromboprophylaxis of total hip and knee arthroplasty, with LMWH suggested in preference to other recommended options.[22] The American Heart Association/American Stroke Association Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack from 2014 offer similar recommendations to previously published guidelines.[30]

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Immunomodulator Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201401	ACTEMRA INJ 200/10ML	1	1	10	28	$ 517.09
201401	ACTEMRA INJ 400/20ML	2	2	60	29	$ 4,404.75
201401	ACTEMRA INJ 80MG/4ML	1	1	16	1	$ 741.00
201401	CIMZIA PREFL KIT 200MG/ML	5	5	6	139	$ 10,811.88
201401	ENBREL INJ 25/0.5ML	1	1	2.04	25	$ 1,293.26
201401	ENBREL INJ 25MG	4	4	24	114	$ 7,750.06
201401	ENBREL INJ 50MG/ML	8	7	31.36	227	$ 20,654.16
201401	ENBREL SRCLK INJ 50MG/ML	21	19	82.32	601	$ 48,728.23
201401	HUMIRA KIT 20MG/0.4	1	1	2	30	$ 2,557.42
201401	HUMIRA KIT 40MG/0.8	8	8	20	228	$ 20,508.45
201401	HUMIRA PEN KIT 40MG/0.8	28	27	60	800	$ 63,947.24
201401	ORENCIA INJ 125MG/ML	5	5	20	140	$ 10,166.24
201401	ORENCIA INJ 250MG	8	8	772	8	$ 9,459.32
201401	REMICADE INJ 100MG	10	10	49.3	37	$ 32,156.28
201401	SIMPONI INJ 50MG	1	1	0.5	14	$ 2,591.07
201401	XELJANZ TAB 5MG	4	4	195	120	$ 7,302.30
201402	ACTEMRA INJ 200/10ML	1	1	10	28	$ 737.30
201402	ACTEMRA INJ 400/20ML	1	1	20	28	$ 1,469.84
201402	ACTEMRA INJ 80MG/4ML	1	1	16	1	$ 741.00
201402	CIMZIA PREFL KIT 200MG/ML	4	4	4	113	$ 11,317.16
201402	ENBREL INJ 25/0.5ML	1	1	2.04	25	$ 1,293.26
201402	ENBREL INJ 25MG	5	5	32	142	$ 10,331.83
201402	ENBREL INJ 50MG/ML	6	6	22.54	165	$ 14,846.37
201402	ENBREL SRCLK INJ 50MG/ML	22	21	90.16	623	$ 49,063.27
201402	HUMIRA KIT 40MG/0.8	5	5	10	140	$ 5,306.93
201402	HUMIRA PEN KIT 40MG/0.8	26	23	56	744	$ 58,829.14
201402	ORENCIA INJ 125MG/ML	3	3	12	84	$ 7,746.75
201402	ORENCIA INJ 250MG	7	7	21	7	$ 6,488.62
201402	REMICADE INJ 100MG	12	12	57.5	43	$ 40,938.50
201402	SIMPONI INJ 50MG	3	2	1.5	58	$ 8,130.13
201402	XELJANZ TAB 5MG	3	3	180	90	$ 6,737.32
201403	ACTEMRA INJ 162/0.9	1	1	1.8	28	$ 1,317.50
201403	ACTEMRA INJ 200/10ML	1	1	10	28	$ 737.30
201403	ACTEMRA INJ 400/20ML	3	3	80	57	$ 5,869.83
201403	ACTEMRA INJ 80MG/4ML	1	1	16	1	$ 809.00
201403	CIMZIA PREFL KIT 200MG/ML	5	4	5	139	$ 14,146.45
201403	ENBREL INJ 25/0.5ML	3	2	6.12	81	$ 3,879.78
201403	ENBREL INJ 25MG	3	3	20	86	$ 5,574.49
201403	ENBREL INJ 50MG/ML	7	6	27.44	197	$ 18,072.39
201403	ENBREL SRCLK INJ 50MG/ML	26	25	117.6	793	$ 64,545.53
201403	HUMIRA KIT 40MG/0.8	10	10	22	271	$ 18,092.87
201403	HUMIRA PEN KIT 40MG/0.8	28	28	60	801	$ 60,422.69
201403	HUMIRA PEN KIT CROHNS	1	1	6	30	$ 7,662.75
201403	ORENCIA INJ 125MG/ML	3	3	12	84	$ 7,746.75
201403	ORENCIA INJ 250MG	11	11	830	11	$ 16,912.14

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YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201403	REMICADE INJ 100MG	8	7	29	8	$ 24,377.95
201403	SIMPONI INJ 50MG	3	3	51	45	$ 5,592.06
201403	XELJANZ TAB 5MG	4	3	240	124	$ 8,982.95
201404	ACTEMRA INJ 162/0.9	2	2	5.4	56	$ 3,947.74
201404	ACTEMRA INJ 200/10ML	2	2	20	2	$ 1,465.08
201404	ACTEMRA INJ 400/20ML	2	2	60	29	$ 4,399.99
201404	ACTEMRA INJ 80MG/4ML	2	2	8	2	$ 586.04
201404	CIMZIA PREFL KIT 200MG/ML	4	3	4	110	$ 11,317.16
201404	ENBREL INJ 25/0.5ML	1	1	2.04	28	$ 1,293.26
201404	ENBREL INJ 25MG	3	3	20	86	$ 6,456.80
201404	ENBREL INJ 50MG/ML	5	5	23.52	141	$ 15,485.86
201404	ENBREL SRCLK INJ 50MG/ML	27	26	117.6	764	$ 77,438.82
201404	HUMIRA KIT 40MG/0.8	12	12	26	329	$ 30,687.88
201404	HUMIRA PEN KIT 40MG/0.8	22	21	46	624	$ 56,262.08
201404	HUMIRA PEN KIT PSORIASI	2	2	8	56	$ 10,220.16
201404	ORENCIA INJ 125MG/ML	4	4	16	112	$ 10,329.00
201404	ORENCIA INJ 250MG	9	9	774	9	$ 10,828.79
201404	REMICADE INJ 100MG	15	14	149.8	15	$ 89,139.18
201404	SIMPONI INJ 50MG	2	2	1	60	$ 5,539.06
201404	XELJANZ TAB 5MG	2	2	120	60	$ 4,491.26
201405	ACTEMRA INJ 162/0.9	1	1	3.6	28	$ 2,630.24
201405	ACTEMRA INJ 200/10ML	2	2	20	2	$ 1,465.08
201405	ACTEMRA INJ 400/20ML	3	2	100	57	$ 7,334.90
201405	ACTEMRA INJ 80MG/4ML	2	2	8	2	$ 586.04
201405	CIMZIA PREFL KIT 200MG/ML	2	2	2	56	$ 5,658.58
201405	ENBREL INJ 25/0.5ML	1	1	2.04	25	$ 1,293.26
201405	ENBREL INJ 25MG	3	3	16	84	$ 5,168.29
201405	ENBREL INJ 50MG/ML	4	4	19.6	112	$ 10,377.91
201405	ENBREL SRCLK INJ 50MG/ML	26	25	109.76	734	$ 69,701.87
201405	HUMIRA KIT 40MG/0.8	11	11	30	314	$ 30,800.94
201405	HUMIRA PEN KIT 40MG/0.8	22	22	48	622	$ 56,260.92
201405	ORENCIA INJ 125MG/ML	4	4	16	112	$ 10,162.64
201405	ORENCIA INJ 250MG	11	10	825	11	$ 14,810.96
201405	REMICADE INJ 100MG	13	13	50.4	13	$ 45,494.67
201405	SIMPONI INJ 50MG	2	2	1	60	$ 5,539.06
201405	XELJANZ TAB 5MG	3	3	180	90	$ 6,736.89
201406	ACTEMRA INJ 200/10ML	4	4	50	31	$ 3,667.47
201406	ACTEMRA INJ 400/20ML	3	3	80	57	$ 5,869.83
201406	ACTEMRA INJ 80MG/4ML	2	2	8	2	$ 586.04
201406	CIMZIA PREFL KIT 200MG/ML	3	3	4	86	$ 8,984.06
201406	ENBREL INJ 25/0.5ML	2	2	4.08	53	$ 2,586.52
201406	ENBREL INJ 25MG	3	3	20	84	$ 6,634.61
201406	ENBREL INJ 50MG/ML	6	6	27.44	169	$ 16,022.89
201406	ENBREL SRCLK INJ 50MG/ML	32	28	129.36	902	$ 88,927.65
201406	HUMIRA KIT 40MG/0.8	11	10	22	297	$ 18,036.47

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YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201406	HUMIRA PEN KIT 40MG/0.8	25	24	58	712	$ 71,635.74
201406	HUMIRA PEN KIT CROHNS	2	2	12	56	$ 15,325.50
201406	ORENCIA INJ 125MG/ML	4	4	16	114	$ 10,329.00
201406	ORENCIA INJ 250MG	6	6	19	6	$ 6,568.34
201406	REMICADE INJ 100MG	11	11	35.8	44	$ 32,326.56
201406	SIMPONI INJ 50MG	3	3	1.5	90	$ 8,308.59
201406	XELJANZ TAB 5MG	3	3	180	90	$ 7,201.18
201407	ACTEMRA INJ 162/0.9	1	1	3.6	28	$ 2,787.77
201407	ACTEMRA INJ 200/10ML	2	2	20	2	$ 1,531.02
201407	ACTEMRA INJ 400/20ML	4	4	100	58	$ 7,664.62
201407	ACTEMRA INJ 80MG/4ML	3	3	12	30	$ 923.36
201407	CIMZIA PREFL KIT 200MG/ML	4	3	4	85	$ 11,317.16
201407	ENBREL INJ 25/0.5ML	1	1	2.04	28	$ 1,382.17
201407	ENBREL INJ 25MG	6	4	40	168	$ 13,802.66
201407	ENBREL INJ 50MG/ML	6	6	23.52	168	$ 13,801.50
201407	ENBREL SRCLK INJ 50MG/ML	29	29	113.68	822	$ 77,586.55
201407	HUMIRA KIT 40MG/0.8	8	8	18	230	$ 19,441.25
201407	HUMIRA PEN KIT 40MG/0.8	26	22	54	703	$ 73,885.66
201407	HUMIRA PEN KIT CROHNS	1	1	6	30	$ 3.60
201407	HUMIRA PEN KIT PSORIASI	3	3	12	86	$ 11,030.40
201407	ORENCIA INJ 125MG/ML	5	5	18	128	$ 12,244.98
201407	ORENCIA INJ 250MG	6	6	19	6	$ 6,568.34
201407	REMICADE INJ 100MG	12	11	41.86	12	$ 36,708.51
201407	SIMPONI INJ 50/0.5ML	1	1	0.5	30	$ 2,769.53
201407	SIMPONI INJ 50MG	1	1	0.5	30	$ 2,769.53
201407	XELJANZ TAB 5MG	3	3	180	90	$ 7,201.18
201408	ACTEMRA INJ 162/0.9	2	2	5.4	56	$ 4,184.03
201408	ACTEMRA INJ 200/10ML	1	1	10	1	$ 129.00
201408	ACTEMRA INJ 400/20ML	4	4	80	31	$ 4,687.82
201408	ACTEMRA INJ 80MG/4ML	2	2	8	29	$ 475.96
201408	CIMZIA PREFL KIT 200MG/ML	2	2	2	56	$ 5,658.58
201408	ENBREL INJ 25/0.5ML	2	2	4.08	42	$ 2,764.34
201408	ENBREL INJ 25MG	5	5	32	142	$ 11,043.08
201408	ENBREL INJ 50MG/ML	7	7	27.44	196	$ 16,561.08
201408	ENBREL SRCLK INJ 50MG/ML	39	36	152.88	1,104	$ 100,601.03
201408	HUMIRA KIT 40MG/0.8	7	6	16	200	$ 16,682.16
201408	HUMIRA PEN KIT 40MG/0.8	27	26	56	766	$ 71,849.01
201408	ORENCIA INJ 125MG/ML	4	4	14	98	$ 9,662.73
201408	ORENCIA INJ 250MG	7	6	21	7	$ 7,945.79
201408	REMICADE INJ 100MG	11	10	44	17	$ 39,722.93
201408	SIMPONI INJ 50/0.5ML	2	2	1	60	$ 5,812.78
201408	XELJANZ TAB 5MG	3	3	180	90	$ 7,201.18
201409	ACTEMRA INJ 162/0.9	1	1	3.6	28	$ 2,787.77
201409	ACTEMRA INJ 200/10ML	1	1	10	1	$ 765.51
201409	ACTEMRA INJ 400/20ML	3	3	60	30	$ 4,597.82

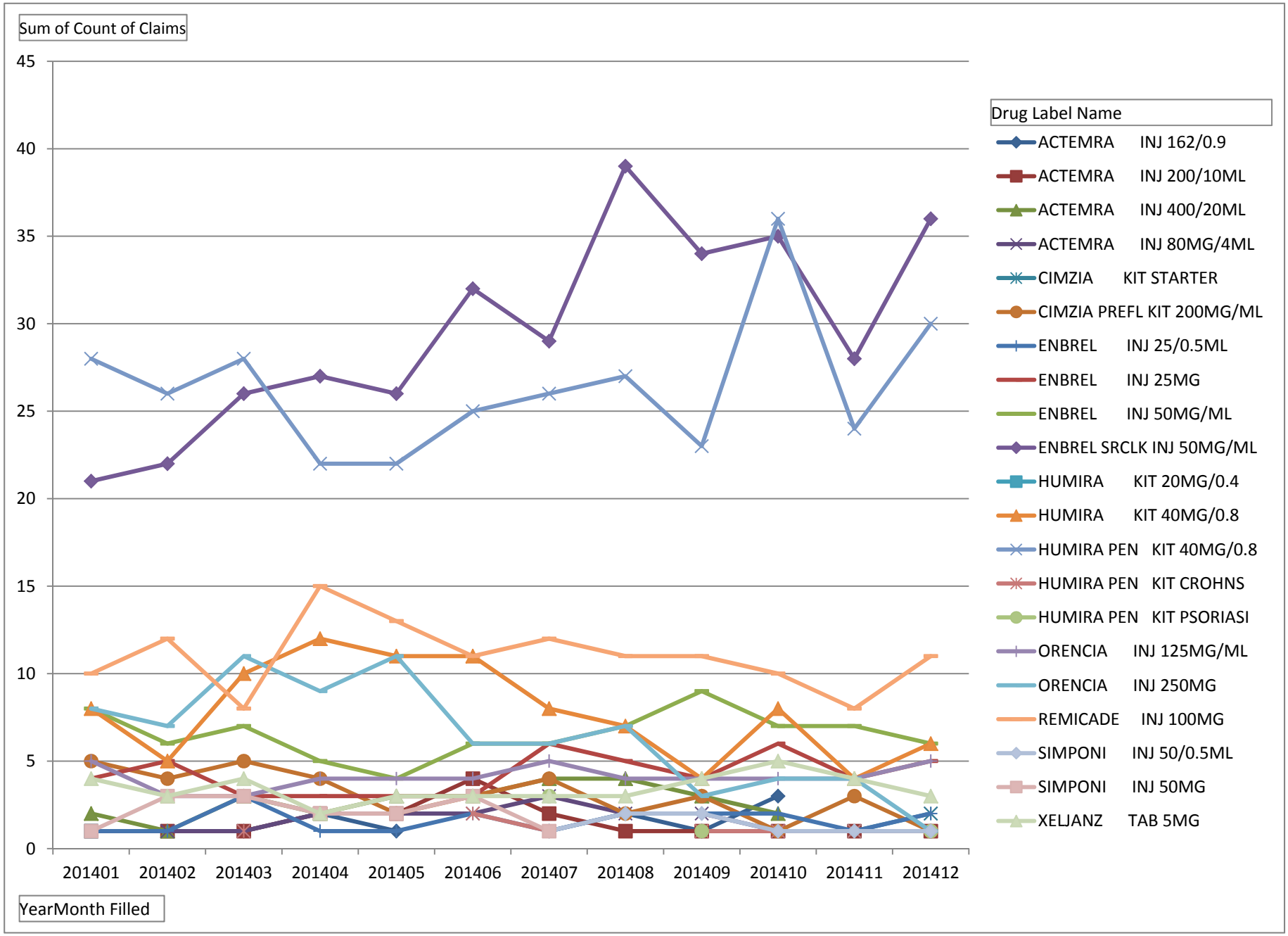
Immunomodulator Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201409	ACTEMRA INJ 80MG/4ML	2	2	8	29	$ 617.16
201409	CIMZIA PREFL KIT 200MG/ML	3	3	4	86	$ 9,122.52
201409	ENBREL INJ 25/0.5ML	2	2	4.08	42	$ 2,764.34
201409	ENBREL INJ 25MG	4	4	24	114	$ 8,283.50
201409	ENBREL INJ 50MG/ML	1	1	3.92	28	$ 3.60
201409	ENBREL INJ 50MG/ML	8	8	31.36	224	$ 19,320.66
201409	ENBREL SRCLK INJ 50MG/ML	7	7	27.44	198	$ 19,317.06
201409	ENBREL SRCLK INJ 50MG/ML	27	27	105.84	764	$ 72,067.39
201409	HUMIRA KIT 40MG/0.8	4	4	8	116	$ 8,280.87
201409	HUMIRA PEN KIT 40MG/0.8	23	23	48	652	$ 63,555.15
201409	HUMIRA PEN KIT CROHNS	1	1	6	28	$ 8,267.73
201409	HUMIRA PEN KIT PSORIASI	1	1	4	28	$ 5,513.40
201409	ORENCIA INJ 125MG/ML	1	1	4	28	$ 2,760.10
201409	ORENCIA INJ 125MG/ML	3	3	12	84	$ 8,280.30
201409	ORENCIA INJ 250MG	3	3	9	3	$ 2,595.45
201409	REMICADE INJ 100MG	11	11	45.55	40	$ 43,096.99
201409	SIMPONI INJ 50/0.5ML	2	2	1	60	$ 6,086.50
201409	XELJANZ TAB 5MG	4	4	240	120	$ 9,601.43
201410	ACTEMRA INJ 162/0.9	3	3	9	84	$ 6,971.80
201410	ACTEMRA INJ 200/10ML	1	1	10	1	$ 90.00
201410	ACTEMRA INJ 400/20ML	2	2	40	2	$ 2,340.02
201410	ACTEMRA INJ 80MG/4ML	1	1	4	1	$ 165.00
201410	CIMZIA PREFL KIT 200MG/ML	1	1	1	28	$ 2,829.29
201410	ENBREL INJ 25/0.5ML	2	2	4.08	42	$ 2,764.34
201410	ENBREL INJ 25MG	6	4	40	170	$ 13,802.66
201410	ENBREL INJ 50MG/ML	7	7	27.44	196	$ 16,561.08
201410	ENBREL SRCLK INJ 50MG/ML	35	33	145.04	988	$ 97,062.30
201410	HUMIRA KIT 40MG/0.8	8	8	18	212	$ 16,685.76
201410	HUMIRA PEN KIT 40MG/0.8	36	30	78	1,076	$ 88,450.13
201410	HUMIRA PEN KIT CROHNS	1	1	6	28	$ 8,267.73
201410	ORENCIA INJ 125MG/ML	4	3	16	112	$ 11,040.40
201410	ORENCIA INJ 250MG	4	4	12	4	$ 4,795.90
201410	REMICADE INJ 100MG	10	10	41.15	10	$ 36,939.10
201410	SIMPONI INJ 50/0.5ML	1	1	0.5	30	$ 3,043.25
201410	XELJANZ TAB 5MG	5	4	300	150	$ 12,001.25
201411	ACTEMRA INJ 200/10ML	1	1	20	1	$ 1,531.02
201411	CIMZIA KIT STARTER	1	1	6	30	$ 16,951.96
201411	CIMZIA PREFL KIT 200MG/ML	3	3	4	84	$ 11,312.41
201411	ENBREL INJ 25/0.5ML	1	1	2.04	28	$ 1,382.17
201411	ENBREL INJ 25MG	4	4	28	114	$ 9,878.53
201411	ENBREL INJ 50MG/ML	7	6	27.44	196	$ 13,805.10
201411	ENBREL SRCLK INJ 50MG/ML	28	28	109.76	788	$ 78,356.34
201411	HUMIRA KIT 40MG/0.8	4	4	8	114	$ 5,742.96
201411	HUMIRA PEN KIT 40MG/0.8	24	22	48	682	$ 59,692.33
201411	HUMIRA PEN KIT CROHNS	1	1	6	28	$ 8,267.73

Immunomodulator Utilization 2014

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt
201411	ORENCIA INJ 125MG/ML	4	4	16	114	$ 10,696.19
201411	ORENCIA INJ 250MG	4	4	12	4	$ 3,973.74
201411	REMICADE INJ 100MG	8	8	35.8	41	$ 33,900.36
201411	SIMPONI INJ 50/0.5ML	1	1	0.5	30	$ 3,043.25
201411	XELJANZ TAB 5MG	4	4	240	120	$ 9,601.00
201412	ACTEMRA INJ 162/0.9	1	1	1.8	28	$ 1,396.26
201412	ACTEMRA INJ 200/10ML	1	1	20	1	$ 1,531.02
201412	ACTEMRA INJ 80MG/4ML	2	1	24	2	$ 1,837.22
201412	CIMZIA KIT STARTER	2	2	6	58	$ 16,956.72
201412	CIMZIA PREFL KIT 200MG/ML	1	1	1	28	$ 2,829.29
201412	ENBREL INJ 25/0.5ML	2	2	4.08	42	$ 2,981.96
201412	ENBREL INJ 25MG	5	5	28	144	$ 10,427.34
201412	ENBREL INJ 50MG/ML	6	5	23.52	168	$ 11,916.00
201412	ENBREL SRCLK INJ 50MG/ML	36	33	156.8	1,070	$ 110,150.50
201412	HUMIRA KIT 40MG/0.8	6	5	14	158	$ 17,858.87
201412	HUMIRA PEN KIT 40MG/0.8	30	26	64	818	$ 89,297.80
201412	HUMIRA PEN KIT PSORIASI	1	1	4	28	$ 5,948.58
201412	ORENCIA INJ 125MG/ML	5	4	20	140	$ 13,891.61
201412	ORENCIA INJ 250MG	1	1	3	1	$ 2,146.74
201412	REMICADE INJ 100MG	11	11	44.35	11	$ 34,150.83
201412	SIMPONI INJ 50/0.5ML	1	1	0.5	29	$ 3,043.25
201412	XELJANZ TAB 5MG	3	3	180	90	$ 7,200.75

Immunomodulator Utilization 2014



L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators
Last Reviewed by the DUR Board: January 23, 2014

Actemra® (tocilizumab)	Cimzia® (certolizumab pegol)
Amevive® (alefacept)	Kineret® (ankinra)
Enbrel® (etanercept)	
Entyvio® (vedolizumab)	Orencia® (abatacept)
Humira® (adalimumab)	Remicade® (infliximab)
Simponi® (golimumab)	Stelara® (ustekinumab)
Simponi® ARIA™ (golimumab)	Xeljanz® (tofacitinib)

Immunomodulator Drugs are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Rheumatoid Arthritis (RA):

1. The recipient has a diagnosis of moderately to severely active RA; and

2. The recipient has had a rheumatology consultation, including the date of the visit; and

3. The recipient has had a negative tuberculin test; and

4. The recipient does not have an active infection or a history of recurring infections; and

5. The recipient has had RA for six months (early RA) and has high disease activity; and an inadequate or adverse reaction of a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or

6. The recipient has had RA for very short (less than intermediate or long-term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline or sulfasalazine); or

7. The recipient has had RA for six months (intermediate or long-term disease duration) and has high disease activity.

b. Psoriatic Arthritis:

1. The recipient has a diagnosis of moderate or severe psoriatic arthritis; and

2. The recipient has had a rheumatology consultation including the date of the visit or a dermatology consultation including the date of the visit; and

3. The recipient had an inadequate response to any one nonsteroidal anti-inflammatory drug (NSAID) or a contraindication to treatment with an NSAID or to any one of the following DMARDs (methotrexate, leflunomide, cyclosporine or sulfasalazine); and

4. The recipient has had a negative tuberculin test; and

5. The recipient does not have active infection or a history of recurring infections.

c. Ankylosing Spondylitis:

1. The recipient has a diagnosis of ankylosing spondylitis; and

2. The recipient has had an inadequate response to NSAIDs; and

3. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalzine, leflunomide, minocycline); and

4. The recipient has had a negative tuberculin test; and

5. The recipient does not have an active infection or a history of recurring infections.

d. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis:

1. The recipient has a diagnosis of moderately or severely active juvenile RA; and

2. The recipient is at least two years of age; and

3. The recipient has at least five swollen joints; and

4. The recipient has three or more joints with limitation of motion and pain, tenderness or both; and

5. The recipient has had an inadequate response to one DMARD; and

6. The recipient has had a negative tuberculin test; and

7. The recipient does not have an active infection or a history of recurring infections.

e. Plaque Psoriasis:

1. The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis; and

2. The agent is prescribed by a dermatologist; and

3. The recipient has failed to adequately respond to a topical agent; and

4. The recipient has failed to adequately respond to at least one oral treatment; and

5. The recipient has had a negative tuberculin test; and

6. The recipient does not have an active infection or a history of recurring infections.

f. Crohn's Disease:

1. The recipient has a diagnosis of moderate to severe Crohn's Disease; and

2. The recipient has failed to adequately respond to conventional therapy (e.g. sulfasalzine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide); or

3. The recipient has fistulizing Crohn's disease, and;

4. The recipient has a negative tuberculin test; and

5. The recipient does not have an active infection or a history of recurring infections.

g. Ulcerative Colitis:

1. The recipient has a diagnosis of moderate to severe ulcerative colitis; and

2. The recipient has failed to adequately respond to one or more of the following standard therapies:

a. Corticosteroids;

b. 5-aminosalicylic acid agents;

c. Immunosuppresants; and/or

d. Thiopurines; and

3. The recipient has a negative tuberculin test; and

4. The recipient does not have an active infection or history of recurring infections.

2. Approval will not be given for the use of more than one biologic at a time (combination therapy).

3. Prior Authorization Guidelines

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Prior authorization approval will be for one year.

L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators
Last Reviewed by the DUR Board: January 23, 2014

Actemra® (tocilizumab)	Cimzia® (certolizumab pegol)
Amevive® (alefacept)	Kineret® (ankinra)
Enbrel® (etanercept)	Orencia® (abatacept)
Humira® (adalimumab)	Remicade® (infliximab)
Simponi® (golimumab)	Stelara® (ustekinumab)
Simponi® ARIA™ (golimumab)	Xeljanz® (tofacitinib)

Immunomodulator Drugs are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Rheumatoid Arthritis (RA):

1. The recipient has a diagnosis of moderately to severely active RA; and

2. The recipient has had a rheumatology consultation, including the date of the visit; and

3. The recipient has had a negative tuberculin test; and

4. The recipient does not have an active infection or a history of recurring infections; and

5. The recipient has had RA for ≤ six months (early RA) and has high disease activity; and an inadequate or adverse reaction of a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or

6. The recipient has had RA for ≥ six months (interme diate or long-term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline or sulfasalazine); or

7. The recipient has had RA for ≥ six months (intermediate or long-term disease duration) and has high disease activity.

b. Psoriatic Arthritis:

1. The recipient has a diagnosis of moderate or severe psoriatic arthritis; and

2. The recipient has had a rheumatology consultation including the date of the visit or a dermatology consultation including the date of the visit; and

3. The recipient had an inadequate response to any one nonsteroidal anti-inflammatory drug (NSAID) or a contraindication to treatment with an NSAID or to any one of the following DMARDs (methotrexate, leflunomide, cyclosporine or sulfasalazine); and

4. The recipient has had a negative tuberculin test; and

5. The recipient does not have active infection or a history of recurring infections.

c. Ankylosing Spondylitis:

1. The recipient has a diagnosis of ankylosing spondylitis; and

2. The recipient has had an inadequate response to NSAIDs; and

3. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalzine, leflunomide, minocycline); and

4. The recipient has had a negative tuberculin test; and

5. The recipient does not have an active infection or a history of recurring infections.

d. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis:

1. The recipient has a diagnosis of moderately or severely active juvenile RA; and

2. The recipient is at least two years of age; and

3. The recipient has at least five swollen joints; and

4. The recipient has three or more joints with limitation of motion and pain, tenderness or both; and

5. The recipient has had an inadequate response to one DMARD; and

6. The recipient has had a negative tuberculin test; and

7. The recipient does not have an active infection or a history of recurring infections.

e. Plaque Psoriasis:

1. The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis; and

2. The agent is prescribed by a dermatologist; and

3. The recipient has failed to adequately respond to a topical agent; and

4. The recipient has failed to adequately respond to at least one oral treatment; and

5. The recipient has had a negative tuberculin test; and

6. The recipient does not have an active infection or a history of recurring infections.

f. Crohn's Disease:

1. The recipient has a diagnosis of moderate to severe Crohn's Disease; and

2. The recipient has failed to adequately respond to conventional therapy (e.g. sulfasalzine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide); or

3. The recipient has fistulizing Crohn's disease, and;

4. The recipient has a negative tuberculin test; and

5. The recipient does not have an active infection or a history of recurring infections.

g. Ulcerative Colitis:

1. The recipient has a diagnosis of moderate to severe ulcerative colitis; and

2. The recipient has failed to adequately respond to one or more of the following standard therapies:

a. Corticosteroids;

b. 5-aminosalicylic acid agents;

c. Immunosuppresants; and/or

d. Thiopurines; and

3. The recipient has a negative tuberculin test; and

4. The recipient does not have an active infection or history of recurring infections.

2. Approval will not be given for the use of more than one biologic at a time (combination therapy).

3. Prior Authorization Guidelines

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Prior authorization approval will be for one year.

Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review encompasses immunomodulator agents used in immune-mediated inflammatory diseases. These agents include interleukin (IL) receptor antagonists (anakinra, tocilizumab), tumor necrosis factor (TNF)-blocking agents (adalimumab, certolizumab, etanercept, golimumab, and infliximab), T-cell activation inhibitor (abatacept), a janus kinase inhibitor (tofacitinib) and an integrin receptor antagonist (vedolizumab). These agents interfere with inflammatory pathways through slightly different mechanisms and are indicated in rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and neonatal-onset multisystem inflammatory disease.[1-14]

  Generally, current consensus guidelines support the use of the TNF-blockers with respect to their Food and Drug Administration (FDA)-approved indications and no one agent is preferred over another.[15-32] As more recent guidelines are published, the recommendations for use of TNF-blockers earlier in therapy is becoming a more common occurance.[23,24,27] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[33]

Table 1. Current Medications Available in the Therapeutic Class[3-14]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®)	Monotherapy or concomitantly with disease modifying antirheumatic drugs other than tumor necrosis factor antagonists for moderately to severely active rheumatoid arthritis in adults; monotherapy or concomitantly with methotrexate for moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients six years of age and older	Prefilled syringe: 125 mg/mL Single use vial: 250 mg	-
Adalimumab (Humira®)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (in pediatric patients four years of age and older; reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis; reducing signs and symptoms in adult patients with active ankylosing spondylitis; reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab; inducing and sustaining clinical remission in adult patients	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine; treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate		
Anakinra (Kineret®)	Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs; treatment of neonatal-onset multisystem inflammatory disease	Prefilled syringe: 100 mg/0.67 mL	-
Certolizumab (Cimzia®)	Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy; treatment of adults with moderately to severely active rheumatoid arthritis; treatment of adults with active psoriatic arthritis; treatment of adults with active ankylosing spondylitis	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	Monotherapy or in combination with methotrexate in reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages two and older; reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and as monotherapy in improving physical function in patients with psoriatic arthritis or in combination with methotrexate in patients who do not respond adequately to methotrexate alone; reducing signs and symptoms in patients with active ankylosing spondylitis; treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	Treatment of adult patients with moderately to severely active rheumatoid arthritis in combination with methotrexate (Simponi® and Simponi Aria®); treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate (Simponi® only); treatment of adult patients with active ankylosing spondylitis (Simponi® only); treatment of moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL, 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	mercaptopurine (Simponi® only)	vial*: 50 mg/4 mL	
Infliximab (Remicade®)	Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely ulcerative colitis who have had an inadequate response to conventional therapy; in combination with methotrexate to reduce signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms in patients with active ankylosing spondylitis; reducing signs and symptoms of active psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function; treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	Single use vial: 100 mg	-
Tocilizumab (Actemra®)	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs; patients two years of age and older with active polyarticular juvenile idiopathic arthritis; patients two years of age and older with active systemic juvenile idiopathic arthritis	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®)	Monotherapy or concomitantly with nonbiologic disease modifying antirheumatic drugs for moderately to severely active rheumatoid arthritis in adults who have had an inadequate response or intolerance to methotrexate	Tablet: 5 mg	-
Ustekinumab (Stelara®)	Treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy Treatment of adult patients (18 years or older) with active psoriatic arthritis alone or in combination with methotrexate.	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Vedolizumab (Entyvio®)	Treatment of adult patients (18 years or older) with moderately to severely active Crohn's disease who have had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids; treatment of adult patients (18 years or older) with moderately to severely active ulcerative colitis who had an inadequate response with, lost response to or were intolerant to a tumor necrosis factor antagonist or immunomodulator or who had demonstrated dependence on corticosteroids	Single use vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[38-128]
- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.[128]
- To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results.[38-128] In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[111] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[112,113] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[115] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.
- Generally, current consensus guidelines support the use of the tumor necrosis factor-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[15-32] As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[23,24,27] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class; however, several other agents have recently gained additional indications.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[15-32]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - In general, no one agent is preferred over another; however, given the paucity of clinical experience and long-term safety data, the use of tofacitinib for rheumatoid arthritis is recommended primarily after biological treatment has failed.[15]

- Other Key Facts:
    - None of the immunomodulators included in this review are available generically.
    - Dosing frequency and route of administration vary between products.
        - Currently none of the agents available may be administered via oral route.
        - Infliximab and vedolizumab are administered intravenously and are the only agents in the class that are not available for subcutaneous administration. A loading- dose of abatacept is recommended to be administered intravenously, but can be given subcutaneously if the patient is not able to received intravenous infusion.
        - Anakinra is administered subcutaneously, but requires more frequent daily administration.
    - Intravenous formulation of golimumab and subcutaneous formulation of tocilizumab are only indicated in the treatment of rheumatoid arthritis.
    - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease.

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Therapeutic Class Review
Immunomodulators

Overview/Summary

Tumor necrosis factor (TNF) is a pro-inflammatory mediator, which is released by lymphocytes. Several conditions have been associated with elevated TNF levels including rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis and Crohn's disease. TNF-blocking agents including adalimumab, certolizumab, etanercept, golimumab, and infliximab interfere with this inflammatory pathway through slightly different mechanisms. Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind to TNF-α, etanercept is a fusion protein that binds to both TNF-α and TNF-β, certolizumab pegol is a pegylated antibody-binding fragment TNF-α blocker.[1-8]

All of the TNF-α blocking agents are approved by the Food and Drug Administration (FDA) for rheumatoid arthritis, and with the exception of intravenous formulation of golimumab, are also approved in ankylosing spondylitis and psoriatic arthritis. In addition to these indications, adalimumab and etanercept are also approved in juvenile idiopathic arthritis; adalimumab, etanercept, and infliximab are approved in plaque psoriasis; adalimumab, certolizumab, and infliximab are approved in Crohn's disease; and adalimumab, golimumab, and infliximab are approved in ulcerative colitis. Furthermore, infliximab is indicated for use in both pediatric Crohn's disease and pediatric ulcerative colitis. All of the TNF-blockers have been shown to be efficacious compared to placebo for their respective indications. These agents have been found to be similar with respect to adverse events and interacting medications.[3-8]

Anakinra is an interleukin (IL)-1 receptor antagonist that competitively inhibits the binding of IL-1 to its affiliated receptor. IL-1 is a pro-inflammatory mediator associated with cartilage breakdown as well as stimulation of bone resorption. Anakinra disrupts this inflammatory process and is FDA-approved for rheumatoid arthritis. This agent may be used alone or in combination with other disease modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine, methotrexate or sulfasalazine.[9] In the treatment of rheumatoid arthritis, anakinra demonstrates modest efficacy compared to TNF-blocking agents.[1] Anakira has also been approved for the treatment of children and adults with neonatal-onset multisystem inflammatory disease (NOMID). NOMID is a form of cryopyrin-associated periodic syndromes (CAPS), a group of rare, inherited, autoinflammatory diseases. Anakinra is the first and only FDA-approved treatment for NOMID.[9]

Another IL antagonist, tocilizumab, binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 mediated signaling through these receptors. IL-6 is a chemical messenger that has been associated with the ongoing inflammatory process. Tocilizumab is indicated for the treatment of adult patients with rheumatoid arthritis who have had an inadequate response to one or more DMARDs and for the treatment of pediatric patients with active polyarticular or systemic juvenile idiopathic arthritis.[10] A third IL antagonist, ustekinumab, is a fully-humanized monoclonal antibody that binds with high affinity to both IL-12 and IL-23 cytokines, which are involved in inflammatory and immune responses. Ustekinumab is indicated for the treatment of active psoriatic arthritis and in the treatment plaque psoriasis in adults who are candidates for phototherapy or systemic therapy.[11]

Abatacept is the only T-cell activation inhibitor in the immunomodulator class of drugs. Abatacept binds to CD80 and CD86 preventing CD28 activation, which is required for the costimulatory signal necessary for full activation of the T-cell. Abatacept is indicated for rheumatoid arthritis and juvenile idiopathic arthritis.[12]

Tofacitinib is an oral janus kinase inhibitor.[13] It is a synthetic chemical compound that interferes with specific signal-transduction pathways and thus cannot be classified as either a conventional synthetic or biological DMARD.[14] Through its broad effect on multiple cytokine pathways, tofacitinib may reduce tissue inflammation and joint damage in rheumatoid arthritis. It is indicated for use in adults with rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with conventional DMARDs, but not biologic DMARDs.[13]

Vedolizumab is a humanized monoclonal antibody that binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-cells across endothelium into inflamed gastrointestinal parenchymal tissue. The interaction of α4β7 integrin with MAdCAM-1 is thought to be an important contributor to the chronic inflammation associated with ulcerative colitis and Crohn's disease. Vedolizumab is FDA-approved for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids and in patients with moderately to severely active ulcerative colitis who had an inadequate response with, lost response to or were intolerant to a TNF antagonist or immunomodulator or who had demonstrated dependence on corticosteroids.[14]

Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[15-32] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[23,24,27] Given the paucity of clinical experience and long-term safety data, the 2013 European League against Rheumatism guidelines recommend that tofacitinib should primarily be used when biological treatment has failed.[15] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[33]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Abatacept (Orencia®)	T-cell activation inhibitor	-
Adalimumab (Humira®)	Tumor necrosis factor-inhibitor	-
Anakinra (Kineret®)	Interleukin-1 inhibitor	-
Certolizumab (Cimzia®)	Tumor necrosis factor-inhibitor	-
Etanercept (Enbrel®)	Tumor necrosis factor-inhibitor	-
Golimumab (Simponi®, Simponi Aria®)	Tumor necrosis factor-inhibitor	-
Infliximab (Remicade®)	Tumor necrosis factor-inhibitor	-
Tocilizumab (Actemra®)	Interleukin-6 inhibitor	-
Tofacitinib (Xeljanz®)	Janus kinase inhibitor	-
Ustekinumab (Stelara®)	Interleukin-12 and Interleukin-23 inhibitor	-
Vedolizumab (Entyvio®)	Integrin receptor antagonist	-

Indications

Table 2. Food and Drug Administration Approved Indications[3-14]

Generic Name	Ankylo-sing Spondy-litis	Crohn's Disease	Juvenile Idio-pathic Arthritis	NO-MID	Plaque Psoriasis	Psoriatic Arthritis	Rheum-atoid Arthritis	Ulcer-ative Colitis
Abatacept			✔ *				✔ *	
Adalimumab	✔	✔ †	✔		✔ ‡	✔ *	✔ *	✔ §
Anakinra				✔			✔ *‖	
Certolizumab	✔	✔ ¶				✔	✔	
Etanercept	✔		✔		✔ #	✔ **	✔	

Generic Name	Ankylo-sing Spondy-litis	Crohn's Disease	Juvenile Idio-pathic Arthritis	NO-MID	Plaque Psoriasis	Psoriatic Arthritis	Rheum-atoid Arthritis	Ulcer-ative Colitis
Golimumab	✔ ††					✔ ††	✔ ‡‡	✔ §††
Infliximab	✔	✔ ¶			✔ §§	✔	✔ ‡‡	✔ ¶
Tocilizumab			✔ ‖‖				✔ ‖	
Tofacitinib							✔ ¶ı ¶ı	
Ustekinumab					✔ #	✔		
Vedolizumab		✔ ##						✔ ##

NOMID=Neonatal-onset multisystem inflammatory disease
*Alone or in combination with disease modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor inhibitors.
†In patients who have had an inadequate response to conventional therapy and if they have also lost response to or are intolerant of infliximab.
‡In patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
§In patients who had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine.
‖In patients who have failed one or more DMARDs.
¶In patients who have had an inadequate response to conventional therapy.
#In patients who are candidates for systemic therapy or phototherapy.
**May be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
††Golimumab (Simponi Aria®) is only indicated in the treated of rheumatoid arthritis.
‡‡In combination with methotrexate.
§§In patients with chronic severe disease who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
‖‖Indicated in the treatment of both active polyarticular and systemic juvenile idiopathic arthritis.
¶ı ¶ı In patients who have had an inadequate response or intolerance to methotrexate; may be used as monotherapy or in combination with methotrexate or other DMARDs.## In adult patients who have had an inadequate response with, lost response to or were intolerant to a tumor necrosis factor blocker or immunomodulator; or who had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids

As a class, the immunomodulators are used off-label for a wide-variety of autoimmune diseases. Anti-tumor necrosis factor (TNF) agents are under investigation for the treatment of Behcet's disease, non-infectious ocular inflammation, pyoderma gangrenosum, and hidradenitis suppurativa.[34] Tofacitinib is currently being studied for the treatment of psoriatic arthritis, ulcerative colitis, and plaque psoriasis.[35]

Pharmacokinetics

Table 3. Pharmacokinetics[3-14,36,37]

Generic Name	Bioavailability (%)	Time to Peak Concentration	Elimination Half-Life
Abatacept	100 (intravenous); 78.6 (subcutaneous)	Not reported	13.0 to 14.3 days
Adalimumab	64	131±56 hours	10 to 18 days
Anakinra	95	3 to 7 hours	4 to 6 hours
Certolizumab	80	54 to 171 hours	14 days
Etanercept	58	69±34 hours	102±30 hours
Golimumab	100 (intravenous); 53 (subcutaneous)	48 to 144 hours (subcutaneous)	14 days
Infliximab	100	Not reported	8 to 10 days
Tocilizumab	100 (intravenous); 80 (subcutaneous)	Not reported	11 to 23 days
Tofacitinib	74%	0.5 to 1.0 hour	3 hours
Ustekinumab	Not reported	7.0 to 13.5 days	14.9 to 45.6 days
Vedolizumab	Not reported	Not reported	25 days

Clinical Trials

Clinical studies evaluating the safety and efficacy of the immunomodulators in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[38-128]

The FDA-approval of adalimumab for the treatment of ankylosing spondylitis (AS) was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients in the adalimumab group achieved an improvement of at least 20% in Assessment in Spondyloarthritis International Society (ASAS), the primary endpoint, compared to placebo (58 vs 21%; P<0.001). An improvement of at least 50% in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients at week 12 (P<0.001). This response was sustained through week 24, with 42% of patients in the adalimumab group achieving at least 50% improvement in BASDAI score compared to 15% in the placebo group (P<0.001).[38]

The FDA-approval of certolizumab for the treatment of AS was based on one randomized, double-blind, placebo-controlled study (N=325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every two weeks and certolizumab 400 mg every four weeks compared to placebo at 12 weeks (57.7 and 63.6% vs 38.3%; P=0.004 and P<0.001, respectively). The difference in ASAS 20 response was sustained through week 24 in both certolizumab treatment groups. Improvements in BASDAI scores were greater in patients treated with certolizumab 200 mg every two weeks and certolizumab 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001) and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively.[39]

The efficacy of etanercept in patients with AS was established in two double-blind, randomized, placebo-controlled trials. Patients treated with etanercept experienced a significantly greater response to treatment compared to placebo (P<0.001).[40] A greater proportion of patients achieved an ASAS 20 response compared to placebo (P<0.001).[41] In an open-label extension study evaluating the long-term safety and efficacy of etanercept in patients with AS, the most common adverse events were injection site reactions, headache and diarrhea after 192 weeks of treatment. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS5/6 response rates were 61% at week 96 and 60% at week 144 and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance.[42] Etanercept and sulfasalazine were compared in a multicenter, randomized, double-blind trial in adult patients with active AS who had failed treatment with nonsteroidal antiinflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept achieved the primary outcome of ASAS 20 at week 16 compared to patients treated with sulfasalazine (P<0.0001). Similarly, a significantly greater proportion of patients achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (P<0.0001 for both).[43]

The FDA-approval of subcutaneous formulation of golimumab for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least three months (N=356). Golimumab with or without a disease modifying antirheumatic drug (DMARD) was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14.[44] The efficacy of infliximab in the treatment of AS was demonstrated in 12- and 24-week double-blind placebo-controlled trials. A significantly greater proportion of patients achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (P<0.0001).[45] At 24 weeks, a significantly greater proportion of patients in the infliximab group achieved ASAS 20 compared to patients in the placebo group (P<0.001).[46]

In a meta-analysis of randomized controlled trials of patients with AS, treatments with tumor necrosis factor (TNF) antagonists, adalimumab, etanercept, golimumab, and infliximab, was more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% confidence interval [CI], 1.91 to 2.56) and 24 weeks of treatment (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab

was associated with the highest likelihood of achieving ASAS 20 response at week 12, though it did not significantly differ from other agents. While treatment with infliximab was associated with the highest likelihood of achieving ASAS 20 response at week 24, this was based on few studies and the confidence interval was large.[47]

In a systematic review of patients with Crohn's disease who had failed a trial with infliximab, the administration of adalimumab was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to four years of treatment.[48] Shao et al performed a meta-analysis evaluating certolizumab use over 12 to 26 weeks for the treatment of Crohn's disease. The results demonstrated that certolizumab was associated with an increased rate of induction of clinical response (relative risk [RR], 1.36; P=0.004) and remission (RR, 1.95; P<0.0001) compared to placebo; however, risk of infection was higher with certolizumab use.[51] In a trial evaluating infliximab for induction of remission, significantly greater proportion of patients achieved remission at four weeks with infliximab compared to placebo (P<0.005).[52] In a trial by Present et al, significantly greater proportion of patients treated with infliximab 5 mg/kg and 10 mg/kg experienced a reduction of at least 50% in the number of fistulas compared to patients treated with placebo (P=0.002 and P=0.02, respectively).[53] In an open-label trial evaluating the use of infliximab in pediatric Crohn's patients, 88.4% responded to the initial induction regimen and 58.6% were in clinical remission at week 10.[54] Treatment with adalimumab, certolizumab, and infliximab was associated with a higher likelihood of achieving clinical response (RR, 2.69; P<0.00001; RR, 1.74; P<0.0001 and RR, 1.66; P=0.0046, respectively) and maintaining clinical remission (RR, 1.68; P=0.000072 for certolizumab and RR, 2.50; P=0.000019 for infliximab; adalimumab, data not reported) compared to placebo in patients with Crohn's disease. Adalimumab and infliximab also had a steroid-sparing effect.[56]

The FDA-approval of vedolizumab for the treatment of Crohn's disease was based on two Phase III randomized, placebo controlled trials, GEMINI-2 and GEMINI-3, which compared vedolizumab 300 mg intravenously (IV) at weeks 0 and 2 (induction phase) followed by 300 mg IV every four or eight weeks (maintenance phase; GEMINI-2) or vedolizumab 300 mg IV at weeks 0, 2 and 6 (GEMINI-3).[57,58] In the GEMINI-2 trial, a significantly greater proportion of patients treated with vedolizumab achieved clinical remission at weeks 6 and 52 compared to placebo. In addition, at week 52, a significantly greater proportion of patients treated with vedolizumab achieved a ≥100-point decrease in Crohn's disease activity index (CDAI-100) compared to the placebo group.[57]

Similarly, in GEMINI-3, a greater proportion of patients in the overall study population were in clinical remission at week six compared to placebo and CDAI-100 at week six was achieved in a greater proportion of patients treated with vedolizumab. In patients who had previously failed treatment with a TNF antagonist, there was no significant difference in the proportion of patients in clinical remission at week six between the vedolizumab and placebo groups.[58]

In a trial by Ruperto et al in pediatric patients (six to 17 years of age) with juvenile idiopathic arthritis, patients treated with placebo experienced significantly more disease flares compared to patients treated with abatacept (P=0.0003). The time to flare was significantly different, favoring abatacept (P=0.0002).[59] Adalimumab was studied in a group of patients (four to 17 years of age) with active juvenile rheumatoid arthritis who had previously received treatment with NSAIDs. Patients were stratified according to methotrexate (MTX) use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. At 16 weeks, 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30. Among those not receiving MTX, flares occurred in 43% of patients receiving adalimumab and 71% receiving placebo (P=0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment.[60] In a trial involving 69 pediatric patients with active polyarticular juvenile rheumatoid arthritis despite treatment with NSAIDs and MTX, etanercept was associated with a significant reduction in flares compared to placebo (28 vs 81%; P=0.003).[61] Ninety-four percent of patients who remained in an open-

label four-year extension met juvenile rheumatoid arthritis 30% definition of improvement; while C-reactive protein levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious adverse events related to etanercept therapy after four years.[62] The approval of tocilizumab for systemic juvenile idiopathic arthritis was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active systemic juvenile idiopathic arthritis and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85 vs 24%; P<0.0001).[64] The approval of tocilizumab for polyarticular juvenile idiopathic arthritis was based on a randomized, placebo-controlled trial (N=166). Children age two to 17 years of age with active polyarticular juvenile idiopathic arthritis who failed MTX were included in the study. The primary endpoint was juvenile idiopathic arthritis ACR 30 flare at week 40. At week 40, tocilizumab treated patients experienced significantly fewer flares at week 40 compared to patients treated with placebo (25.6 vs 48.1%; P<0.0024).[65]

In a randomized, double-blind, double-dummy trial, adalimumab was compared to MTX and placebo in patients with moderate to severe psoriasis despite treatment with topical agents. The primary outcome, the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks, was achieved by significantly greater proportion of patients in the adalimumab group compared to patients in the MTX (P<0.001) and placebo (P<0.001) groups.[67] In the PHOENIX 1 and PHOENIX 2 studies, more than 2,200 patients with moderate to severe psoriasis were randomized to receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter.[68,69] In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (≥75% improvement in psoriasis area and severity at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (P<0.0001 for both). PASI 75 response was better maintained to at least one year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (P<0.0001).[68] In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compare to patients receiving placebo (P<0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every eight weeks. More partial responders at week 28 who received 90 mg every eight weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no response to changes in dosing intensity in partial responders treated with 45 mg. Adverse events were similar between groups.[69] In a study comparing etanercept and ustekinumab, a greater proportion of psoriasis patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7 vs 0.7% of all ustekinumab patients).[70] In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe psoriasis, adalimumab use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (P<0.00001) while etanercept 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (P<0.00001 for both strengths vs placebo). The infliximab group had the greatest response with a risk difference of 77% compared to the placebo group (P<0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab.[71]

In two trials, psoriatic arthritis patients receiving adalimumab 40 mg every other week achieved an ACR 20 at a higher rate compared to placebo. Thirty-nine percent of patients in the active treatment group compared to 16% in the placebo group achieved this endpoint by week 12 (P=0.012) in a trial by Genovese et al (N=100), while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (P<0.001).[72,73] Adalimumab use was associated with an improvement in structural damage, as measured by the Modified Total Sharp Score (mTSS), compared to those receiving placebo (-0.2 vs 1.0; P<0.001).[73] The FDA-approval of certolizumab for psoriatic arthritis was based on the results of a randomized, double-blind, placebo-controlled trial (RAPID-PsA) in adult patients with active psoriatic

arthritis despite DMARD therapy. A greater proportion of patients treated with certolizumab 200 mg every two weeks (58.0%) and certolizumab 400 mg every four weeks (51.9%) achieved an ACR 20 response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons).[74,75] In a 12-week trial in adult patients with psoriatic arthritis despite NSAID therapy, 87% of etanercept treated patients met psoriatic arthritis response criteria, compared to 23% of those on placebo (P<0.0001). A PASI 75 improvement and ACR 20 response was detected in 26 and 73% of etanercept-treated patients compared to 0 (P=0.0154) and 13% (P<0.0001) of placebo-treated patients.[76] In a second trial, the mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75, compared to 3% of placebo patients (P=0.001). Furthermore, health assessment questionnaire scores were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).[77] The FDA-approval of subcutaneous formulation of golimumab for psoriatic arthritis was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active psoriatic arthritis despite NSAID or DMARD therapy (N=405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy.[78] In a trial by Antoni et al, more infliximab treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (P<0.001).[80] The FDA-approval of ustekinumab for psoriatic arthritis was based on the results of two randomized, double-blind, placebo-controlled trials in adult patients with active psoriatic arthritis despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In the PSUMMIT 1 (N=615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; P<0.0001 for both comparisons); responses were maintained at week 52. The results of the PSUMMIT 2 trial (N=315) have not yet been published.[81]

The approval of the subcutaneous formulation of abatacept was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous formulation. The trial enrolled patients with rheumatoid arthritis that had an inadequate response to MTX. The proportion of patients achieving ACR 20 was not significantly different between the groups.[83] The RAPID-1 and RAPID-2 studies compared certolizumab in combination with MTX to placebo plus MTX in adults with active rheumatoid arthritis despite MTX therapy.[87,88] A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks zero, two, and four then 200 mg or 400 mg every two weeks attained ACR 20, ACR 50 and ACR 70 responses after 24 weeks compared to patients treated with placebo and MTX (P≤0.01). The response rates were sustained with active treatment over 52 weeks.[87] The mTSS' were significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo.[87,88] Fleischmann et al evaluated certolizumab monotherapy compared to placebo in patients with active disease who had failed at least one prior DMARD trial. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; P<0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy.[89]

The FDA-approval of subcutaneous formulation of golimumab for rheumatoid arthritis was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients with moderate to severe active disease. A greater percentage of patients from all three trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 compared to patients treated with MTX alone.[92-94] Moreover, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI).[93,94] The FDA-approval of intravenous formulation of golimumab for rheumatoid arthritis was based on one multicenter, randomized, double-blind, controlled trial in 592 patients with moderate to severe active disease. In this trial, significantly higher proportion of patients achieved an ACR 20 response in the golimumab group compared to placebo, when both were added to background MTX therapy.[96]

The efficacy and safety of tocilizumab was assessed in five randomized, double-blind, multicenter studies in patients ages 18 years and older with active rheumatoid arthritis. Patients had rheumatoid arthritis diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was administered every four weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate adverse events were reported, occurring in similar frequencies in all study groups. The most common adverse events in all studies were infections and gastrointestinal symptoms.[97-100,103] AMBITION evaluated the safety and efficacy of tocilizumab monotherapy compared to MTX in patients with active rheumatoid arthritis for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy compared to MTX monotherapy produced greater improvements in rheumatoid arthritis signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. In addition, more patients treated with tocilizumab achieved remission at week 24 compared to patients treated with MTX.[97] The 24-week ADACTA trial in RA patients intolerant to methotrexate treatment found significantly greater improvements in DAS 28 scores and ACR core set measures in patients treated with tocilizumab compared to adalimumab.[111]

In the LITHE study, 1,196 patients with moderate to severe rheumatoid arthritis who had an inadequate response to MTX were randomized to receive 4 mg/kg of tocilizumab, 8 mg/kg of tocilizumab or placebo every four weeks in addition to background MTX. At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the Disease Activity Score using 28 joint counts (DAS28 score <2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001).[100] OPTION evaluated tocilizumab in 623 patients with moderate to severely active rheumatoid arthritis. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo intravenously every four weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with <20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. An ACR 20 was seen in significantly more patients receiving tocilizumab compared to those receiving placebo at week 24 (P<0.001). Moreover, a significantly higher proportion of patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 (P<0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg).[98] In the TOWARD study, investigators examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active rheumatoid arthritis. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response compared to patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60 vs 30%; P value not reported).[99] In the RADIATE trial, investigators evaluated the safety and efficacy of tocilizumab in patients with rheumatoid arthritis refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg weekly) for 24 weeks. ACR 20 responses and safety endpoints were assessed. The results demonstrated that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of rheumatoid arthritis in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with adalimumab and infliximab, irrespective of the type or number of failed TNF antagonists.[102]

A Cochrane review examined abatacept for the treatment of rheumatoid arthritis. ACR 50 response was not significantly different at three months, but was significantly higher in the abatacept group at six and 12 months compared to placebo (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70.[104] The safety and efficacy of adalimumab for the treatment of rheumatoid arthritis was assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses at six months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious.[105] A Cochrane review was performed to compare anakinra to placebo in adult patients with rheumatoid arthritis. Significant improvement in both primary (ACR 20, 38 vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in adverse events noted with anakinra use was the rate of injection site reactions (71 vs 28% for placebo).[106] In another Cochrane review, etanercept was compared to MTX or placebo in adult patients with rheumatoid arthritis and 64% of individuals on etanercept 25 mg twice-weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo after six months of treatment (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39 and 15% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. Etanercept 10 mg twice-weekly was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.50; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose.[107] A meta-analysis by Wiens et al evaluated the efficacy of infliximab in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03).[109] Nixon et al performed a meta-analysis of randomized controlled trials including adalimumab, anakinra, etanercept, and infliximab with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.50; P<0.05).[110]

Treatment with abatacept was compared to treatment with adalimumab, both added to MTX, in a randomized controlled trial (N=646) of RA patients with inadequate response to MTC. After 12 months, the proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%).[112] ACR 20 responses were similar between the two groups following two years of treatment.[113]

ORAL Solo (N=611) was a six-month monotherapy phase 3 trial in which patients with moderate to severe active RA who had an inadequate response or adverse reaction to a DMARD (nonbiologic or biologic) received tofacitinib 5 mg or 10 mg twice daily or placebo. Compared to placebo at month three, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons) and Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR])<2.6 (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively). The reductions from baseline in HAQ-DI scores at month three were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.50 and -0.57 vs -0.19; P<0.001 for both comparisons).[114]

ORAL Standard (N=717) was a 12-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. At six months, ACR20 was achieved in 51.5 and 52.6% of patients treated with tofacitinib 5 mg and 10 mg, 47.2% of patients in the adalimumab group and 28.3% of placebo patients (P<0.001 for all comparisons to placebo). At six months, the DAS28-4(ESR) <2.6 was reached in 6.2% (P≤0.05) and 12.5% (P≤0.001) of patients treated with tofacitinib 5 mg and 10 mg, 6.7% (P≤0.05) of adalimumab group compared to 1.1% of patients in the placebo group. At month three, the reductions from baseline in HAQ-DI scores were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.55 and -0.61 vs 0.24; P≤0.001 for both comparisons) and adalimumab compared to placebo (-0.49 vs 0.24; P≤0.001).[115]

ORAL Step (N=399) was a six-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to at least one TNF-blocking agent received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Compared to placebo at month three, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (41.7 and 48.1 vs 24.4%; P<0.0024 and P<0.0001, respectively) and DAS28-4(ESR)<2.6 (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively). At month three, the reductions from baseline in HAQ-DI scores were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons).[116]

ORAL Scan (N=797) is an ongoing two-year phase 3 trial with a planned analysis at one year in which patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Compared to placebo at month six, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (51.5 and 61.8 vs 25.3%; P<0.0001 for both comparisons), achieved reductions in radiographic progression as demonstrated by mTSS (0.12 and 0.06 vs 0.47; P=0.0792 and P≤0.05, respectively), and had DAS28-4(ESR) <2.6 (7.2 and 16.0 vs 1.6%; P value not reported for the first comparison and P<0.0001 for the second comparison). At month three, the reductions from baseline in HAQ-DI scores were greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.40 and -0.54 vs -0.15; P value not reported for the first comparison and P<0.0001 for the second comparison).[117]

ORAL Sync (N=792) was a 12-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to a nonbiologic DMARD received tofacitinib 5 mg or 10 mg twice daily or placebo added to DMARD. Compared to placebo at month six, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons) and had DAS28-4(ESR) <2.6 (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). At month three, the reductions from baseline in HAQ-DI scores were greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.44 and -0.53 vs -0.16; P<0.001 for both comparisons).[118]

Two meta-analyses conducted by He at al and Berhan et al, respectively, confirmed greater efficacy of tofacitinib compared to placebo in RA patients for the primary endpoints of ACR20 and ACR50 response rates, and improvements in HAQ-DI score, all of which reached statistical significance for tofacitinib dosages ≥5 mg.[119,120]

Infliximab demonstrated effectiveness in ulcerative colitis in two trials. Studies ACT 1 and ACT 2 evaluated infliximab compared to placebo for this indication. In both trials, clinical response at week eight was significantly higher in patients treated with infliximab 5 mg/kg or 10 mg/kg compared to placebo (all P<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies.[121] A randomized, open-label trail evaluated infliximab as different dosing intervals for the treatment of pediatric ulcerative colitis. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%).[122]

The FDA-approval of adalimumab for the inducing and sustaining clinical remission of patients with active ulcerative colitis was based on the results of two placebo-controlled studies. In both studies adalimumab initially dosed at 160 mg, then 80 mg at week 2 and 40 mg every other week thereafter showed significant

improvements in proportion of patients that were in remission after 8 weeks of treatment (P<0.05 in each study).[123,124] Patients also demonstrated significant decreases compared to placebo (P<0.05 in each study) in rectal bleeding, stool frequency and physician global assessment scores. In the study by Sandborn et al, remission observed by week 8 was sustained out to 52 weeks in 8.5% of the patients as did mucosal healing in 18.5% of patients (P<0.05 for all). In this study, it was noted that larger proportion of patients were also able to discontinue corticosteroid use at week 52 (13.3%) vs placebo (5.7%) and achieve remission (P=0.035).[124] It was noted that a treatment arm in the Reinisch et al trial that utilized a lower dose of adalimumab (initial dose 80 mg, then 40 mg every other week thereafter) did not show significant improvements in remission rates, clinical response or symptom improvement when compared to placebo.[123]

The FDA-approval of subcutaneous formulation of golimumab for the treatment of moderately to severely active ulcerative colitis was based on the results of two multicenter, randomized, double-blind, placebo-controlled clinical trials (PURSUIT-SC and PURSUIT-M).[125,126] PURSUIT-SC study included a phase 2 dose-finding and phase 3 dose-confirmation trials. In phase 2 trial, patients were randomized to placebo or one of four golimumab treatment groups: 400 mg at week zero and 200 mg at week two (400 mg/200 mg), 200 mg at week zero and 100 mg at week two (200 mg/100 mg), or 100 mg at week zero and 50 mg at week two (100 mg/50 mg). In phase 3 trial, 774 patients were randomized to placebo or to one of two golimumab treatment groups: 400 mg at week zero and 200 mg at week two or 200 mg at week zero and 100 mg at week two. In phase 2 trial, changes from baseline in Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group; P=0.038, P=0.332 and P=0.038, respectively). In phase 3 trial, the proportion of patients with clinical response at week six was greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons). Rates of clinical remission, mucosal healing and mean changes in Inflammatory Bowel Disease Questionnaire scores were significantly greater in both golimumab groups than the placebo group. [125] PURSUIT-M was a randomized-withdrawal maintenance trial that evaluated 464 patients who achieved clinical response with golimumab induction. Patients were randomized to receive golimumab 50 mg, golimumab 100 mg or placebo every four weeks. The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Rates of clinical remission at both weeks 30 and 54 were significantly greater in the golimumab 100 mg group than the placebo (27.8 vs 15.6%; P=0.004); however, the differences in the rates of mucosal healing and corticosteroid-free clinical remission were not statistically significant between both golimumab groups and placebo.[126]

The FDA-approval of vedolizumab for the treatment of ulcerative colitis was based on one Phase III randomized, placebo-controlled trial, GEMINI-1, which evaluated the safety and efficacy of vedolizumab 300 mg IV at weeks 0 and 2 followed by 300 mg IV every four or eight weeks compared to placebo. In the double-blind cohort, a significantly greater proportion of patients treated with vedolizumab achieved clinical response at week six compared to placebo (47.1 vs 25.5%; 95% CI, 11.6 to 31.7; P<0.001). In the open-label vedolizumab cohort, 44.3% of patients achieved a clinical response and 19.2% achieved clinical remission. In the maintenance phase, a significantly greater proportion of patients treated with vedolizumab every four or eight weeks achieved clinical remission at week 52 compared to placebo (44.8 and 41.8% vs 15.9% respectively; 95% CI, 14.9 to 37.2; P<0.001).[127]

Neonatal-onset multisystem inflammatory disease (NOMID) is a rare autoinflammatory disorder that presents around birth with systemic inflammation and rash and may develop with severe organ manifestations involving the eyes, ears, bones and central nervous system. Progressive cognitive impairment and physical disability is a consequence of the organ damage with mortality rates estimated at up to 20% before adulthood. Anakinra recently became the first and only FDA-approved treatment for patients with NOMID. The approval was the result of a single trial in 43 NOMID patients over 60 months that demonstrated sustained improvements in patients' diary scores, physician global scores of disease activity, patient/parent pain scores, and inflammatory markers (all P<0.001 at 36 and 60 months). In addition, most patients showed stable or improved hearing as well as stable visual acuity and peripheral vision.[128]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ankylosing Spondylitis				
van der Heijde et al[38] Adalimumab 40 mg every other week vs placebo Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of AS based on the modified New York criteria with active disease BASDAI score ≥4, a total back pain score ≥4 by VAS (VAS, 0 to 10 cm) or a duration of morning stiffness ≥1 hour	N=315 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, and ASAS partial remission	Primary: An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (P<0.001). Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52 vs 18%; P<0.001). Adalimumab, compared to placebo, resulted in a significant improvement in other measures of disease activity such as a 50% improvement in BASDAI at week 12 (45 vs 16%; P<0.001) which was sustained through week 24 (42 vs 15%; P<0.001). ASAS 5/6 and ASAS 40 responses were attained in 49 vs 13% and 40 vs 13% of adalimumab vs placebo patients at week 12 (P<0.001) and 45 vs 12% and 39 vs 13% at week 24 (P<0.001), respectively. Partial remission was achieved in 21 vs 4% at week 12 and 22 vs 6% at week 24 in the adalimumab and placebo groups, respectively (P<0.001).
Landewe et al[39] (RAPID-axSpA) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg)	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of AS based on the ASAS criteria, with active disease BASDAI score ≥4, spinal pain ≥4, CRP>7.9 mg/L and/or sacroiliitis on MRI, chronic back pain ≥3 months, inadequate	N=325 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, change from baseline in BASFI, BASDAI, and BASMI linear at week 12 and 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (57.7%) and CZP 400 mg every four weeks (63.6%) achieved ASAS 20 response at week 12 compared to placebo (38.3%; P=0.004 and P<0.001, respectively). Secondary: The difference in ASAS 20 response was sustained through week 24 in both CZP treatment groups (P<0.001). Improvements in BASFI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.0 and -2.0 vs -0.5; P<0.001) and at 24 weeks (-2.2 and -2.2 vs -0.4; P<0.001 for both comparisons), respectively.

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vs placebo Patients receiving placebo who did not achieve an ASAS 20 response at weeks 14 and 16 were randomized to active treatment at week 16. Concurrent DMARDs (SSZ and MTX) were allowed.	response or intolerance to ≥1 NSAID or ≥2 weeks each for ≥2 NSAIDs in the last ≥30 days			Improvements in BASDAI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001) and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively. Improvements in BASMI linear scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-0.6 and -0.5 vs -0.1; P<0.001 and P<0.05, respectively) and at 24 weeks (-0.5 and -0.5 vs -0.1; P<0.001 for both comparisons), respectively.
Gorman et al[40] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs, NSAIDs, and oral corticosteroids.	DB, RCT Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments	N=40 4 months	Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, and joint swelling Secondary: Physician's global assessment of disease activity, measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels,	Primary: A response to treatment was detected in 80% of individuals receiving etanercept as opposed to 30% of individuals receiving placebo (P=0.004). Primary endpoints were reported as follows for the etanercept and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 vs 60.0±65.0 minutes (P<0.001); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (P<0.001); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (P=0.17); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (P<0.001); and the BASFI scores (0=none to 10=severe limitations), 2.2±2.1 vs 3.1±3.0 (P<0.001). Secondary: Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to those taking placebo including, physician's global assessment of disease activity (23.0±10.6; P<0.001), chest expansion (3.5±1.9 vs 2.9±1.7 cm; P=0.006), Modified Newcastle Enthesis Index, which is a measure of 17 enthesis on a four point pain scale (0.0±3.0 vs 1.5±8.0; P=0.001), ESR level (8.5±12.8 vs 16.5±18.7 mm/hour; P<0.001) and CRP level (0.7±1.1 vs 2.0±2.8 mg/dL; P=0.003).

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			and adverse events	Injection site reactions and minor infections were the most commonly reported adverse events. The incidence in overall adverse events or specific events did not differ significantly.
Calin et al[41] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).	DB, MC, RCT Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=84 12 weeks	Primary: ASAS 20 response Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI, acute phase reactants, spinal mobility tests, and safety	Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (P<0.001). Secondary: The etanercept group was associated with the higher rates of ASAS 50 and 70 responses (48.9 and 24.4%) compared to placebo (10.3 and 10.3%) at week 12. However, only the differences in ASAS 50 response reached statistical significance at this assessment point (P<0.001). ASAS 70 response was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; P<0.05). The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3 vs 15.9% (P=0.003); nocturnal and total pain, 43.1 vs 6.2% (P=0.000); patient's global assessment, 37.0 vs 12.6% (P=0.11); functional impairment (BASFI), 35.4 vs 3.4% (P=0.000); BASDAI composite score, 43.6 vs 13.6% (P=0.001); and BASDAI fatigue score, 42.6 vs -4.9% (P=0.000). Injection site reactions occurred more frequently with etanercept compared to placebo (33 vs 15%; P<0.05).
Davis et al[42] Etanercept 25 mg twice weekly until week 72, then 50 mg once weekly Stable doses of corticosteroids and NSAIDs were required 2 weeks prior to enrollment; stable doses of HCQ,	ES, OL Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=257 Up to 192 weeks	Primary: Safety (adverse events, serious adverse events, infections, serious infections, and death) and efficacy (ASAS 20 response, ASAS 5/6	Primary: After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported. For etanercept treatment the exposure adjusted serious event rate/patient year was 0.08, the exposure adjusted infection rate/patient year was 1.10, and the exposure adjusted serious infection rate/patient year was 0.02. Injection site reactions were reported in 22.2% of patients, which lead to the withdrawal of 0.4% of patients.

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MTX, or SSZ were required if deemed necessary.			response, and partial remission rates) Secondary: Not reported	A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% of patients were considered responders at week 192. ASAS 5/6 response rates were 61% at week 96 and 60% at week 144. Partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance. Secondary: Not reported
Braun et al[43] ASCEND Etanercept 50 mg once weekly vs SSZ titrated to 3 g daily in divided doses	DB, MC, RCT Patients ≥18 years of age with active AS (diagnosed according to modified New York criteria) who failed treatment with ≥1 NSAID taken for ≥3 months at the maximum recommended dose and were determined to be candidates for SSZ therapy by the investigators	N=566 16 weeks	Primary: Proportion of patients achieving ASAS 20 response at week 16 Secondary: Proportion of patients achieving ASAS 20 response at weeks two, four, eight and 12; proportion of patients achieving ASAS 40 response and ASAS 5/6 response at all time points	Primary: At week 16, significantly greater proportion of patients in the etanercept group achieved ASAS 20 response compared to the SSZ group (75.9 vs 52.9%; P<0.0001). Secondary: Significantly greater proportion of patients in the etanercept group achieved ASAS 20 response at week two compared to patients in the SSZ group; this difference was maintained throughout the time points (P<0.0001 for all). Significantly greater proportion of patients in the etanercept group achieved ASAS 40 and ASAS 5/6 responses compared to patients in the SSZ group at all time points (P<0.0001 for all). At week 16, a greater proportion of patients achieved ASAS 40 and ASAS 5/6 responses in the etanercept group compared to the SSZ group (59.8 vs 32.6%; P<0.0001 and 45.5 vs 21.2%; P<0.0001, respectively). The rates of adverse events and serious adverse events were similar between the two groups.
Inman et al[44] Golimumab 50 mg once	DB, MC, PC, RCT Patients ≥18 years	N=356 24 weeks	Primary: ASAS 20 response at week	Primary: Treatment with golimumab with or without a DMARD, compared to placebo with or without a DMARD, resulted in a significant improvement in signs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who were on stable doses of HCQ, MTX, NSAID, oral corticosteroid and/or SSZ were permitted in the study.	of age with a diagnosis of AS and no evidence of active TB and/or no evidence of latent TB on screening		14 Secondary: Not reported	and symptoms as demonstrated by ASAS 20 response at week 14 (59 vs 22%; P≤0.001). All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group compared to the placebo group at week 14. Secondary: Not reported
Braun et al[45] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs placebo Concurrent use of NSAIDs not exceeding the baseline dose was allowed.	DB, MC, PC, RCT Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score ≥4 and spinal pain score ≥4	N=70 12 weeks	Primary: Improvement from baseline in BASDAI by 50% at week 12 Secondary: Improvement from baseline in spinal pain, BASFI, BASMI, SF-36, CRP, and ESR	Primary: A greater proportion of patients achieved a 50% improvement in BASDAI at week 12 in the infliximab group (53%; 95% CI, 37 to 69) compared to the placebo group (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until week 12 (P<0.0001). Secondary: At week 12, the infliximab group had a significant mean improvement from baseline in spinal pain (P<0.0001), BASFI (P<0.0023), BASMI (P<0.0001), CRP (P<0.0001), and ESR (P<0.0001); while there was no significant difference in the placebo group. At 12 weeks, there were significant improvements from baseline in the physical component and mental component of the SF-36 in the infliximab group (P<0.0001); however, only the improvement in the physical component was significantly greater compared to the placebo group (P<0.0001). A greater proportion of patients reported infections in the infliximab group (51%) compared to the placebo group (35%; difference, 16%; 95% CI, -7 to

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				40; P=0.227). A greater proportion of patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to the placebo group (3 vs 0; P=0.239).
van der Heijde et al[46] (ASSERT) Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18 vs placebo Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	MC, PC, RCT Adult patients (median age of 40) with AS based on the modified New York criteria for at least three months with a BASDAI score ≥4, spinal pain assessment score ≥4 on a VAS and a normal chest radiograph within three months, and negative TB screening	N=279 24 weeks	Primary: Proportion of patients with ASAS 20 at week 24 Secondary: ASAS 40 response, ASAS partial remission, ASAS 5/6, disease activity (BASDAI, night pain, patient's global assessment and CRP), physical function (BASFI), range of motion (BASMI), other musculoskeletal assessments (swollen joint count and degree of tenderness) and quality of life (SF-36)	Primary: After 24 weeks, significantly greater proportion of patients were ASAS 20 responders in the infliximab group (61.2%) compared to the placebo group (19.2%; P<0.001). The difference was significant at week two and continued to week 24. Secondary: Over the 24-week study period, significantly greater proportion of patients were ASAS 40 responders in the infliximab group compared to the placebo group (P<0.001). At 24 weeks 47% of patients were ASAS 40 responders in the infliximab group compared to 12% in the placebo group (P<0.001). Significantly greater proportion of patients treated with infliximab achieved ASAS 5/6 (49%) compared to placebo treated patients (8%; P<0.001). Significantly greater proportion of patients achieved a partial ASAS response in the infliximab group (22.4%) compared to the placebo group (1.3%; P<0.001). The median improvement in all measures of disease activity (BASDAI, night pain, patient's global assessment and CRP) was significantly greater in the infliximab treated patients compared to placebo treated patients (P<0.001). The patients in the infliximab group had a significantly greater median improvement in BASFI compared to patients in the placebo group (P<0.001). There was a significantly greater median improvement in BASMI in the infliximab group compared to the placebo group (P=0.019). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to the placebo treated patients (P=0.019). There was a significantly greater improvement in the physical component of the SF-36 in the infliximab group compared to the placebo group (P<0.001); there was no significant difference in the mental component (P=0.547). Compared to patients in the placebo group, a greater proportion of patients in the infliximab group experienced at least on adverse event (82.2 vs 72.0%), reported at least one infection (42.6 vs 36.0%) and had severe

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				adverse reactions (3.5 vs 2.7%). Of the adverse events that occurred in at least 5% of patients in either group, the rates of pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.
Machado et al[47] Infliximab vs etanercept vs adalimumab vs golimumab vs certolizumab vs control Concurrent use of stable doses of other medications was allowed.	MA RCTs of patients with AS based on the modified New York criteria	N=2,820 (18 trials) 6 to 104 weeks	Primary: Proportion of patients with ASAS 20 at 12- or 14 weeks and at 30 weeks of follow-up Secondary: ASAS 40 response, ASAS 5/6, ASAS partial remission, BASDAI, BASDAI 50, BASFI, and BASMI, withdraws and safety outcomes at 12 or 14 weeks and 30 weeks of follow-up	Primary: Patients treated with TNF-blockers were more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% CI, 1.91 to 2.56) and 24 weeks (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab was associated with the highest RR for ASAS 20 response after 12 or 14 weeks (RR, 2.74; 95% CI, 1.78 to 4.22), followed by adalimumab (RR, 2.33; 95% CI, 1.45 to 3.74), etanercept (RR, 2.13; 95% CI, 1.75 to 2.58), and infliximab (RR, 1.82; 95% CI, 1.16 to 2.58) compared to controls. Treatment with infliximab was associated with the highest RR for ASAS 20 response after 24 weeks (RR, 3.18; 95% CI, 1.99 to 5.08), followed by etanercept (RR, 2.53; 95% CI, 1.80 to 3.57) and adalimumab (RR, 2.15; 95% CI, 0.96 to 4.83) compared to controls. Secondary: Patients treated with TNF-blockers were more likely to achieve ASAS 40 response after 12 or 14 weeks (RR, 2.77; 95% CI, 2.05 to 3.75) and 24 weeks (RR, 3.32; 95% CI, 2.44 to 4.51) compared to controls. Patients treated with TNF-blockers were more likely to achieve ASAS 5/6 response after 12 or 14 weeks (RR, 3.52; 95% CI, 2.17 to 5.71) and 24 weeks (RR, 4.25; 95% CI, 2.80 to 6.46) compared to controls. Patients treated with TNF-blockers were more likely to achieve partial remission after 12 or 14 weeks (RR, 4.79; 95% CI, 2.46 to 9.34) and 24 weeks (RR, 4.43; 95% CI, 2.62 to 7.49) compared to controls. Patients treated with TNF-blockers achieved greater improvements in the disease activity (BASDAI) after 12 weeks (mean difference, -1.64; 95% CI, -2.06 to -1.22) and after 30 weeks (mean difference, -1.79; 95% CI, -2.27 to 1.31) compared to controls.

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				Patients treated with TNF-blockers were more likely to achieve BASDAI 50 response at 12 or 14 weeks (RR, 2.87; 95% CI, 2.23 to 3.69) and at 24 weeks (RR, 3.39; 95% CI, 2.46 to 4.67) compared to controls. Patients treated with TNF-blockers achieved greater improvements in physical function (BASFI) at 12 weeks (mean difference, -1.39; 95% CI, -1.59 to -1.19) and at 24 weeks (mean difference, -1.52; 95% CI, -1.72 to -1.31) compared to controls. Patients treated with TNF-blockers achieved greater improvements in vertebral mobility (BASMI) at 12 weeks (mean difference, -0.53; 95% CI, -0.72 to -0.35) and at 24 weeks (mean difference, -0.60; 95% CI, -0.87 to -0.33) compared to controls. Meta-analysis of safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks (P value not reported).
Crohn's Disease				
Ma et al[48] Adalimumab	SR OL and RCT cohort studies of patients with CD who had either lost response, were intolerant or refractory to infliximab	N=1,810 (15 trials) 8 weeks to 4 years	Primary: Short-term and long-term efficacy Secondary: Adverse events	Primary: Short-term clinical response or remission was evaluated in nine trials. Forty-one to 83% of patients achieved a clinical response at four weeks, while 12 to 67% of participants attained clinical remission. Long-term remission rates ranged from 31 to 82% at six months and 19 to 68% at one year. Secondary: Serious adverse events were reported in 0 to 19% of patients and included sepsis, cellulitis, and fungal pneumonia.
Lofberg et al[49] (CARE) Adalimumab 160 mg at week zero, followed by 80 mg at week two, followed by 40 mg every other	MC, OL Patients 18 to 75 years of age with a radiologic or endoscopic diagnosis of CD for	N=945 20 weeks	Primary: Remission rates, proportion of patients free of EIM at week 20 Secondary:	Primary: The proportion of patients in remission who received adalimumab was 43% at week four (95% CI, 40 to 46) and increased to 52% (95% CI, 49 to 55) at week 20. There was a significantly higher remission rate at week 20 among adalimumab-treated patients who were also infliximab naïve compared to patients exposed to infliximab (62 vs 42; P<0.001).

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week At week 12 or later, patients who experienced a disease flare or did not respond to treatment could increase the adalimumab dose to 40 mg weekly.	≥4 months and a HBI >7 points at screening		Fistula healing, remission rates based on concomitant therapies and adverse events	A shorter disease duration (less than two years and between two and five years) was associated with higher rates of clinical remission at week four compared to a disease duration longer than five years (50, 52, and 38%, respectively; P<0.001); however the remission rates at 20 weeks were not significantly different (58, 56, and 50%, respectively; P=0.136). Overall, 53% of patients had at least one EIM at baseline, compared to 30% at week 20. Of these, 79% had resolution of at least one EIM and 51% were free of EIM signs and symptoms following 20 weeks of adalimumab treatment. The EIM resolution rates were similar across adalimumab-treated patients regardless of prior infliximab use (P=0.100) and prior infliximab response and those who discontinued treatment for other reasons (P=0.625). Secondary: Complete fistula healing occurred in 26% of patients at week 20. Fistula closure rates were numerically higher in the infliximab-naïve group at week 20 (33%) compared to the infliximab-experienced group (22%); however, the difference was not significant (P=0.275). Fistula healing rates were similar in nonresponders to infliximab compared to those who discontinued infliximab for other reasons (19 vs 23%; P=0.973). Of patients taking corticosteroids at baseline, 37% were able to discontinue them by week 20; Eleven percent and 14% of patients achieved a steroid-free remission at weeks 12 and 20, respectively. Seven percent of patients taking immunosuppressants at baseline were able to discontinue them at week 20. There were similar rates of clinical remission at week 20 between patients taking and not taking steroids at baseline (52% in both groups; P=0.976). By week 20, the rates of clinical remission were 55 and 49%, respectively, in patients who were and were not taking immunosuppressants at baseline (P=0.052). Adverse events occurred in 80% of patients and 11% of patients who

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				discontinued treatment due to adverse events. Serious adverse events were reported in 19% of patients. The adverse events profiles were similar among patients who were exposed to infliximab previously and those who were treatment naïve. The most common adverse event categories were "gastrointestinal disorders" and "CD'' indicating a worsening of patient's underlying disease.
Watanabe et al[50] (Induction study) Adalimumab 160 mg at week zero, followed by 80 mg at week two (ADA 160/80 group) vs adalimumab 80 mg at week zero, followed by 40 mg at week two (ADA 80/40 group) vs placebo (Maintenance study) adalimumab 40 mg every other week vs placebo Patients achieving a Clinical Response 70 (decrease from baseline in	2 DB, MC, PC, RCT Patients 15 to 75 years of age, with moderate to severely active CD, CDAI score 220 to 450 for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation	N=90 (induction) N=83 (maintenance) 56 weeks (4 weeks induction study and 52 week maintenance study)	Primary: Induction study Proportion of patients in clinical remission (CDAI <150) at week four Maintenance Clinical remission (CDAI <150) at week 52 Secondary: Induction study Proportion of patients in clinical remission at week two and with CR-100 or CR-70 (CDAI decrease ≥100 or ≥70) at week four, changes from baseline in CDAI and IOIBD at week two and week four and changes in SF-36 MCS and PCS,	Primary: Induction A greater proportion of patients treated with ADA 160/80 and ADA 80/40 achieved a clinical remission by week four compared to placebo (33 and 18 vs 12%, respectively; P value not reported). Maintenance By week 52, a significantly greater proportion of patients treated with adalimumab 40 mg achieved a clinical remission compared to placebo (P<0.05). Secondary: Induction At week two, clinical remission rates were higher with ADA 160/80 and ADA 80/40 compared to placebo (18 and 15 vs 4%, respectively; P value not reported). At week four, significantly greater proportion of patients receiving ADA 160/80 or ADA 80/40 experienced a CR-100 (50 and 46 vs 17%, respectively; P<0.05 for both) compared to placebo. At week four, significantly greater proportion of patients receiving ADA 160/80 experienced a CR-70 (70 vs 30%; P=0.0062); however, the improvement with the ADA 80/40 was not statistically significant. The changes in CDAI from baseline to week two and four, respectively, were, -75.9 and -101.3 in the ADA 160/80 group, -74.4 and -81.3 in the ADA 80/40 group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from baseline to week two and week

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CDAI ≥70 points at week four) entered the blinded maintenance trial.			and IBDQ scores in each treatment group at week four Maintenance Proportion of patients in clinical remission, (CDAI decrease ≥100 or ≥70) every four weeks, changes from baseline of the induction to week 52 in CDAI, IOIBD, SF-36 MCS and PCS scores, and IBDQ	four, respectively, were -1.2 and -1.5 in the ADA 160/80 group, -0.7 and -0.8 in the ADA 80/40 group, and -0.4 and -0.5 in the placebo group. ADA 160/80 or ADA 80/40 significantly improved SF-36 MCS from baseline to week four compared to placebo. (6.2 and 5.5 vs -1.6, respectively; P<0.05 for both). There were no statistically significant differences in SF-36 PCS and IBDQ between patients receiving ADA 160/80 compared to patients receiving placebo. Maintenance Adalimumab therapy was more effective compared to placebo at each of the four-week evaluations throughout the 52-week trial compared to placebo with regard to CR-100 (P≤0.05) and CR-70 (P≤0.01). Adalimumab was more effective compared to placebo with regard to maintaining clinical remission at weeks eight, 36, 36, 40, 48 and 52 (P<0.05). The mean changes in CDAI from baseline of the induction trial to week zero and week 52, respectively, were -147.7 and -83.7 in the adalimumab-treated patients and -139.0 and -9.1 in the placebo-treated patients. The mean changes in IOIBD from baseline to week zero and week 52, respectively, were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively. Adalimumab 40 mg was associated with statistically significant improvements in SF-36 MCS and IBDQ compared to placebo at eight weeks (12.0 vs 2.0; P=0.03 and 34.8 vs 8.3; P=0.05, respectively); however, the changes were not significantly different at 52 weeks.
Shao et al[51] Certolizumab vs placebo	MA DB, RCTs in patients with moderate to severe CD	N=1,040 (3 trials) 12 to 26 weeks	Primary: Clinical response (a decrease ≥100 points from baseline in CDAI score) and clinical remission (CDAI score	Primary: Certolizumab was associated with an increased rate of induction of clinical response (RR, 1.36; 95% CI, 1.10 to 1.68; P=0.004) and remission (RR, 1.95; 95% CI, 1.41 to 2.70; P<0.0001) compared to placebo. Secondary: Only infection was reported more frequently with certolizumab compared to placebo (60.6 vs 40.7%).

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			≤150 points) at week four Secondary: Safety	
Targan et al[52] Infliximab 5 mg/kg vs infliximab 10 mg/kg vs infliximab 20 mg/kg vs placebo	DB, MC, PC, RCT Adult patients with CD for six months with CDAI scores 220 to 400 and previously receiving mesalamine (for ≥8 weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for ≥8 weeks and a stable dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)	N=108 12 weeks	Primary: Decrease from baseline in CDAI ≥70 points at four weeks without a change in concomitant medications Secondary: Not reported	Primary: At week four, the primary endpoint was reached in 81, 50, 64 and 17% in the 5 mg/kg, 10 mg/kg, 20 mg/kg and placebo groups, respectively. The overall response of the infliximab groups was significantly higher (65%) compared to the placebo group (P<0.001). At week two, 61% of the infliximab treated patients had a response compared to 17% of the placebo treated patients (P<0.001). A greater proportion of patients was in remission (CDAI score <150) in the infliximab group at two weeks (27%) compared to the placebo group (4%; P=0.06). At week four, 33% of the infliximab treated patients were in remission compared to 4% of the placebo treated patients (P<0.005). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo treated patients (12%; P=0.008); however, the remission rate was not significantly different at 12 weeks (24 vs 8%; P=0.31). Secondary: Not reported
Present et al[53] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs infliximab 10 mg/kg at weeks 0, 2 and 6	DB, MC, PC, RCT Patients 18 to 65 years of age with ≥1 confirmed draining abdominal or perianal fistulas of ≥3 months as a complication of CD	N=94 18 weeks	Primary: Reduction ≥50% from baseline in number of draining fistulas at two or more consecutive study visits Secondary:	Primary: There were significantly greater response rates in the infliximab 5 (68%) and 10 mg/kg (56%) groups compared to the placebo group (26%; P=0.002 and P=0.02, respectively). The response rates were not significantly different between the two infliximab groups. Secondary: A greater proportion of patients in the infliximab 5 (55%) and 10 mg/kg (38%) groups had complete response compared to the placebo group (13%; P=0.001 and P=0.04, respectively). In the infliximab group, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Proportion of patients with a complete response (absence of any draining fistula at two consecutive visits), length of time to beginning of response, and duration of response	median time to the onset of response was two weeks compared to six weeks in the placebo group. The duration of response was approximately three months in patients that reached the primary endpoint. The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.
Hyams et al[54] (REACH) Infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 8 weeks at weeks 14, 22, 30, 38 and 36 or every 12 weeks at weeks 18, 30 and 42 vs infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 12 weeks at weeks 18, 30 and 42	OL, MC, RCT Patients 6 to 17 years of age with a PCDAI >30 at baseline and who initiated immunomodulator therapy (azathioprine, mercaptopurine or MTX) ≥8 weeks before screening and at stable dose for two weeks	N=112 46 weeks	Primary: Clinical response at week 10 (decrease from baseline to week 10 in PCDAI ≥15 points and total PCDAI no more than 30) Secondary: Maintenance of clinical response and remission (PCDAI ≤10)	Primary: At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9). Secondary: At week 10, 58.6% of patients were in clinical remission (95% CI, 49.8 to 68.0). At week 54, 63.4 and 55.8% of patients treated with infliximab every eight weeks achieved clinical response and clinical remission, respectively, compared to 33.3 and 23.5% of patients treated with infliximab every 12 weeks (P=0.002 and P<0.001, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all P<0.001). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all P<0.001). Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.
Van Assche et al[55] (SWITCH) Adalimumab 80 mg at	OL, PRO, RCT Patients ≥18 years with luminal CD	N=73 54 weeks	Primary: Proportion of patients in the adalimumab	Primary: There was a statistically significant increase in the preference of adalimumab over infliximab for patients who changed from infliximab to adalimumab therapy at all evaluation points (P<0.05), except week 56

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week zero and 40 mg every other week Patients not randomized to adalimumab continued prior infliximab at 5 mg/kg at their regularly scheduled interval. Patients with a disease flare were able to intensify treatment as follows: adalimumab 40 mg every week and in the infliximab group, a decrease of the dosing interval with two-week decrements.	treated with infliximab maintenance therapy started for ≥6 months with a complete clinical response (PGA assessment of signs and symptoms, but the CDAI at baseline <200) with stable infliximab dosing intervals of ≥6 weeks		group preferring adalimumab over infliximab and proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or who had to stop the assigned anti-TNF agent Secondary: Proportion of patients with an injection- or infusion-related reaction and proportion of patients with an increase in the CDAI of >100 above baseline and IBDQ	(P=0.08). Dose intensification or early treatment termination occurred significantly more frequently over 54 weeks in patients switched to adalimumab (47%) compared to those who continued infliximab (16%; P=0.003). Significantly more patients initiating adalimumab therapy discontinued therapy due to loss of response or intolerance compared those who continued infliximab therapy (28 vs 2%; P<0.01). Of note, the patient who discontinued infliximab was successfully treated with adalimumab and eight of the 10 patients who stopped adalimumab treatment returned to infliximab therapy. The reasons for early discontinuation of treatment were loss of tolerance in six of 10 patients on adalimumab and in the one patient receiving infliximab. Four other patients in the adalimumab group stopped for loss of efficacy. Refractory eczema with fatigue or arthralgias (n=2), general malaise and diarrhea following injections (n=2) and fatigue plus inability to comply with injections (n=2) led to adalimumab intolerance and an infusion reaction to infliximab intolerance. Secondary: There was no difference in the change from baseline in CDAI at time of early termination in the adalimumab group (184 vs 78; P=0.10). Dose intensification occurred in 27.7% of patients in the adalimumab group, three of which later stopped adalimumab for loss of response, and in and 13.5% of patients in the infliximab group (P=0.20). The median time to dose intensification was not significantly different between the adalimumab and infliximab treatment arms (24 vs 32 weeks; P=0.64). An increase in CDAI ≥100 points was observed in 18.9% of patients in the infliximab group and in 27.7% of patients in the adalimumab group while on the initially assigned treatment. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Behm et al[56] Adalimumab, certolizumab, or infliximab vs placebo	SR RCTs including patients ≥18 years of age with CD who had a clinical response or clinical remission with a TNF-α blocker, or patients with CD in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocker or placebo	N=3,586 (9 trials) Duration varied	Primary: Clinical remission, clinical response, and steroid-sparing effects Secondary: Not reported	Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; P<0.00001), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported). Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; P=0.000072) and clinical response (RR, 1.74; 95% CI, 1.41 to 2.13; P<0.00001) compared to placebo. Infliximab was more effective than placebo at maintaining fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; P=0.012), clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; P=0.000019), clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; P=0.0046, and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; P=0.014). Secondary: Not reported
Sandborn et al[57] (GEMINI-2) Vedolizumab 300 mg intravenous at weeks 0 and 2 (induction) followed by vedolizumab 300 mg intravenous every four or eight weeks (maintenance) vs placebo Stable doses of oral prednisone (≤30 mg/day)	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with Crohn's disease for ≥3 months, a score of 220 to 450 on the CDAI and one of the following: a CRP >2.87 mg/mL, colonoscopy showing ≥3 large ulcers of ≥10 aphthous ulcers or fecal calprotectin >250 µg/g stool plus	N=1,115 52 weeks	Primary: Induction Clinical remission (CDAI ≤150), CDAI-100 response at week six Maintenance Clinical remission at week 52 Secondary: Induction Mean change in CRP from baseline to week	Primary: Induction In the double-blind cohort, a greater proportion of patients treated with vedolizumab achieved clinical remission at week six (14.5 vs 6.8%; P=0.02). A numerically greater proportion of patients treated with vedolizumab achieved a CDAI-100 response (31.4 vs 25.7%; P=0.23). Among the patients included in the open-label vedolizumab cohort, 17.7% achieved a clinical remission and 34.4% had a CDAI-100 response at week six. Maintenance At week 52, 39% of patients receiving vedolizumab every eight weeks and 36.4% of patients receiving vedolizumab every four weeks were in clinical remission, compared to 21.6% of patients in the placebo group (P<0.001 and P=0.004, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or budesonide (≤9 mg/day), immunosuppressive agents, mesalamine and antibiotics were permitted.	evidence of ulcers on CT or MRE, small-bowel radiography or capsule endoscopy. All patients had no response or unacceptable side effects from one of more of the following: glucocorticoids, immunosuppressive agents or TNF antagonists.		six Maintenance CDAI-100 response, glucocorticoid-free remission, durable clinical remission (defined as clinical remission at ≥80% of study visits, including final visit) at week 52	Secondary: Induction In the double-blind cohort, the mean changes in CRP levels from baseline to week six were similar for both the vedolizumab and placebo groups. Maintenance At week 52, a significantly greater proportion of patients receiving vedolizumab achieved a CDAI-100 response and glucocorticoid-free remission compared to placebo; however, the proportion of patients with a durable clinical remission was not significantly different between vedolizumab and placebo.
Sands et al.[58] † (GEMINI-3) Vedolizumab 300 mg intravenous at weeks 0, 2 and 6 vs placebo	DB, MC, PC, RCT Patients 18 to 80 years of age with moderately to severely active CD (CDAI score of 220 to 400 points within seven days before enrollment and one of the following: a screening CRP level >2.87 mg/mL, a colonoscopy within past four months that documented ulcerations or a fecal calprotectin level >250 µg/g stool during screening with	N=416 10 weeks	Primary: Proportion of patients in clinical remission at week six Secondary: Proportions of patients in the overall and TNF antagonist failure populations in remission at week 10, proportions of patients in the overall and TNF antagonist failure populations with remission at both week 6 and 10	Primary: For the TNF antagonist failure population, there was no statistically significant difference in the proportion of patients in clinical remission at week six between the vedolizumab and placebo groups (15.2 vs 12.2%; P=0.433). Secondary: For the TNF antagonist failure population, a greater proportion of patients treated with vedolizumab were in clinical remission at week 10 (26.6 vs 12.1%; P=0.001; RR, 2.2; 95% CI, 1.3 to 3.6). Furthermore, a greater proportion of vedolizumab-treated patients also had a CDAI-100 response at week six (39.2 vs 22.3%; P=0.001; RR, 1.8; 95% CI, 1.2 to 2.5) and at week 10 (46.8 vs 24.8%; P<0.0001; RR, 1.9; 95% CI, 1.4 to 2.6). The between-group difference in remission rates at weeks 6 and 10 was no statistically significant (12.0 vs 8.3%; P=0.276; RR, 1.4; 95% CI, 0.7 to 2.8). For the overall population, a greater proportion of patients treated with vedolizumab were in clinical remission at week 6 (19.1 vs 12.1%; P=0.048; RR, 1.6; 95% CI, 1.0 to 2.5). Furthermore, a greater proportion of the overall population was in remission at week 10 with vedolizumab compared to placebo (28.7 vs 13.0%; P<0.0001; RR, 2.2; 95% CI, 1.4 to 3.3). The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	features of active CD supported by small bowel imaging) with known involvement of the ileum and/or colon at ≥3 months prior to enrollment. All patients had experienced an inadequate response, loss of response or intolerance to TNF antagonists, immunosuppressives or corticosteroids within previous five years.		and the proportion of patients in the TNF antagonist failure population with a CDAI-100 response at week six	between-group difference in remission rates at weeks 6 and 10 was statistically significant (15.3 vs 8.2%; P=0.025; RR, 1.9; 95% CI, 1.1 to 3.2). In the overall population, a greater proportion of patients in the vedolizumab group achieved a CDAI-100 response at week six (39.2 vs 22.7%; P=0.0002; RR, 1.7; 95% CI, 1.5 to 2.6) and at week 10 (47.8 vs 24.2%; P<0.0001; RR, 2.0; 95% CI, 1.5 to 2.6).
Juvenile Idiopathic/Rheumatoid Arthritis				
Ruperto et al[59] Abatacept 10 mg/kg every 28 days vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 6 to 17 years of age with JIA with at least 5 active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=122 (RCT); 190 (OL lead in period) 6 months (4-month OL lead in)	Primary: Time to flare Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables, and assessment of safety and tolerability	Primary: In the placebo group, the median time to flare was six months; however, insufficient events occurred in the abatacept group to assess median time to flare (P=0.0002). Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to the abatacept group (53 vs 12%; P=0.0003). The HR for patients in the abatacept group to experience a flare compared to the placebo group was 0.31 (95% CI, 0.16 to 0.59). After six months or at the time of first flare, 82% of the abatacept group and 69% of the placebo group improved by ≥30% as measured by ACR (P=0.1712), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (P=0.0071), 53% of the abatacept group and 31% of the placebo group improved by ≥70% as measured by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ACR and 40% of the abatacept group and 16% of the placebo group improved by ≥90% as measured by ACR. In the abatacept group, 30% had inactive disease compared to 11% in the placebo group (P=0.0195). Adverse events were similar between the groups.
Lovell et al[60] Adalimumab 24 mg/m^2 (maximum of 40 mg) every other week with or without MTX vs placebo Patients were stratified according to MTX use and received OL adalimumab 24 mg/m^2 (maximum of 40 mg) every other week for 16 weeks. The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.	DB, MC, OL, RCT Patients 4 to 17 years of age with active JRA who had previously received treatment with NSAIDs	N=171 48 weeks	Primary: Rate of disease flare in patients not receiving MTX Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety	Primary: Among patients not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63 vs 38% (P=0.03), 63 vs 35% (P=0.03), 63 vs 27% (P=0.002) and 42 vs 27% (P=0.17) in the adalimumab and placebo groups, respectively. In patients not receiving MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were reported in 57 vs 32% (P=0.06), 53 vs 32% (P=0.10), 47 vs 29% (P=0.16) and 30 vs 18% (P=0.28) in the adalimumab and placebo groups, respectively. The most frequently noted adverse events were mild to moderate in nature and included infections and injection site reactions. There were seven cases of serious infection reported with adalimumab use.
Lovell et al[61] Etanercept 0.4 mg/kg twice weekly vs placebo	DB, MC, OL, RCT Patients 4 to 17 years of age with active polyarticular JRA despite treatment with NSAIDs and MTX	N=69 7 months	Primary: Rate of disease flare Secondary: Median time to flare, safety	Primary: Seventy-four percent (51/69) of patients demonstrated improvement and were included in the DB part of the trial. The rate of disease flare was significantly higher in the placebo group compared to the etanercept group (81 vs 28%; P=0.003). Secondary: The median time to flare was reported as 116 days in the active treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received etanercept 0.4 mg/kg twice weekly for up to 3 months in the OL part of the study; the patients whose condition improved were then randomly assigned to either etanercept or placebo. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	≥10 mg/m^2/week			arm compared to 28 days with placebo (P<0.001). During the OL segment of the study the adverse events most often reported included injection-site reaction, upper respiratory tract infections, headache, rhinitis and gastrointestinal side effects. There were no differences noted between groups during the latter part of the study.
Lovell et al[62] Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly Intra-articular and soft-tissue injections of corticosteroids were permitted after 12 continuous weeks of etanercept. MTX could be added to treatment after one year. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or	Ongoing ES, MC, OL by Lovell et al[22] (updated efficacy and safety results from the study)	N=58 Median of 4 years	Primary: JRA 30% DOI Secondary: JRA 50% DOI, JRA 70% DOI, an articular severity score (0 to 926), assessment of pain (Likert scale, 0 to 10), CRP levels, safety	Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI. Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively. At four years, the median CRP level was lowered to 0.1 mg/dL from 3.4 mg/dL at baseline, the median articular severity score was decreased to 18 from 88 at baseline, and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline. Duration of morning stiffness was only assessed through one year and was reported as 5 minutes at month 12 (from 53 minutes at baseline). After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/ patient year.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
equivalent) were allowed.				
Horneff et al[63] Etanercept 0.4 mg/kg twice weekly Combination treatment with MTX or oral corticosteroids was permitted.	MC, OL Patients 4 to 17 years of age with active idiopathic juvenile arthritis despite treatment with MTX	N=322 Up to 48 months, median of 12 months	Primary: Change in indices of disease activity, 30, 50, and 70% improvement in idiopathic juvenile arthritis Secondary: Safety	Primary: At 12 months, the mean number of tender joints, swollen joints, and joints with limited range of movement were reduced to 1.7 (SD, 3.5), 2.6 (SD, 4.7), and 7.1 (SD, 8.9) from a baseline of 9.1 (SD, 9.5), 8.4 (SD, 9.0), and 11.8 (SD,11.8), respectively. The duration of morning stiffness was decreased to 7 (SD, 23) minutes from 45 (SD, 65) minutes and CHAQ scores (on a scale of 0=best to 3=worst) were decreased to 0.4 (SD, 0.6) from 1.0 (SD, 0.8). Patient's and PGA scores (on a scale of 0=best to 100=worst) were reduced to 16 (SD, 18) and 20 (SD, 23) from 56 (SD, 27) and 67 (SD, 25), respectively. At last report (30 months) a 30, 50, and 70% improvement was noted in approximately 60, 48, and 28% of patients remaining on etanercept, respectively. Significant improvements in all indices of disease activity were detected at all points of time (months one, three, six, 12, 18, 24, and 30; P<0.0001 with the exception of swollen joint count at 30 months; P<0.0005 and duration of morning stiffness; P<0.001). Secondary: There were 20 reports of infection or infection related events. Discontinuation of treatment was reported in 53 patients, of which 11 cases were secondary to adverse events.
De Benedetti et al[64] TENDER (abstract) Tocilizumab 8 mg/kg every 2 weeks for patients ≥30 kg or 12 mg/kg every 2 weeks for patients <30 kg vs placebo	PC, RCT Patients 2 to 17 years of age with active systemic JIA for ≥6 months with an inadequate response to NSAIDs and corticosteroids	N=112 12 weeks	Primary: Proportion of patients with JRA ACR 30 response plus absence of fever at week 12 Secondary: Not reported	Primary: At week 12, significantly greater proportion of patients treated with tocilizumab achieved JRA 30 response plus absence of fever (85%) compared to patients treated with placebo (24%; P<0.0001). Significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 50, JRA ACR 70, and JRA ACR 90 responses compared to patients in the placebo group (P<0.0001). Secondary: Not reported
Brunner et al[65] CHERISH (abstract)	DB, PC, RCT (OL lead in period)	N=166 24 weeks	Primary: Proportion of patients with JIA	Primary: Tocilizumab treated patients experienced significantly fewer JIA ACR 30 flare at week 40 compared to patients treated with placebo (25.6 vs 48.1%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tocilizumab 8 mg/kg every 4 weeks for patients ≥30 kg vs 8 mg/kg every 4 weeks for patients <30 kg vs 10 mg/kg every 4 weeks for patients <30 kg vs placebo	Patients 2 to 17 years of age with active polyarticular JIA for ≥6 months who failed MTX		ACR 30 flare relative to week 16 Secondary: Proportion of patients with JIA ACR 30, ACR 50, and ACR 70 responses	P<0.0024). Secondary: At week 40, significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 30 (74.4 vs 54.3%; P=0.0084), JRA ACR 50 (73.2 vs 51.9%; P=0.0050), and JRA ACR 70 (64.6 vs 42.0%; P=0.0032) response compared to patients in the placebo group. The degree of improvement was lower for these endpoints in the tocilizumab 8 mg/kg (<30 kg body weight) group compared to the other two tocilizumab groups (10 mg/kg for patients weighing <30 kg and 8 mg/kg for patients weighing ≥30 kg).
Psoriasis				
Bagel et al[66] Etanercept 50 mg twice-weekly for 12 weeks followed by etanercept 50 mg weekly plus placebo weekly for 12 additional weeks (Group A) vs placebo twice-weekly for 12 weeks followed by etanercept 50 mg twice-weekly for 12 additional weeks (Group B)	DB, MC, PC, RCT Patients ≥18 years of age with stable moderate-to-severe plaque psoriasis covering ≥10% of BSA for ≥6 months and PASI scores ≥10 and ≥30% of SSA affected, with PSSI scores ≥15	N=124 24 weeks	Primary: Percentage change in PSSI score at week 12 Secondary: Percentage change in the PSSI score at week 24 for Group B patients, the proportion of patients achieving PSSI 75 improvement at week 12, patient	Primary: At week 12, Group A experienced a significantly greater mean improvement in PSSI score compared to Group B (86.8 vs 20.4%; P<0.001) with significant improvements as early as week four of treatment. Secondary: At week 24, both Group A and Group B experienced improvements in PSSI scores from baseline (90.6 vs 79.1%, respectively; P value not reported). A significantly greater proportion of patients in Group A compared to Group B experienced a PSSI 75 at week 12 (86 vs 11%; P<0.0001). Significantly more etanercept-treated patients were either satisfied or very satisfied at week 12 compared to placebo (P<0.0001). At week 24, after etanercept treatment, Group B patients' satisfaction increased significantly over their first 12 weeks on placebo (P<0.0001). More than two thirds of Group A patients continued to be satisfied or very satisfied at week 24.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients discontinued the use of background therapies.			satisfaction with treatment at week 12, and safety	The rates of adverse events were comparable between groups, both at week 12 (etanercept vs placebo) and week 24 (etanercept 50 mg twice-weekly vs once-weekly). No serious adverse events were reported at week 12; however, by week 24, three patients had reported serious events. The most commonly reported adverse events were upper respiratory tract infection, injection site reactions, headache, sinus congestion, cough, and ear infection.
Saurat et al[67] (CHAMPION) Adalimumab 80 mg at week 0, then 40 mg every other week from week 1 through week 15 vs MTX 7.5 mg at week 0, then increased to 10 mg weekly at week 2, then increase to 15 mg weekly at week 4; at week 8, patients not achieving PASI 50 had the dose of MTX increased to 15 mg weekly; at week 12, patients not achieving PASI 50 at week 12 and 8 had the dose of MTX increased to 25 mg weekly vs placebo	DB, DD, MC, RCT Patients ≥18 years of age with moderate to severe psoriasis (>10% of BSA and PASI ≥10), plaque psoriasis for >1 year, stable plaque psoriasis for >2 months, that are candidates for systemic therapy of phototherapy, with plaque psoriasis despite treatment with topical agents and treatment naïve to TNF-antagonists and MTX	N=271 16 weeks	Primary: Proportion of patients achieving PASI 75 at week 16 relative to baseline Secondary: Proportion of patients achieving PASI 50, PASI 90, PASI 100, and PGA	Primary: At 16 weeks, significantly more patients in the adalimumab group (79.6%) achieved PASI 75 compared to the MTX group (35.5%; RD, 43.7%; 95% CI, 30.8 to 56.7; P<0.001) and placebo group (18.9%; RD, 60.5%; 95% CI, 44.5 to 76.6; P<0.001). The difference in treatment groups was seen starting at two weeks for adalimumab vs MTX (P<0.05) and at four weeks for adalimumab vs placebo (P<0.001). Secondary: At week 16, PASI 100 was achieved in significantly more patients in the adalimumab group (16.7%) compared to the MTX group (7.3%; P<0.04) and the placebo group (1.9%; P<0.001).Significantly more patients achieved PASI 50, PASI 90 and a PGA of clear or minimal in the adalimumab group compared to the MTX and placebo groups (P<0.001 for all). Rates of reported infectious adverse events were not significantly different between the groups (P value not reported). Total adverse events and serious adverse events were similar.
Leonardi et al[68]	DB, MC, PC, PG,	N=766	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(PHOENIX-1) Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received a subcutaneous injection at week 0, 4, and then every 12 weeks thereafter.	RCT Patients ≥18 years of age with a diagnosis of plaque psoriasis for ≥6 months, candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	≤76 weeks	Proportion of patients achieving PASI 75 at week 12 Secondary: Not reported	Significantly more patients in both the 45 and 90 mg ustekinumab groups achieved the primary endpoint of PASI 75 at week 12 than did those in the placebo group (difference in response rate, 63.9%; 95% CI, 57.8 to 70.1; P<0.0001 and 63.3%; 95% CI, 57.1 to 69.4; P<0.0001 for 45 and 90 mg vs placebo, respectively. The onset of efficacy was rapid, with higher proportions of ustekinumab-treated patients achieving at least 50% improvement from baseline in PASI 50 by week two (P=0.0008 for 45 mg and P=0.0005 for 90 mg vs placebo) and PASI 75 by week four (P<0.0001 for each comparison vs placebo). Maximum efficacy was observed at week 24 in the 45 and 90 mg groups (PASI 75 response, 76.1% in 45 mg group and 85.0% in 90 mg group). Among patients re-randomized at week 40, maintenance of PASI 75 was better in patients receiving maintenance therapy than in patients withdrawn from therapy through at least one year (P<0.0001), The median percentage improvement in PASI remained stable to at least week 76. Secondary: Not reported
Papp et al[69] (PHOENIX-2) Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received an injection at week 0, 4, and	DB, MC, PC, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	N=1,230 ≤52 weeks	Primary: Proportion of PASI 75 responders at week 12 Secondary: Proportion of patients with a physician's global assessment score of cleared or minimal at week 12, change in dermatology	Primary: Significantly more patients in both ustekinumab groups achieved PASI 75 at week 12 than did patients in the placebo group (difference in response rate, 63.1%; 95% CI, 58.2 to 68.0; P<0.0001 and 72.0%; 95% CI, 67.5 to 76.5; P<0.0001 for 45 and 90 mg vs placebo, respectively). Secondary: A greater proportion of patients in each ustekinumab group achieved a physician's global assessment of psoriasis of cleared or minimal at week 12 than did those in the placebo group (difference in response rate, 63.1%; 95% CI, 58.1 to 68.1; P<0.0001 for 45 mg vs placebo and 68.6%; 95% CI, 63.9 to 73.4; P<0.0001 for 90 mg vs placebo). Median changes in dermatology life quality index were greater in the ustekinumab groups than in the placebo group (mean of differences vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then every 12 weeks thereafter. Partial responders at week 28 were re-randomized to continue dosing every 12 weeks or escalate to dosing every 8 weeks.			life quality index, the number of visits with PASI 75 response between weeks 40 and 52	placebo, -8.0; 95% CI, -8.0 to -7.0; P<0.0001 for 45 mg and -9.0; 95% CI, -9.0 to -8.0; P<0.0001 for 90 mg vs placebo). A total of 22.7% of patients in the 45 mg group and 15.8% of patients in the 90 mg group were partial responders at week 28. Compared to patients responding to dosing every 12 weeks, partial responders tended to have higher bodyweight, more marked or severe disease as measured by physician's global assessment, and a higher incidence of PsA. Among the re-randomized partial responders, dosing intensification did not result in greater efficacy compared to continuing treatment every 12 weeks, as assessed by the number of visits between weeks 40 and 52 (four visits) at which patients achieved PASI 75 response (mean, 1.75 visits in the every eight week group and 1.56 in the every 12 week group; P=0.468). There was a lack of response to intensified dosing in the individuals receiving 45 mg, both in terms of number of visits at which patients achieved PASI 75 response (mean, 1.13 vs 1.54 visits; P=0.210), and in terms of PASI 75 rates over time. This is in contrast to patients receiving intensified 90 mg dosing, which resulted in a greater number of visits with PASI 75 response (mean, 2.63 vs 1.58 visits; P=0.014) and higher PASI 75 response rate (68.8% of patients with dosing every eight weeks vs 33.3% of patients with dosing every 12 weeks; difference in response rate, 35.4%; 95% CI, 12.7 to 58.1 at week 52 for dosing every eight weeks vs dosing every 12 weeks; P=0.004).
Griffiths et al[70] Etanercept 50 mg twice weekly vs ustekinumab 45 mg at weeks 0 and 4 vs	MC, PG, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI	N=903 12 weeks	Primary: PASI 75 at week 12 Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group (73.8%) than in the etanercept group (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; P<0.001 for each comparison

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ustekinumab 90 mg at weeks 0 and 4 Patients without a response to etanercept at week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA involvement, and had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab		between PASI at week 12 and 12 weeks after retreatment	vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (P<0.001, for each comparison vs etanercept). Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Schmitt et al[71] Adalimumab, cyclosporine, efalizumab*, etanercept, or infliximab vs placebo	MA RCTs in patients with moderate to severe psoriasis	16 trials Duration varied	Primary: PASI 75 Secondary: Tolerability	Primary: Compared to placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; P<0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; P<0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; P<0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48; P<0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35; P<0.00001) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; P<0.00001). Secondary: Average monthly rates of serious adverse events were 0.5% with adalimumab, 2.3% with cyclosporine, 1.2% with efalizumab, 0.6% with etanercept 50 mg twice weekly and 1.1% with infliximab. This outcome was not reported in with etanercept 25 mg twice weekly. Withdrawals due to adverse events occurred on average in 0.3% of adalimumab-treated patients, 16.1% of cyclosporine-treated patients, 1.2% of efalizumab-treated patients, 0.5% of patients on the lower dose of

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				etanercept and 0.4% of patients on the higher dose of etanercept and 1.3% of infliximab-treated individuals/month.
Psoriatic Arthritis				
Genovese et al[72] Adalimumab 40 mg every other week vs placebo Patients who completed a 12 week blinded phase could elect to receive OL therapy.	DB, MC, RCT Patients with moderately to severely active PsA with an inadequate response to DMARD therapy	N=100 24 weeks	Primary: ACR 20 response at week 12 Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic lesions, and quality of life	Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (P=0.012). Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25 and 14%, respectively) compared to patients on placebo at week 12 (2 and 0%, respectively; P=0.001 for ACR 50 and P=0.013 for ACR 70). A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (P=0.007). At week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; P≤0.001) and disability were statistically significantly improved with adalimumab. Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (P=0.027), bodily pain (P=0.007), general health (P=0.017) and mental health (P=0.009). OL adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 and 57%, respectively, observed at week 24. Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%). Adalimumab use was not associated with serious infections.
Mease et al[73] Adalimumab 40 mg every	DB, MC, PG, RCT Patients ≥18 years	N=315 24 weeks	Primary: ACR 20 response at 12	Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared to 14% of the placebo-treated patients (P<0.001).

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other week vs placebo Stable doses of MTX were allowed and corticosteroid or DMARD rescue therapy was permitted in patients without at least a 20% reduction in swollen and tender joints by week 12.	of age with moderately to severely active PsA with active psoriatic skin lesions or a documented history of psoriasis and a history of inadequate response to NSAIDs		weeks, change in mTSS at week 24 Secondary: ACR 20 response at 24 weeks, ACR 50 and ACR 70 response at weeks 12 and 24, measures of joint disease, disability, quality of life, and severity of skin disease in patients with psoriasis involving at least 3% of BSA	The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (P<0.001). Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (P<0.001). An ACR 50 response was detected in 36% of adalimumab-treated individuals at 12 weeks and 39% of adalimumab-treated individuals at week 24 compared to 4 and 6% of those on placebo, respectively (P<0.001 for both outcomes). An ACR 70 response was found in 20% in the adalimumab arm and 1% in the placebo arm at 12 weeks and 23 and 1% at 24 weeks (P<0.001). PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26 and 23% on placebo, respectively (P value not reported). Among the 69 adalimumab treated patients evaluated with the PASI, 59% achieved a PASI 75 improvement response at 24 weeks, compared to 1% of placebo-treated patients (P<0.001). Disability and quality of life measures were also significantly improved with adalimumab treatment compared to placebo treatment (P<0.001 for changes in both HAQ-DI and SF-36 PCS scores at weeks 12 and 24). Changes in SF-36 MCS scores were not statistically significant between groups at both week 12 (P=0.708) and week 24 (P=0.288). The rates of overall and serious adverse events were similar among groups.
Mease et al[74] and van der Heijde et al[75] (RAPID-PsA)	DB, MC, PC, RCT Patients ≥18 years	N=409 24 weeks	Primary: ACR 20 response at week	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (58.0%) and CZP 400 mg every four weeks (51.9%) achieved an ACR 20

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Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs placebo Concurrent MTX (up to 25 mg/week), SSZ (up to 3 g/day), leflunomide (up to 20 mg/day) at stable doses or oral corticosteroids (≤10 mg/day prednisone or equivalent) were allowed.	of age with adult-onset active PsA for ≥6 months despite treatment with ≥1 DMARD		12, change from baseline in mTSS at week 24 Secondary: ACR 20 at week 24, HAQ-DI at week 24, PASI 75 (in patients with least 3% body surface area psoriatic skin involvement) at week 24, and change from baseline in mTSS at week 24	response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons). Secondary: A greater proportion of patients treated with CZP 200 mg every two weeks (63.8%) and CZP 400 mg every four weeks (56.3%) achieved an ACR 20 response at week 24 compared to placebo (23.5%; P<0.001 for both comparisons). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with CZP compared to placebo (combined CZP groups: -0.50 vs -0.19; P<0.001). In patients with least 3% body surface area psoriatic skin involvement at baseline, a greater proportion of patients treated with CZP 200 mg every two weeks (62.2%) and CZP 400 mg every four weeks (60.5%) achieved PASI 75 at week 24 compared to placebo (15.1%; P<0.001 for both comparisons). Prespecified imputation analysis led to an estimated mean mTSS change from baseline that was not statistically different between CZP and placebo groups (combined CZP groups: 18.3 vs 28.9; P≥0.05). Post hoc analysis using the median mTSS of the entire population to impute missing values in patients with fewer than two analyzable mTSS suggested that patients treated with CZP had reduced radiographic progression compared to placebo patients (combined CZP groups: 0.06 vs 0.28; P=0.007).
Mease et al[76] Etanercept 25 mg twice weekly vs placebo Patients on stable doses	DB, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=60 12 weeks	Primary: PsARC, PASI 75 at 12 weeks Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI	Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared to 23% of placebo-controlled patients (P<0.0001). PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (P=0.0154). Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared to 13% of placebo-treated patients (P<0.0001), while

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.			75, and improvement in target psoriasis lesions	approximately 48 and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (P=0.0001 for ACR 50; P value not reported for ACR 70). Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in PASI, compared to none of the placebo-treated patients (P=0.0154). Median target lesion improvements were 50 and 0%, for etanercept and placebo, respectively (P=0.0004). There were no significant differences detected in the rate of adverse events between groups.
Mease et al[77] Etanercept 25 mg twice weekly vs placebo Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week extension. Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.	DB, MC, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=205 72 weeks	Primary: ACR 20 response Secondary: ACR 50 response, ACR 70 response, change in mTSS, PsARC, PASI 75, SF-36 Health Survey, HAQ, and safety	Primary: At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared to 15% of placebo patients (P<0.0001), and results were sustained at 24 and 48 weeks. Secondary: At 24 weeks, ACR 50 and ACR 70 responses were achieved in approximately 40 and 15% of etanercept patients and 5 and 1% of placebo patients, respectively (P values not reported). The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001). A PsARC response was achieved by 72 and 70% of etanercept patients at weeks 12 and 24, respectively vs 31 and 23% of placebo patients (P values not reported). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared to 3% of placebo patients (P=0.001). SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups.

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				HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reactions occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).
Kavanaugh et al[78] Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who had used or were currently using MTX, an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were enrolled.	MC, PC, RCT Patients ≥18 years of age with a diagnosis of PsA and active PsA despite current or previous DMARD or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening	N=405 24 weeks	Primary: ACR 20 response at week 14 Secondary: Not reported	Primary: Golimumab 50 mg with or without MTX compared to placebo with or without MTX, resulted in a significant improvement in signs and symptoms as demonstrated by ACR 20 response at week 14 (51 vs 9%; P<0.001). Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Secondary: Not reported
Antoni et al[79] Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 vs placebo	DB, MC, PC, PG, RCT Patients ≥18 year of age with active PsA for ≥6 months, inadequate response to current or previous	N=200 24 weeks	Primary: ACR 20 response at week 14 Secondary: PsARC, PASI 75, duration of morning stiffness,	Primary: At week 14, there was significantly more patients in the infliximab group that achieved an ACR 20 response (58%) compared to the placebo group (11%; P<0.001). This difference continued through week 24 (54 vs 16%; P<0.001). Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to the placebo group (27%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	DMARDs or NSAIDs, ≥1 qualifying lesion and negative serum RF		dactylitis in hands and feet, and presence or absence of enthesopathy in the feet and SF-36	P<0.001) at week 14 and continued through week 24 (70 vs 32%; P<0.001). At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18 and 12%) compared to the placebo group (30 and 34%; P=0.025 and P<0.001, respectively). Fewer patients in the infliximab group had enthesopathy compared to the placebo group at week 14 (22 vs 34%; P=0.016) and week 24 (20 vs 37%; P=0.002). A significantly higher proportion of patients achieved PASI 75 in the infliximab group compared to the placebo group at weeks 14 and 24 (64 vs 2%; P<0.001 and 60 vs 1%; P<0.001, respectively). At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to the placebo group (both P<0.001). There was also significant improvement at week 24 in the physical and mental components of the SF-36 in the infliximab group compared to the placebo group (P<0.001 and P=0.047, respectively). Adverse events were similar between the groups. There were a higher proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to the placebo group (4 vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to the placebo group (1 vs 6%).
Baranauskaite et al[80] (RESPOND) Infliximab 5 mg/kg infusions at weeks 0, 2, 6 and 14 plus MTX 15 mg/week vs	MC, OL, PC, PRO Patients ≥18 years of age who were treatment naïve and had active psoriasis in combination with peripheral articular disease with ≥1 of the	N=115 16 weeks	Primary: Proportion of subjects achieving an ACR 20 response at week 16 Secondary: Proportions of	Primary: In the ITT analysis, an ACR 20 response at week 16 was achieved by significantly more patients treated with infliximab plus MTX compared to patients treated with MTX alone (86.3 vs 66.7%; P=0.021). Secondary: The ACR 50 (72.5 vs 39.6%; P=0.0009) and ACR 70 (49.0 vs 18.8%; P=0.0015) response rates at week 16 were also significantly higher in the infliximab plus MTX group at 16 weeks compared to those receiving MTX alone.

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MTX 15 mg/week The use of NSAIDs and oral steroids (maximum dose 10 mg/day of prednisone or equivalent) was allowed if the dose was stable within four weeks before screening and kept stable throughout the study.	following for three or more months before screening: distal interphalangeal joint involvement; polyarticular arthritis in the absence of rheumatoid nodules; arthritis mutilans; or asymmetric peripheral arthritis		patients with ACR 50 and ACR 70 responses, PASI 75 in subjects whose baseline PASI was 2.5 or greater, EULAR response, DAS28 scores, number of digits with dactylitis, Maastricht AS enthesitis score, fatigue scores, and duration of morning stiffness and safety	In patients with a PASI ≥2.5 or at baseline, a PASI 75 response at week 16 occurred in 97.1% of patients receiving infliximab plus MTX compared to 54.3% of patients receiving MTX alone (P<0.0001). By week 16, the mean reduction in PASI score was 93.3% for patients treated with infliximab plus MTX compared to 67.4% of patients treated with MTX alone (P=0.0029). The mean DAS28 at week 16 improved by 56.5% in the infliximab plus MTX patients compared to 29.7% of patients receiving MTX alone (P<0.0001). The EULAR response at week 16 was achieved in 98% of patients receiving infliximab plus MTX compared to 72.9% of those receiving MTX alone (P<0.0001). A median reduction of two digits with dactylitis was observed at week 16 in the patients treated with infliximab plus MTX, while no reduction was observed in the MTX monotherapy group (P=0.0006). Patients treated with infliximab plus MTX experienced a median reduction of two sites with enthesitis at week 16 compared to a reduction of one site in the MTX alone group (P=0.082). A significantly greater reduction from baseline in fatigue scores occurred in the infliximab plus MTX group compared to the MTX monotherapy group at week 16 (70.8 vs 44.0%, respectively; P=0.0003). At week 16, the median change in the duration of morning stiffness was -0.92 hour with combination treatment vs -0.50 hour with MTX alone (P=0.0015). The incidence of adverse events was higher in patients receiving infliximab plus MTX compared to MTX alone. Most adverse events were mild or moderate in severity. One adverse event in each group was considered

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				severe: increased transaminases in the infliximab plus MTX group and renal colic in the MTX-alone group. Treatment related adverse events were reported in 45.6% of the infliximab plus MTX group and 24.1% in the MTX alone group. The most frequent treatment-related adverse event involved hepatic enzyme increases.
McInnes et al[81] (PSUMMIT 1) Ustekinumab 45 mg at weeks 0, 4, and every 12 weeks vs ustekinumab 90 mg at weeks 0, 4, and every 12 weeks vs placebo Patients receiving placebo were switched to ustekinumab 45 mg at week 16 (if they did not have an improvement of at least 5% in tender and swollen joints) or at week 24 (if they had an improvement at week 16). Patients receiving ustekinumab 45 mg were switched to ustekinumab 90 mg if they did not have an improvement of least	DB, MC, PC, RCT Patients ≥18 years of age with active PsA for ≥6 months despite treatment with DMARDs for ≥3 months or NSAIDs for ≥4 weeks, or both, or with intolerance to these treatments	N=615 52 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50, ACR 70, HAQ-DI, and PASI 75 at week 24	Primary: A greater proportion of patients treated with ustekinumab 45 mg (42.4%) and ustekinumab 90 mg (49.5%) achieved an ACR 20 response at week 24 compared to placebo (22.8%; P<0.0001 for both comparisons). Secondary: A greater proportion of patients treated with ustekinumab 45 mg (24.9%) and ustekinumab 90 mg (27.9%) achieved an ACR 50 response at week 24 compared to placebo (8.7%; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (12.2%) and ustekinumab 90 mg (14.2%) achieved an ACR 70 response at week 24 compared to placebo (2.4%; P=0.0001 and P<0.0001, respectively). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with ustekinumab 45 mg (median change -0.25) and ustekinumab 90 mg (median change -0.25) compared to placebo (median change 0; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (57.2%) and ustekinumab 90 mg (62.4%) achieved PASI 75 at week 24 compared to placebo (11.0%; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5% in tender and swollen joints at week 16. The use of a DMARD or an NSAID was allowed if the dose was stable for three months and four weeks before the start of the study, respectively.				
Rheumatoid Arthritis				
Westhovens et al[82] Abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every four weeks plus MTX 15 mg/weekly vs placebo plus MTX 15 mg/weekly	DB, MC, PC, RCT Patients ≥18 years of age with RA for ≤2 years and ≥12 tender and 10 swollen joints, CRP ≥0.45 mg/dL, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet; patients were either MTX-naive or had previous exposure of 10 mg/week or less for three weeks or less, with none administered	N=509 24 months	Primary: Remission rates (DAS28 <2.6) and structural damage at year one (Genant-modified Sharp scoring system maximum score of 290) Secondary: ACR 50 responses, MCR (ACR 70 maintained for >6 consecutive months); DAS28 scores, erosion score (maximum possible 145) and joint-space narrowing score (JSN; maximum possible 145), physical function	Primary: A significantly higher proportion of patients in the abatacept group achieved DAS28-defined remission compared to the placebo group after one year of treatment (41.4 vs 23.3%, respectively; P<0.001). The mean change in structural damage at year one, measured using the Genant-modified Sharp scoring system total scores, was significantly lower in patients treated with abatacept compared to patients treated with placebo (0.63 vs 1.06, respectively; P=0.040). Secondary: A higher proportion of patients treated with abatacept achieved an ACR 50 (57.4 vs 42.3%; P<0.001), ACR 70 (42.6 vs 27.3%; P<0.001) and ACR 90 (16.4 vs 6.7%; P=0.001) compared to patients treated with placebo after one year of treatment. After one year of abatacept therapy, 27.3% of patients achieved an MCR (ACR 70 maintained for more than six consecutive months) compared to 11.9% of patients receiving placebo alone (P<0.001). Following one year of abatacept treatment, disease activity was significantly reduced compared to patients receiving placebo (-3.22 vs -2.49; P<0.001). Patients treated with abatacept achieved significantly greater improvements from baseline in total score and erosion score compared to patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(improvement of >0.3 units from baseline in the; HAQ-DI), SF-36 scores, proportion of patients achieving ACR 70 and ACR 90 responses, and the proportion of patients without radiographic progression and safety	randomized to the placebo group (P=0.040 and P=0.033, respectively). The changes from baseline in JSN scores were similar between the abatacept and placebo groups (P=0.246). The proportion of patients with no radiographic progression in the abatacept group at one year was 61.2% (95% CI, 55.0 to 67.3) compared to the group receiving placebo 52.9% (95% CI, 46.6 to 59.2), with an estimated difference of 8.3% (95% CI, 21.0 to 17.5). A significantly greater proportion of patients in the abatacept group compared to the placebo group experienced a change from baseline in HAQ-DI score ≥0.3 units following one year of therapy (71.9 vs 62.1%; P=0.024). Abatacept treatment was associated with statistically significant improvements in the mental and physical components of the SF-36 questionnaire compared to the placebo group (P<0.05 for both). The most frequently reported adverse events in the abatacept group were nausea, upper respiratory tract infection and headache. Six deaths were reported; two (0.8%) in the abatacept group and four (1.6%) in the placebo Of the two deaths in the abatacept group, one patient had pneumonia and severe gastrointestinal bleeding and the other had an acute myocardial infarction. The most frequent infections in patients treated with abatacept and placebo respectively, were upper respiratory tract infection in 26 (10.2%) and 26 (10.3%) patients, nasopharyngitis in 21 (8.2%) and 26 (10.3%) patients and influenza in 19 (7.4%) and 23 (9.1%) patients. Serious infections occurred in five (2.0%) abatacept-treated patients (pneumonia, gastroenteritis, cellulitis, pseudomonal lung infection and postoperative wound infection, one patient each) and five (2.0%) patients receiving placebo (pneumonia, three patients; gastroenteritis, one patient; and breast cellulitis and staphylococcal infection, both in the same patient). No patients in the abatacept group discontinued due to an infection.

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				In the abatacept treatment group, autoimmune disorders were reported in six patients compared to five patients in the placebo group. Sixteen patients in the abatacept treatment group experienced infusion related reaction compared to five patients receiving placebo.
Genovese et al[83] Abatacept subcutaneous 125 mg days 1 and 8 then weekly (intravenous loading dose of ~10 mg/kg was also administered on day 1) vs abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every 4 weeks	DB, DD, MC, RCT Patients with RA (defined by ACR 1987 criteria) and functional class I, II and III (defined by ACR 1991 revised criteria) that had an inadequate response to ≥3 months of MTX therapy (≥15 mg/week), with ≥10 swollen joints, ≥12 tender joints and CRP ≥0.8 mg/dL	N=1,457 6 months	Primary: Proportion of patients achieving ACR 20 at six months Secondary: Proportion of patients achieving ACR 50 and ACR 70	Primary: The proportion of patients achieving ACR 20 with abatacept subcutaneous (76.0%; 95% CI, 72.9 to 79.2) and abatacept intravenous (75.8%; 95% CI, 72.6 to 79.0) was not significantly different (estimated between group difference, 0.3%; 95% CI, -4.2 to 4.8). Secondary: The proportion of patients achieving ACR 50 with abatacept subcutaneous and abatacept intravenous (51.5 vs 50.3%) was not significantly different. The proportion of patients achieving ACR 70 with abatacept subcutaneous and abatacept intravenous (26.4 vs 25.1%) was not significantly different. Adverse events were also similar between the groups.
Keystone et al[84] (ATTUNE) Abatacept 125 mg subcutaneously once weekly	OL Patients ≥18 years of age with active RA previously refractory to either MTX or anti-TNFs who had received ≥4 years of intravenous abatacept in either of two previous RCTs	N=128 12 months	Primary: Safety at three months Secondary: Immunogenicity at three months, and efficacy at 12 months	Primary: Up to month three, adverse events occurred in 39.8% of patients; no individual adverse events were reported in ≥5% of patients. One adverse event (musculoskeletal pain) led to discontinuation. Overall, 75.6% of patients experienced an adverse event during the cumulative period. After month three, 12 further adverse events were reported, of which three led to discontinuation (breast cancer, sarcoidosis and brain neoplasm). No deaths were reported in the study or during follow-up. Infections reported up to month three (more than one patient) included nasopharyngitis (n=4), urinary tract infection (n=3), bronchitis (n=2), gastroenteritis (n=2), sinusitis (n=2) and upper respiratory tract infection (n=2). No serious infections, malignancies or autoimmune events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were reported during the first three months. Serious infections, malignancies or autoimmune events occurring after month three were as follows: one serious infection (pneumonia)), two malignancies (breast and uterine cancer) and two autoimmune events occurred (sarcoidosis and erythema nodosum). Secondary: Eight patients were seropositive based on ELISA through month three. Of these eight, six were already positive prior to enrolment. All seropositive patients continued treatment. Adverse events experienced by the seropositive patients were not consistent with immune-mediated toxicities, except for one patient who developed sarcoidosis and discontinued treatment. None of these patients had an abatacept-induced seropositive result based on the ECL assay. At baseline, mean DAS28 and HAQ-DI scores in the overall population were 3.39 and 0.94, respectively. Improvements in disease activity and physical function achieved during intravenous treatment were maintained through month 12 of subcutaneous treatment.
Haraoui et al[85] (CanACT) Adalimumab 40 mg subcutaneously every other week	MC, OL, PRO Patients ≥18 years of age with RA diagnosed according to the 1987 revised ACR criteria with active disease, (≥5 swollen joints (of 66 joints evaluated) and one of the following: positive RF, ≥1 joint erosions present on x-ray, or a HAQ-DI score ≥1 and an unsatisfactory	N=879 12 weeks	Primary: Mean change in DAS28 Secondary: Proportion of patients achieving clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2) at week 12, proportion achieving EULAR-	Primary: Patients treated with adalimumab achieved significantly lower DAS28 scores at week 12 compared to baseline (4.2 vs 6.1; P<0.001). Secondary: Following 12 weeks of treatment with adalimumab, 15.3 and 28.9% of patients achieved clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2), respectively (P values not reported). At week 12, 25.9% of patients treated with adalimumab were considered EULAR responders to treatment. The proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response at 12 weeks was 58.4, 30.6 and 12.7%, respectively (P values not reported). At week eight, the proportion of patients who experienced an ACR 20, ACR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	responses or intolerance to prior antirheumatic therapies		moderate and good response, ACR 20, ACR 50, and ACR 70) responses at weeks four, eight, and 12, mean changes in ACR core components [tender joint count, swollen joint count, ESR, physician and patient assessments, and HAQ-DI	50 and ACR 70 response was 52.2, 21.7 and 7.2%, respectively (P values not reported). At week four, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response, was 37.6, 10.6 and 2.4%, respectively (P values not reported). Patients treated with adalimumab experienced a decrease in the number of tender joints at week 12 compared to baseline (6.8 vs 19.9; P value not reported) and the number of swollen joints was reduced from 13.2 at baseline to 6.4 after 12 weeks (P value not reported). As measured on a VAS, patient's assessment of pain decreased from a 66.2 at baseline to 37.3 following adalimumab therapy. Patients' assessment of disease activity decreased from 65.1 at baseline to 37.4 at follow up. Similarly physician assessment of disease activity decreased from 63.6 at baseline to 29.0 (P values not reported). The mean HAQ-DI score improved by an average of 0.5 units from 1.5 at baseline to 1.0 after 12 weeks of adalimumab treatment. In addition, the ESR decreased from a mean of 30.3 mm/h at baseline to 20.0 mm/h at 12 weeks (P<0.001). Adverse events were reported in 43.4% of patients treated with adalimumab. Most adverse events were mild to moderate in intensity. The most commonly reported adverse events were injection site reactions (9.9%), headache (5.2%), injection site erythema (3.5%), nausea (3%) and rash (2.8%). Of the treatment-emergent adverse events considered by the investigator to be related to study drug, injection site reaction and headache were the most frequently reported (≥5% of patients).
Keystone et al[86] Adalimumab 40 mg subcutaneous injection every other week	ES, OL Patients ≥18 years of age with RA (defined by ACR 1987 criteria)	N=202 10 years	Primary: ACR 20, ACR 50, ACR 70, DAS28-CRP <3.2, clinical remission (DAS 28-CRP <2.6 or	Primary: At year 10, 64.2, 49.0, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively. Mean DAS28-CRP was 2.6, with 74.1% achieving DAS28-CRP <3.2 at year 10.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients received concurrent MTX therapy.	despite ≥3 months of MTX (12.5 to 25 mg/week), tender joint count ≥9 out of 68, swollen joint count ≥6 out of 66, CRP ≥1 mg/L, and positive for RF or at least one bony erosion		SDAI ≤3.3), SDAI, HAQ-DI score, and mTSS at 10 years Secondary: Not reported	The proportions of patients achieving DAS28-CRP and SDAI clinical remission states were 59.0 and 33.2%, respectively. From baseline to year 10, mean HAQ-DI was reduced by 50%, with 42.2% of patients achieving HAQ-DI <0.5 or normal functionality. Mean change from baseline to year 10 in mTSS was 2.8 units (annual progression rate of approximately 0.3 units/year), suggesting minimal radiographic progression over 10 years. Secondary: Not reported
Keystone et al[87] (RAPID 1) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics,	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria), for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=982 52 weeks	Primary: ACR 20 at 24 weeks, mean change from baseline in mTSS at 52 weeks Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI, ACR 20 at 52 weeks, ACR 50, and ACR 70 at 24 weeks	Primary: A significantly greater number of ACR 20 responders at 24 weeks were found in the CZP 200 mg group (58.8%) and CZP 400 mg group (60.8%) compared to the placebo group (13.6%; P<0.001). There was no significant difference detected between the two CZP regimens. mTSS were significantly lower with CZP 200 mg (0.4 Sharp units) and 400 mg (0.2 Sharp units) vs placebo (2.8 Sharp units; P<0.001). Secondary: Active treatment was associated with reduced mTSS at 24 weeks compared to placebo (0.2 Sharp units for 200 and 400 mg vs 1.3 Sharp units for placebo; P<0.001). The HAQ-DI score at 52 weeks was -0.60 with CZP 200 mg, -0.63 with CZP 400 mg and -0.18 with placebo (P<0.001). ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (P<0.001 vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1 and 21.4%) and CZP 400 mg (39.9 and 20.6%) compared to placebo (7.6 and 3.0%; P<0.001) at week 24.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				Infections and infestations occurred in 56.4% of CZP 200 mg patients, 58.4% of CZP 400 mg patients and 56.9% of placebo patients with serious infections occurring in 5.3, 7.3 and 2.2% of CZP 200 mg, 400 mg and placebo patients, respectively. The most frequent adverse events reported included headache, hypertension and back pain.
Smolen et al[88] (RAPID 2) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria) for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=619 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, mTSS, SF-36 Health Survey and individual ACR core set variables, and safety	Primary: ACR 20 was attained by significantly more individuals receiving CZP 200 mg (57.3%) and CZP 400 mg (57.6%) compared to placebo (8.7%; P≤0.001). Secondary: ACR 50 and ACR 70 were achieved in a significantly greater number of patients in the CZP 200 mg group (32.5 and 15.9%, respectively) and CZP 400 mg group (33.1 and 10.6%, respectively) vs placebo (3.1 and 0.8%, respectively; P≤0.01). CZP 200 mg (0.2; 95% CI, -1.0 to 0.6) and CZP 400 mg (-0.4 mg; 95% CI, -0.7 to -0.1) were associated with a significantly lower change in mTSS than placebo (1.2; 95% CI, 0.5 to 2.0; P≤0.01 compared to CZP 200 mg; P≤0.001 compared to CZP 400 mg). Active treatment resulted in greater improvements in SF-36 scores vs placebo (P<0.001) and ACR core components vs placebo (P<0.001). Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of CZP 400 mg patients and 0% of placebo patients. Tuberculosis was reported in five patients receiving certolizumab.
Fleischmann et al[89] (FAST4WARD)	DB, MC, RCT Patients 18 to 75	N=220 24 weeks	Primary: ACR 20 at 24 weeks	Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Certolizumab 400 mg every 4 weeks vs placebo Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	years of age with adult onset RA (defined by ACR 1987 criteria) for ≥6 months, with active disease and failed at least one prior DMARD		Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, and safety	Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (22.7 vs 3.7%; P<0.001 and 5.5 vs 0%; P≤0.05, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; P<0.001). Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (P<0.001), arthritis pain (P≤0.05) and fatigue (P<0.001). Headache, nasopharyngitis, upper respiratory tract infections, diarrhea and sinusitis occurred in at least 5% of certolizumab patients. There were no reports of tuberculosis or opportunistic infections throughout the study.
Weinblatt et al[90] (REALISTIC) Certolizumab 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks vs placebo	DB, MC, RCT Patients ≥18 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥3 months, with active disease and failed at least one prior DMARD	N=1063 12 weeks	Primary: ACR 20 at 12 weeks Secondary: ACR 50, ACR 70, DAS 28, and ACR component scores	Primary: ACR 20 achievement at 12 weeks was significantly higher with certolizumab (51.1%) than placebo (25.9%; P < 0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (26.6 vs 9.9%; P<0.001 and 13.0 vs 2.8%; P<0.001, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). At 12 weeks, 81.1% of patients on certolizumab achieved a DAS28 improvement of at least 1.2 vs 56.5% with placebo (P<0.001). The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches. Injection and infusion-site reactions occurred in 5.8% of certolizumab patients and 1.0% placebo patients.
Tanaka et al[91]	DB, MC, PC, RCT	N=269	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(GO-FORTH) Golimumab 50 mg once every four weeks and MTX (Group 3) vs golimumab 100 mg once every four weeks and MTX (Group 2) vs placebo and MTX (Group 1)	Patients 20 to 75 years of age with RA (diagnosed with ACR 1987criteria) with RA for ≥3 months and were receiving 6 to 8 mg/week oral MTX for RA for ≥3 months before study and active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/ baseline) and ≥2 of the following criteria at screening/ baseline: CRP >1.5 mg/dL, ESR by the Westergren method of >28 mm/hour, morning stiffness lasting ≥30 minute, radiographic evidence of bone erosion, or anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive	24 weeks	Proportion of patients achieving ACR 20 at week 14 Secondary: Proportion of patients achieving an ACR 50 and ACR 70 response, ACR-N Index of Improvement, DAS28(ESR) response DAS28(ESR) remission (score <2.6), HAQ-DI, and safety	There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab 50 and 100 mg groups compared to the placebo group (74.7 and 72.1 vs 27.3%; P<0.0001). Secondary: Similarly, more patients in the golimumab 50 and 100 mg groups achieved an ACR 50 compared to the placebo group (43.0 and 37.9 vs 9.1%; P≤0.005). More patients receiving golimumab 50 or 100 mg achieved an ACR 70 compared to patients receiving placebo (22.1 and 13.8 vs 2.3%; P≤0.005). The ACR-N index of improvement was significantly higher in patients receiving golimumab 50 mg (30%) and golimumab 100 mg (25.85%) compared to placebo (20.00; P<0.001 for both). Significantly more patients in the golimumab 50 mg and 100 mg treatment groups achieved DAS28(ESR) scores for response to treatment compared to placebo (79.5 and 85.5 vs 37.6%; P<0.0001). A higher proportion of patients receiving golimumab 50 mg or 100 mg achieved DAS28(ESR) for remission compared to placebo at 14 weeks (31.4 and 18.4 vs 3.4%; P<0.0001). Patients randomized to golimumab 100 mg and 50 mg treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.32 and 0.39 vs 0.07; P<0.0001). By week 16, 72.7, 75.6 and 78.2% of patients receiving placebo, golimumab 100 mg and 50 mg, respectively, had adverse events. Infections were the most common adverse event in the placebo (39.8%), golimumab 100 mg (38.4%) and golimumab 50 mg (33.3%) treatment groups at week 24. Serious adverse events were relatively uncommon through week 16, occurring in one patient (1.1%) in receiving placebo (intervertebral disc protrusion), one patient (1.2%) in the golimumab 100 mg group (ileus) and two patients receiving golimumab 50 mg (2.3%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				By week 24, 11 (5.5%) of the 201 patients treated with golimumab 50 mg or 100 mg had discontinued golimumab due to the following adverse events: infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).
Emery et al[92] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	DB, PC, RCT MTX naïve patients ≥18 years of age with a diagnosis of active RA for ≥3 months and not previously treated with a TNF-blocker	N=637 24 weeks	Primary: ACR 50 response at week 24 Secondary: ACR 20, 70, 90 responses at week 24	Primary: The golimumab monotherapy group was not statistically different from the MTX monotherapy group in ACR response (P=0.053). However, post-hoc modified intent-to-treat analysis (excluding three untreated patients) of the ACR 50 response showed statistically significant difference between the two groups (P=0.049). Secondary: The combined golimumab and MTX groups had greater proportion of patients achieve an ACR 20 response at week 24 compared to placebo and MTX groups (P=0.028 for both groups). ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.
Keystone et al[93] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated	N=444 24 weeks	Primary: ACR 20 response at week 14, change from baseline in HAQ at week 24 Secondary: ACR 50, 70, 90 responses and	Primary: At week 14, an ACR 20 response was achieved by 33.1% of placebo and MTX-treated patients, 44.4% of golimumab 100 mg and placebo-treated patients (P=0.059), 55.1% of golimumab 50 mg and MTX-treated patients (P=0.001), and 56.2% of golimumab 100 mg and MTX-treated patients (P<0.001). At week 24, the median improvements from baseline in the HAQ-DI scores were -0.13 (P=0.240), -0.38 (P=0.001), and -0.50 (P<0.001), respectively. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	with a TNF-blocker		ACR-N EULAR response, remission according to DAS 28, and sustained remission (DAS 28 remission at week 14 and maintained through week 24)	ACR 50 and ACR-N response was significant for all the groups except placebo and MTX; ACR 70 was significant for all the groups except the placebo and MTX and golimumab and placebo groups; ACR 90 was not significant for any of the groups. Greater proportion of patients in the golimumab and MTX groups achieved significant EULAR response. At week 24, clinical remission was achieved by 6.0% of placebo and MTX-treated patients, 12.0% (P=0.087) of golimumab 100 mg and placebo-treated patients, 20.2% (P=0.001) of golimumab 50 mg and MTX-treated patients, and 22.5% (P<0.001) of golimumab 100 mg and MTX-treated patients, respectively. Sustained remission was achieved by 0.8%, 6.3% (P=0.018), 10.2% (P=0.001), and 11.9% (P<0.001), respectively.
Smolen et al[94] (GO-AFTER) Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response at week 14, DAS 28 response at week 14, ACR 20 response at week 24, and improvement from baseline in HAQ scores at week 24	Primary: Golimumab 50 and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3 and 37.9 vs 18.1%, respectively; P<0.001). ACR 20 responders at week 14 among patients who discontinued previous TNF-blocker therapy due to lack of efficacy included 35.7 and 42.7% of patients in the golimumab 50 and 100 mg groups, respectively, compared to 17.7% of patients in the placebo group (P=0.006, golimumab 50 mg vs placebo; P<0.001, golimumab 100 mg vs placebo). Secondary: ACR 50 response at week 14 was significant for the golimumab-treated groups compared to the placebo group. DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2 and 59.5 vs 30.3%, respectively; P<0.001). ACR 20 response at week 24 was significant for the golimumab-treated groups compared to the placebo group. At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Smolen et al[95] (GO-AFTER Extension) Golimumab 50 mg once every 4 weeks (Group 1) vs golimumab 50 mg once every 4 weeks. Dose could be increased to 100 mg if <20% improvement in both tender and swollen joint counts at week 16 of the original study occurred. (Group 2) vs golimumab 100 mg once every 4 weeks (Group 3)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=459 160 weeks	Primary: ACR 20 Secondary: ACR 50/70,DAS 28, SDAI, and HAQ score	Primary: At week 160, 62.7, 66.7 and 56.8% of patients achieved ACR20 response and 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Secondary: At week 160, 17.3, 14.8 and 23.5% of patients achieved ACR70 response Groups 1, 2 and 3, respectively. DAS 28 response for groups 1, 2 and 3, response was 71.8, 83.8 and 71.4%, respectively. Remission as measured by DAS 28 for groups 1, 2 and 3, response was 16.9, 12.5 and 21.5%, respectively. SDAI remission for groups 1, 2 and 3, response was 11.4, 8.8 and 23.1%, respectively. SDAI scores for low disease activity (3.3 to 11) for groups 1, 2 and 3, response was 34.3, 28.8 and 25.6%, respectively. At week 160, 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively.
Weinblatt et al[96] (GO-FURTHER) golimumab 2 mg/kg, at weeks 0 and 4 and every 8 weeks plus MTX vs placebo and MTX	DB, MC, PC, RCT Adult patients with RA for ≥3 months and were receiving 15 to 25 mg/week oral MTX for RA for ≥4 weeks before study and active RA (≥6/66 swollen joints and ≥6/68 tender joints at screening/ baseline) and CRP >1.0 mg/dL, anti- cyclic	N=592 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: DAS28 and HAQ-DI week 14, ACR 50 at week 24, and safety	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab group compared to the placebo group (58.5 and 24.9%: P<0.001). Secondary: Significantly more patients in the golimumab treatment groups achieved DAS28 scores for moderate-good response to treatment compared to placebo at 14 weeks (81.3 vs 40.1%; P<0.001). Patients randomized to golimumab treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.5 vs 0.19; P<0.001). Significantly higher proportion of patients randomized to golimumab groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	citrullinated peptide antibody-positive and/or rheumatoid factor-positive			achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Adverse events reported at rates ≥1.0% higher in the golimumab group vs placebo were observed for infections and infestations (24.3 vs 20.8%); nervous system disorders (6.8% vs 4.1%); gastrointestinal disorders (6.6 vs 5.6%); skin and subcutaneous tissue disorders (6.6% vs 3.6%); respiratory, thoracic and mediastinal disorders (4.8 vs 2.5%); vascular disorders (3.8 vs 2.5%); and metabolism and nutrition disorders (2.3 vs 0.0%).
Jones et al[97] (AMBITION) Tocilizumab 8 mg/kg every 4 weeks vs MTX 7.5 to 20 mg every week or placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on	DB, DD, PG, RCT Patients ≥18 years of age, with moderate to severe RA for ≥3 months, oral glucocorticoids (up to 10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dose was stable for ≥6 weeks	N=673 24 weeks	Primary: Proportion of patients achieving ACR 20 response at week 24 Secondary: Proportion of patients with ACR 50/70 responses at week 24 and the time to onset of ACR 20/50/70 responses, changes from baseline at week 24 in 28-joint count DAS 28, the proportion of patients in clinical	Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (P<0.001). Compared to the placebo arm, a larger proportion of patients treated with tocilizumab also achieved an ACR 20 response at week eight (55.6 vs 13.1%; 95% CI, 0.34 to 0.52). Secondary: The proportion of patients achieving ACR 50 (44.0%) and ACR 70 (28.0%) at week 24 was also statistically significant for tocilizumab as compared to MTX (P<0.001). Improvements in DAS 28 at week 24 were greater in the tocilizumab group than in the MTX group. Additionally, the proportion of patients in remission at week 24 was higher with tocilizumab (P<0.001). By week 24, tocilizumab patients were five times more likely to achieve DAS 28 remission and four times more likely to achieve at least a moderate response (OR vs MTX, 4.24; 95% CI, 2.92 to 6.14). A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			remission (DAS 28 <2.6), with low disease activity (DAS 28 ≤3.2) and with good/ moderate responses at week 24, improvement in physical function was assessed by change from baseline at week 24 in HAQ-DI, and adverse events	There was no statistically significant difference with regard to the number of adverse events experienced in the tocilizumab group compared to the MTX group (79.9 vs 77.5%; P=0.484). Infection rates/patient year were also found to be similar (1.06 vs 1.09). However, skin and subcutaneous infections were reported more frequently in the tocilizumab group (4.1 vs 1.4%; P value not reported).
Smolen et al[98] (OPTION) Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs tocilizumab 4 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs placebo every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	DB, PC, PG, RCT Patients ≥18 years of age, with moderate to severe RA >6 months duration, who had an inadequate response to MTX; all other DMARDs were discontinued before the start of the study, oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if doses were stable for six	N=622 24 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50/70, DAS 28, and EULAR responses at week 24, difference in HAQ-DI, SF-36, and FACIT-F, scores from baseline, and adverse events	Primary: At week 24, significantly greater proportion of patients receiving tocilizumab 4 and 8 mg/kg had an ACR 20 response than patients who received placebo (59 and 48 vs 26%, respectively; P<0.0001 for both). Secondary: Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups achieved ACR 50 (31 and 44 vs 11%, respectively; P<0.0001) and ACR 70 at week 24 (12 and 22 vs 2%, respectively; P<0.0001) compared to patients in the placebo group. Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups had reduced disease activity as measured by a DAS 28 score <2.6 (13.0 and 27.0 vs 0.8%, respectively; P<0.0002 for 4 mg/kg and P<0.0001 for 8 mg/kg groups) compared to the placebo group. EULAR response was also found to be significantly decreased in both tocilizumab 4 and 8 mg/kg groups (21 and 38 vs 3%, respectively; P<0.0001 for both) compared to the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	weeks or more			Greater improvements in physical function were seen in both tocilizumab 4 and 8 mg/kg groups as assessed by the HAQ-DI score (-0.52 and -0.55 vs -0.34, respectively; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg). Significant differences were seen with regard to changes in the SF-36 physical score in both tocilizumab 4 and 8 mg/kg groups (9.7 and 9.5 vs 5.0, respectively; P<0.0001 for both) and in the SF-36 mental score (5.7 and 7.3 vs 2.7, respectively; P<0.0394 for 4 mg/kg and P<0.0012 for 8 mg/kg). The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab 4 and 8 mg/kg groups (7.3 and 8.6 vs 4.0, respectively; P<0.0063 for 4 mg/kg and P<0.0001 for 8 mg/kg). Greater proportions of patients in the tocilizumab 4 and 8 mg/kg groups reported experiencing at least one adverse event compared to the placebo group (71 and 69 vs 63%, respectively). The rate of all infections/100 patient years was 98.7 in the tocilizumab 4 mg/kg group, 101.9 in the 8 mg/kg group, and 96.1 in the placebo group.
Genovese et al[99] (TOWARD) Tocilizumab 8 mg/kg plus DMARD every 4 weeks vs placebo plus DMARD every 4 weeks	DB, MC, PC, RCT Patients ≥18 years of age, with moderate to severe RA, who received stable doses of permitted DMARDs (MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and leflunomide) for ≥8 weeks prior to study entry and oral glucocorticoids (≤10 mg/day of	N=1,220 24 weeks	Primary: ACR 20 responses at week 24 Secondary: ACR 50/70 responses at week 24, number of swollen and tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events	Primary: At week 24, the proportion of patients in the tocilizumab group that were ACR 20 responders was significantly higher than in the control group (61 vs 25%; P<0.0001). No obvious differences were seen in ACR 20 response with regard to patients who received two or more DMARDs. Secondary: At week 24, significantly more patients in the tocilizumab group achieved ACR 50 and ACR 70 responses when compared to the placebo group (ACR 50, 30 vs 9%; ACR 70, 21 vs 3%; P<0.0001 for both). Compared to baseline, a significant decrease was seen in the number of swollen and tender joints in patients receiving tocilizumab when compared to the placebo group (swollen joint count, -10.3 vs -4.9; tender joint count, -15.7 vs -8.5; P<0.0001). Mean DAS 28 improved incrementally over time with greater changes in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	prednisone or equivalent) and NSAIDs or COX2 inhibitors if the doses were stable for ≥6 weeks			tocilizumab group seen by week 24 (-3.17 and -1.16, respectively; P<0.0001). Remission rates at week 24 were also higher in the tocilizumab group when compared to the placebo group (30 vs 3%; P<0.0001). By week 24, 80% of patients in the tocilizumab group and 38% of patients in the placebo group achieved a good or moderate EULAR response (P<0.0001). At week 24, 60% of patients in the tocilizumab group had a clinically meaningful improvement in physical function as compared to 34% with placebo (change from baseline in HAQ ≥0.3). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to the placebo group for the disability index of the HAQ (-0.5 vs -0.2; P<0.0001) and FACIT-F scores (8.0 vs 3.6; P<0.0001). Mean improvements from baseline in SF-36 scores were higher for both physical and mental components at week 24 in the tocilizumab group (8.9 vs 4.1 and 5.3 vs 2.3, respectively; P<0.0001 for both). The occurrence of adverse events was found to be higher with tocilizumab (73 vs 61%). The most frequently occurring adverse events in both groups were infections and infestations (37.4 vs 31.6%), gastrointestinal disorders (20.8 vs 14.7%), and musculoskeletal and connective tissue disorders (13.0 vs 17.9%). Infections with a higher incidence in the tocilizumab group were upper respiratory infections (9 vs 7%), other respiratory infections (12 vs 10%), and skin and subcutaneous tissue infections (5 vs 3%).
Kremer et al[100] (LITHE) Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs tocilizumab 4 mg/kg plus	DB, MC, PC, PG, RCT Patients with RA, as determined by ACR criteria that was moderate to severe and lasted for ≥6 months; inadequate response to MTX	N=1,196 12 months	Primary: Change from baseline in the total Genant-modified Sharp score and change in HAQ-DI Secondary:	Primary: The proportion of patients without radiographic progression (change in total Genant-modified Sharp score ≤0 from baseline to week 52) was significantly higher in patients treated with tocilizumab 8 or 4 mg/kg (84 and 81 vs 67%; P<0.0001). The AUC of the change in the HAQ-DI score from baseline to week 52 demonstrated a significantly greater decrease in the 8 and 4 mg/kg tocilizumab groups compared to the placebo group (-144.1 and -128.4 vs -58.1 units; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MTX (stable, 10 to 25 mg weekly) for four weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for four weeks Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry.	therapy, defined as a swollen joint count of ≥6, a tender joint count of ≥8, and either CRP level ≥1 mg/dl or an ESR ≥28 mm/hour; and had ≥1 radiographically confirmed joint erosion despite having received MTX for ≥12 weeks before baseline		Change from baseline in erosion and JSN scores (at week 24 and 52), total Genant-modified Sharp score at week 24, proportions of patients with no progression of total, erosion, or JSN scores, ACR 20, ACR 50, and ACR 70, change in DAS 28, and proportions of patients with low levels of disease activity (DAS28 ≤3.2) and DAS remission (DAS28 <2.6).	Secondary: At week 52, the ACR 20, ACR 50, and ACR 70 response rates were higher in patients treated with tocilizumab compared to placebo; however the difference was only statistically significant for the 8 mg/kg group compared to the placebo group (P<0.0001 for all response rate comparisons). The DAS28 scores were reduced over 52 weeks in all treatment groups, with mean improvements of -3.8, -3.0, and -2.0 in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively; however, the difference was only significant with the 8 mg/kg dose compared to placebo (P<0.0001). At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the DAS28 score (<2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001). DAS28 remission rates continued to improve between weeks 24 and 52, with the highest proportion of patients in remission in the tocilizumab 8 mg/kg treatment group. The progression of structural damage from baseline to week 52 was reduced by 74 and 70% with tocilizumab 8 and 4 mg/kg, respectively, compared to patients treated with placebo (P<0.0001). The total Genant-modified Sharp score at week 52 showed a decreased frequency and severity of disease progression with tocilizumab therapy.
Yazici et al[101] (ROSE) Tocilizumab 8 mg/kg plus DMARD every four weeks vs placebo plus DMARD every four weeks	DB, MC, PC, RCT Patients ≥18 years of age with active RA for ≥6 months and an inadequate clinical response to DMARD in addition to ≥6 swollen joints and ≥6 tender joints at screening and	N=619 24 weeks	Primary: ACR 50 response at week 24 Secondary: ACR 20, ACR 50, ACR 70, EULAR response, DAS28, clinically meaningful	Primary: A significantly higher proportion of patients randomized to receive tocilizumab achieved an ACR 50 response at week 24 compared to placebo (30.1 vs 11.2%; P<0.0001). Secondary: A higher proportion of patients randomized to receive tocilizumab achieved an ACR 20 response at all time points evaluated compared to placebo (P<0.0001). Similarly, an ACR 50 response was achieved in significantly more patients in the tocilizumab group compared to placebo at all treatment weeks except week 16 (P<0.05 at all time points). A significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Permitted DMARD (at stable doses ≥7 weeks before study) included MTX, chloroquine, hydroxychloroquine, parenteral gold, SSZ, azathioprine and leflunomide. Doses were required to remain stable throughout the study; however, dose reductions were allowed as clinically warranted for safety reasons.	baseline, with either a CRP ≥95.24 nmol/l or an ESR ≥28 mm/h or greater at screening		improvement (change from baseline in DAS28 of ≥1.2), patients achieving low disease activity (DAS28 ≤3.2), clinical remission (DAS28 <2.6), ESR and CRP levels, FACIT-F, and RAPID3 scores	proportion of patients in the tocilizumab group compared to the placebo group achieved an ACR 70 response at all time points from week eight onward (P<0.05 for all time points). A higher proportions of patients achieved a EULAR good response in the tocilizumab group compared to placebo at all time points starting at week four (13.2 vs 2.0%; P<0.0001). The mean DAS28 score decreased from baseline to week 24 in both treatment groups starting at week four; however, the improvement was significantly greater in tocilizumab group compared to placebo (P<0.0001). Significantly more patients achieved a clinically meaningful decrease in DAS28 (≥1.2 points from baseline) in the tocilizumab group compared to the placebo group at all time points from week four onward (87.9 vs 53.4%; P<0.0001). Moreover, a greater proportion of patients randomized to receive tocilizumab achieved a low disease activity (P<0.0001) and clinical remission at week 24 (P<0.0001) compared to those in the placebo group. There were significantly greater improvements from baseline in the RAPID3 scores at 24 weeks in the tocilizumab treatment group compared to placebo (-2.33 vs -1.29; P<0.0001). There was a statistically significant improvement in mean FACIT-F scores over 24 weeks of treatment with tocilizumab compared to placebo (P<0.05). Patients treated with tocilizumab achieved significantly lower mean CRP levels at all time points evaluated compared to the placebo group (P<0.0001). Similarly, the mean ESR was significantly reduced from baseline to a greater degree with tocilizumab compared to the placebo group at week 24 (-34.72 vs -5.70 mm/h; P<0.0001).
Emery et al[102] (RADIATE) Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg	DB, PC, PG Patients ≥18 years of age with moderate to severe	N=499 24 weeks	Primary: ACR 20 responses Secondary:	Primary: ACR 20 was achieved at week 24 by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control group respectively (P<0.001). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weekly) for 4 weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks	active RA with failure to respond to one or more TNF antagonists within the past year; patients must have discontinued TNF agents (Enbrel®, Humira®, Remicade®) or DMARDs (other than MTX) before enrolling		DAS 28, number of patients requiring rescue therapy, and adverse events	Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments. Secondary: DAS 28 remission rates at week 24 were dose related, being achieved in 30.1, 7.6, and 1.6% of 8 mg/kg, 4 mg/kg and control groups (P<0.001 for 8 mg/kg; P=0.053 for 4 mg/kg vs control). Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both tender and swollen joints). More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after week 16 compared to 11% of patients in the 8 mg/kg group. Adverse events noted were mild or moderate with overall incidences of 84.0% in the tocilizumab 8 mg/kg group, 87.1% in the tocilizumab 4 mg/kg group, and 80.6% in the placebo plus MTX group. The most common adverse events were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in the control group (11.3%) than in the tocilizumab 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Dougados et al[103] (ACT-RAY) Tocilizumab 8 mg/kg plus MTX (stable >15 mg weekly) every 4 weeks vs tocilizumab 8 mg/kg plus placebo every 4 weeks	DB, PC, PG Patients ≥18 years of age with active RA with failure to respond to > 12 weeks of MTX treatment (stable dose >15 mg week for 6 weeks prior to study)	N=556 24 weeks	Primary: DAS 28 remission Secondary: DAS 28 low disease activity, ACR 20, ACR 50, ACR 70, ACR 90, and adverse events	Primary: DAS 28 remission rates at week 24 were 40.4% with the tocilizumab/MTX group vs 34.8% with tocilizumab monotherapy (P=0.19). Secondary: DAS 28 scored for low disease activity was significantly lower with combination therapy (tocilizumab/MTX) at week 24 that with the with tocilizumab monotherapy (61.7 vs 51.4%; P=0.029). ACR 20/50/70/90 was 71.5%/45.5%/24.5%/5.8% with tocilizumab/MTX. ACR 20/50/70/90 was 70.3%/40.2%/25.4%/5.1% with tocilizumab monotherapy. The differences between treatment groups were not considered significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events noted were comparable in each treatment group with 6.1% of patients on tocilizumab/MTX reporting a serious adverse event while 5.8% reported a serious adverse event with tocilizumab monotherapy. Discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab/MTX patients and 2.5% and 18.5% of tocilizumab monotherapy patients, respectively. Increases in alanine aminotransferase elevations from normal at baseline to greater than upper limit of normal and to more than three times upper limit of normal at one or more time points during 24 weeks occurred in 48.8% and 7.8% on tocilizumab/MTX and in 27.6% and 1.2% of tocilizumab monotherapy patients, respectively.
Maxwell et al[104] Abatacept 2 to 10 mg/kg alone or in combination with DMARDs or biologics vs placebo or DMARDs or biologics	SR RCTs of patients ≥16 years of age with RA meeting the ACR 1987 revised criteria	N=2,908 (7 trials) ≥3 months	Primary: ACR 50 response and safety Secondary: ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, and changes in HAQ and SF-36	Primary: At three months, the ACR 50 response in the abatacept group was not significantly higher than the control group (RR, 2.50; 95% CI, 0.52 to 11.96). At six and 12 months, the ACR 50 response was significantly higher in the abatacept group compared to the control group (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82, respectively). At one year the NNT in order to achieve ACR 50 was 5 (95% CI, 4 to 7). The RR for adverse events with abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections with abatacept compared to controls (OR, 1.91; 95% CI, 1.07 to 3.42). However, after removing a study in which patients were treated with combination of etanercept and abatacept, the OR decreased to 1.82 (95% CI, 1.00 to 3.32). Abatacept treated patients had increased number of headaches and infusion reactions (RR, 1.45; 95% CI, 1.20 to 1.74 and RR, 1.30; 95% CI, 1.13 to 1.50). Secondary: ACR 20 response was achieved in significantly more patients treated with abatacept compared to controls at six and 12 months (RR, 1.79; 95% CI, 1.59 to 2.02 and RR, 1.79; 95% CI, 1.55 to 2.07, respectively) but not at three months (RR, 1.70; 95% CI, 0.93 to 3.12). More patients treated with abatacept achieved an ACR 70 at six and 12 months (RR, 3.53; 95% CI, 2.41 to 5.16 and RR, 4.02; 95% CI, 2.62 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				6.18) but not at three months (RR, 5.00; 95% CI, 0.25 to 100.20). There was a statistically significant reduction in the progression of joint damage at 12 months with abatacept (mean difference, -0.27; 95% CI, -0.42 to -0.12). The abatacept treated patients were significantly more likely to reach low DAS (DAS 28 <3.2) compared to controls at six and 12 months (RR, 3.36; 95% CI, 2.28 to 4.96 and RR, 4.33; 95% CI, 2.84 to 6.59), and a NNT of 4 (95% CI, 3 to 5). At 12 months, patients in the abatacept group were significantly more likely to achieve DAS remission (DAS 28 <2.6) with RR of 12.74 (95% CI, 4.76 to 34.15). For clinically meaningful improvement on the HAQ; RR, 1.69 (95% CI, 1.51 to 1.90) in favor of abatacept. There was an absolute difference of 24% (95% CI, 16 to 32) and a NNT to achieve HAQ >0.3 of 5 (95% CI, 4 to 7). Improvement in the physical component of the SF-36 was significantly more likely in the abatacept group (RR, 1.90, 95% CI, 1.52 to 2.39). There was no significant difference between the groups in likelihood of scoring worse. The RR of scoring the same was 0.66 in favor of placebo (95% CI, 0.56 to 0.78). There were significantly fewer patients that scored worse on the mental component of the SF-36 (RR, 0.64; 95% CI, 0.44 to 0.94). Scoring the same was not significantly different between the groups. A score of better was significantly higher in the abatacept group (RR, 1.42; 95% CI, 1.14 to 1.76).
Navarro-Sarabia et al[105] Adalimumab 20, 40, 80 mg every week to every other week, alone or in combination with DMARDs vs placebo or placebo plus	SR RCTs of patients with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either failed MTX or other DMARDs therapy,	N=2,381 (6 trials) 12 to 52 weeks	Primary: ACR, EULAR responses, DAS 28, components of ACR responses, and radiographic data Secondary: Safety	Primary: Adalimumab 40 mg every other week was associated with a RR of 1.52 to 4.63 to attain an ACR 20 response at 24 weeks with a NNT of 1.9 to 5.4. The RR to achieve an ACR 50 response was 4.63 (95% CI, 3.04 to 7.05) and NNT was 3.0 (95% CI, 2.0 to 6.0). The RR to achieve an ACR 70 response was reported as 5.14 (95% CI, 3.14 to 8.41) and a NNT of 7 (95% CI, 5 to 13).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DMARDs	or DMARD naive			At 52 weeks, the RRs were reported for ACR 20, ACR 50 and ACR 70 as 2.46 (95% CI, 1.87 to 3.22), 4.37 (95% CI, 2.77 to 6.91) and 5.15 (95% CI, 2.60 to 10.22) and NNTs were 2.9, 3.1 and 5.3, respectively. A significantly slower rate of radiological progression was detected with either adalimumab 40 mg every other week or 20 mg every week in combination with MTX compared to placebo plus MTX, at 52 weeks. Adalimumab monotherapy (40 mg every other week) was associated with a RR of 1.91 (95% CI, 1.17 to 3.10), 2.84 (95% CI, 1.58 to 5.12) and 7.33 (95% CI, 2.25 to 33.90) to achieve an ACR 20, ACR 50 and ACR 70 response, respectively, with NNTs of 5 (95% CI, 3 to 9), 7 (95% CI, 4 to 20) and 9 (95% CI, 3 to 38), respectively at 24 weeks. Secondary: Only one study demonstrated that adalimumab was associated with a significantly higher risk of developing serious infection (RR, 7.64; 95% CI, 1.02 to 57.18; NNH, 30.2).
Mertens et al[106] Anakinra 50 to 150 mg daily vs placebo	SR RCTs of patients >18 years of age with RA	N=2,876 (5 trials) 24 weeks	Primary: Patients achieving ACR 20 Secondary: Patients achieving ACR 50 and ACR 70, and safety	Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to patients taking placebo (23%; RR, 1.61; 95% CI, 1.32 to 1.98). It was concluded that this 15% difference represented a modest yet clinically meaningful difference. Secondary: Both ACR 50 and ACR 70 were obtained at a significantly greater rate with anakinra as opposed to placebo (18 vs 7%; RR, 2.52; 95% CI, 1.56 to 4.03 and 7 vs 2%; RR, 3.71; 95% CI, 1.44 to 9.57, respectively). Anakinra was also associated with significant improvements in HAQ, visual analog score, Larsen radiographic scores and change in ESR compared to placebo. The number of withdrawals, deaths, adverse events and infections were not significantly different between active treatment and placebo. However, injection site reaction was significantly more prevalent in the anakinra group vs the placebo group (71 vs 28%).
Blumenauer et al[107]	SR	N=949	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Etanercept 10 mg or 25 mg twice weekly alone or in combination with MTX vs MTX or placebo	RCTs of patients ≥16 years of age meeting the ACR 1987 revised criteria for RA with evidence of active disease as demonstrated by ≥2 of the following: tender joint count, swollen joint count, duration of early morning stiffness >30 minutes, acute phase reactants such as Westergren ESR or CRP	(3 trials) ≥6 months	ACR 20, ACR 50, ACR 70 responses, and erosion scores Secondary: Safety	At six months, 64% of individuals on etanercept 25 mg attained an ACR 20 response vs 15% of patients on control with either MTX alone or placebo (RR, 3.8; 95% CI, 2.5 to 6.0; NNT, 2). ACR 50 was achieved by 39% in the etanercept group compared to 4% in the control group (RR, 8.89; 95% CI, 3.61 to 21.89; NNT, 3). An ACR 70 response was reported in 15 and 1% of etanercept and control patients, respectively (RR, 11.31; 95% CI, 2.19 to 58.30; NNT, 7). Etanercept 10 mg was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and JSN were not significantly reduced by either etanercept dose, however etanercept 25 mg was associated with a significantly reduced total Sharp score (WMD, -10.50; 95% CI, -13.33 to -7.67). Secondary: Injection site reactions were reported in 34% of patients on etanercept 10 mg compared to 9% of controls (RR, 3.86; 95% CI, 2.59 to 5.77; NNH, 4) and 41% of patients receiving etanercept 25 mg vs 9% of controls (RR, 4.77; 95% CI, 3.26 to 6.97; NNH, 3.1). The number of withdrawals was reported less frequently in the etanercept 25 mg group (4%) compared to the control group (8%; RR, 0.50; 95% CI, 0.27 to 0.94) and no difference was found between the etanercept 10 mg group and control in the rate of discontinuation.
van Vollenhoven et al[108] (SWEFOT) Infliximab 3 mg/kg at weeks zero, two and six then every eight weeks plus MTX 20 mg weekly	MC, OL, PG, RCT Patients ≥18 years of age with RA (ACR) criteria, no previous DMARD treatment, no oral	N=487 24 months	Primary: Proportion of patients achieving a EULAR-define good response (a decrease of	Primary: At month 18, there was no statistically significant difference in the proportion of patients achieving an EULAR-defined good response for patients treated with infliximab compared to conventional therapy (38 vs 29%, respectively; 95% CI, 0.93 to 1.85). Furthermore there was no statistically significant difference between the treatment groups at 24 months (38 vs 31%, respectively; P=0.204).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Group B) vs MTX 20 mg weekly plus SSZ 1,000 mg twice-daily plus hydroxychloroquine 400 mg daily (Group A)	glucocorticoid treatment or stable glucocorticoid treatment for ≥4 weeks of at most 10 mg daily prednisolone (or equivalent), a DAS28 >3.2		DAS28 by ≥1.2 and a resulting DAS28 ≤3.2 or less Secondary: EULAR and ACR responses at months 18 and 24, radiological outcomes at months 24	Secondary: At 18 months, no statistically significant differences were reported between infliximab and conventional therapy with regard to ACR 20 (45 vs 34%, respectively; 95% CI, 0.99 to 1.82) ACR 70 (17 vs 11%, respectively; 95% CI, 0.86 to 2.98) or EULAR good or moderate response (58 vs 47%, respectively; 95% CI, 0.97 to 1.56). There was, however, a statistically significant difference favoring infliximab with regard to ACR 50 (30 vs 19%, respectively; 95% CI, 1.02 to 2.46). At 24 months there was no statistically significant difference between infliximab and conventional therapy with regard to ACR 20 response (40 vs 33%, respectively; P=0.259), ACR 50 (30 vs 22%; P=0.134), ACR 70 (16 vs 14%; P=0.566) or EULAR good to moderate response (59 vs 50%; P=0.166). Radiological outcomes were not statistically significant between infliximab and conventional therapy at 24 months with regard to total score (P=0.118), erosion score (P=0.0730) or joint-space narrowing score (P=0.054).
Wiens et al[109] Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX vs placebo plus MTX	MA RCTs of adult patients with RA	N=2,129 (7 trials) ≥14 weeks	Primary: ACR 20, ACR 50, and ACR 70 response Secondary: Safety and discontinuation of therapy	Primary: Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to the control group (RR, 1.87; 95% CI, 1.43 to 2.45). An ACR 50 was achieved in 33% of infliximab treated patients and 12% of controls (RR, 2.68; 95% CI, 1.79 to 3.99). The RR of achieving an ACR 70 was 2.68 (95% CI, 1.78 to 4.03) with 17 and 5% of infliximab and control groups achieving an ACR 70, respectively. After ≥1 year of treatment, 62% of patients in the infliximab group and 26% of controls achieved an ACR 20 (RR, 2.33; 95% CI, 1.90 to 2.87). An ACR 50 was achieved in 43% of the infliximab treated patients and 27% of controls (RR, 1.61; 95% CI, 1.14 to 2.27). The RR for reaching ACR 70 was 1.69 (95% CI, 0.87 to 3.28), and 29% of patients in the infliximab group compared to 17% of patients in the control group achieved an ACR 70. Secondary: There were no statistically significant differences in serious adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a higher number of patients that withdrew due to adverse events in the infliximab group compared to the placebo group (7 vs 3%; RR, 2.05, 95% CI, 1.33 to 3.16); however, fewer patients in the infliximab group withdrew due to lack of efficacy compared to the control group (4 vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).
Nixon et al[110] Adalimumab, anakinra, etanercept, or infliximab with or without MTX vs MTX or placebo	MA RCTs of patients with a clinical diagnosis of RA	N=6,694 (13 trials) ≥6 months	Primary: ACR 20 response and ACR 50 response Secondary: Not reported	Primary: The OR for an ACR 20 response was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab, all compared to placebo. The OR to achieve an ACR 50 response with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) with infliximab, all compared to placebo. The addition of MTX to any of the agents was found to enhance the efficacy of each treatment. The TNF blockers in combination with MTX were associated with higher ACR 20 and ACR 50 responses than anakinra and MTX (OR, 6.35 vs 3.20 and OR, 8.53 vs 4.56, respectively). Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50 response (adalimumab vs anakinra; OR, 1.88; 95% CI, 0.83 to 4.49 and OR, 1.84; 95% CI, 0.84 to 3.70; adalimumab vs etanercept; OR, 0.89; 95% CI, 0.42 to 1.79 and OR, 0.94; 95% CI, 0.50 to 1.62; adalimumab vs infliximab; OR, 0.92; 95% CI, 0.39 to 2.37 and OR, 0.96; 95% CI, 0.48 to 1.90; etanercept vs anakinra; OR, 2.11; 95% CI, 0.90 to 5.68 and OR, 1.94; 95% CI, 0.87 to 4.36; infliximab vs anakinra; OR, 2.05; 95% CI, 0.74 to 5.50 and OR, 1.93; 95% CI, 0.79 to 4.29; and infliximab vs etanercept; OR, 0.97; 95% CI, 0.34 to 2.33 and OR, 0.98; 95% CI, 0.45 to 1.93. However, the TNF blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI, 1.05 to 3.50; P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Gabay et al[111] (ADACTA) Tocilizumab 8 mg/kg vs adalimumab 40 mg every 2 weeks	DB, PG, RCT Patients ≥18 years of age with RA > 6 months, intolerant to MTX or were inappropriate for continued MTX treatment	N=326 24 weeks	Primary: DAS 28 improvement Secondary: Percentage of patients with: a remission response (DAS28 <2.6); low disease activity (DAS28 ≤ 3.2); improvements of at least 20%, 50%, or 70% in ACR Score (ACR 20, ACR 50, and ACR 70); and with a EULAR good Response, and a EULAR good or moderate response	Primary: The change from baseline in DAS28 was significantly greater in the tocilizumab group (-3.3) than in the adalimumab group (-1.8) patients (difference -1.5; 95% CI, -1.8 to -1.1; P<0·0001). Secondary: DAS 28 remission rates at week 24 were achieved in 39.9% with tocilizumab and 10.5% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0·0001). The proportion of patients with low disease activity (DAS 28 ≤3.2) at 24 weeks was 51.5% in tocilizumab group and 19.8% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0.0001). The proportion of patients on tocilizumab vs adalimumab with improvements of at least 20% in ACR score was 65.0 vs 49.4%, respectively, a 50% improvement was seen in 47.2 vs 27.8% respectively and a 70% improvement was observed in 32.5 vs 17.9%, respectively. The proportion of patients on tocilizumab vs adalimumab with a EULAR good response was 51.5 vs 19.8%, respectively, and percentage with a EULAR good or moderate was response 77.9 vs 54.9%, respectively.
Weinblatt et al[112] Abatacept 125 mg subcutaneously once weekly and MTX	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous	N=646 12 months	Primary: Noninferiority, assessed based on ACR20 at one year Secondary: ACR 50, ACR 70, DAS 28, remission	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (46.2 and 46%, respectively; 95% CI not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.	biologic therapy		response (DAS28 <2.6), low disease activity (DAS28 ≤ 3.2), and HAQ-DI	The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (29.2 and 26%, respectively; 95% CI not reported). Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.30 and -2.27, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (43.3 and 41.9%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (59.3 and 61.4%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (60.4 and 57.0%, respectively; difference, 3.4%; 95% CI, -4.5 to 11.3%).
Schiff et al[113] Abatacept 125 mg subcutaneously once weekly and MTX vs adalimumab 40 mg subcutaneously every	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 2 years	Primary: ACR20 at two years Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤3.2), HAQ-DI, and mTSS	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; 95% CI not reported). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (44.7 and 46.6%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (31.1 and 29.3%, respectively; 95% CI not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.				Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.35 and -2.33, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (50.6 and 53.3%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (65.3 and 68.0%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (54.1 and 48.8%, respectively; 95% CI not reported). The non-progression rate (change from baseline mTSS ≤smallest detectable change of 2.2) was 84.8% (95% CI, 80.4 to 89.2) vs 83.8% (95% CI, 79.4 to 88.3) in the abatacept and adalimumab groups, respectively.
Fleischmann et al[114] (ORAL Solo) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L), and inadequate response or adverse reaction to at least one DMARD; all DMARDs except	N=611 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR50, and ACR70 response rates, change from baseline in	Primary: Greater proportions of patients receiving tofacitinib 5 mg and tofacitinib 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline, -0.50 and -0.57 vs -0.19; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively); however, improvement was not statistically significant. Secondary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	stable doses of antimalarial agents had to be discontinued; the use of NSAIDs and glucocorticoids (≤10 mg of a prednisone equivalent daily) was permitted		HAQ-DI score, DAS28-4(ESR) and DAS28-4(CRP), proportion of patients with DAS28-4(ESR) and DAS28-4(CRP) <2.6 and ≤3.2 at all visits up to month six, and FACIT-F scores at month three	met the criteria for an ACR50 response at month three than those receiving placebo (31.1 and 36.8 vs 12.5%; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR70 response at month three than those receiving placebo (15.4 and 20.3 vs 5.8%; P=0.003 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) <2.6 at month six were 9.8 and 14.2%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three than those receiving placebo (12.5 and 17.0 vs 5.3%; P=0.02 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) ≤3.2 at month six were 22.0% and 28.0%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) <2.6 at month three than those receiving placebo (18.7 and 24.4 vs 5.0%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) <2.6 at month six were 26.6 and 34.3%, respectively). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) ≤3.2 at month three than those receiving placebo (28.2 and 36.8 vs 6.7%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) ≤3.2 at month six were 43.6 and 50.8%, respectively. The least-squares mean changes from baseline at month three in FACIT-F

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				scores were 6.7 points with the tofacitinib 5 mg and 8.0 points with the tofacitinib 10 mg doses, as compared to 2.8 points with placebo (P<0.001).
van Vollenhoven et al[115] (ORAL Standard) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo Patients were also receiving MTX 7.5 to 25 mg weekly with an incomplete response.	DB, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L)	N=717 12 month	Primary: ACR20 response rate at month six, change in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI, and DAS28-4(ESR) over time	Primary: Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab met the criteria for an ACR20 response at month six than those receiving placebo (51.5, 52.6, and 47.2 vs 28.3%; P<0.001 for all comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab at month three than those receiving placebo (least-squares mean changes from baseline: -0.55, -0.61 and -0.49 vs -0.24; P≤0.001 for all comparisons). Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (6.2, 12.5, and 6.7 vs 1.1%; P≤0.05, P≤0.001, and P≤0.05, respectively). Secondary: Compared to placebo, significantly greater proportions of patient receiving active treatments achieved ACR50 and ACR70 responses and the changes from baseline in DAS28-4(ESR) and HAQ-DI scores over time (P≤0.05 for all comparisons). A significant difference in ACR20 and ACR50 responses with each tofacitinib treatment as compared to placebo was noted after one month (P≤0.001 for all comparisons). Data on comparison between adalimumab and placebo was not reported.
Burmester et al[116] (ORAL Step) Tofacitinib 5 mg twice daily vs	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of moderate to severe active RA (≥6 tender	N=399 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI score at month three, and	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (41.7 and 48.1 vs 24.4%; P=0.0024 and P<0.0001, respectively). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg and 10 mg twice daily at month three

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tofacitinib 10 mg twice daily vs placebo for 3 months, followed by tofacitinib 5 mg or 10 mg twice daily Patients were also receiving oral or parenteral MTX continuously for ≥4 months at a stable dose of 7.5 to 25 mg weekly for ≥6 weeks. Stable background doses of antimalarial agents (≥8 weeks) were permitted.	or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response or intolerance to ≥1 TNF-blocking agents		proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR) and DAS28-3(CRP), rates of DAS28-4(ESR) and DAS28-3(CRP) <2.6 and ≤3.2, patient's assessment of arthritis pain, and FACIT-F at all visits	than those receiving placebo (least-squares mean changes from baseline: -0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively). Secondary: Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily met the criteria for an ACR20 response at all visits through month three (P≤0.05 for all visits, except P<0.0001 for 10 mg group vs placebo at month three). Compared to placebo, significantly greater proportion of patients in the tofacitinib 5 mg twice daily group achieved ACR50 at all visits through month three (P≤0.05 at two week and one month visits and P<0.0001 at three month visit). Compared to placebo, significantly greater proportion of patients in the tofacitinib 10 mg twice daily group achieved the ACR50 at three month study visit (P<0.0001); however, responses at two week and at one month visits were not significantly different (P values not reported). Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR70 at one month and three months visits (P≤0.05 for all visits, except P<0.001 for 5 mg group vs placebo at month three). The responses between both active treatment groups and placebo at two week visit were not significantly different (P values not reported). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 10 mg twice daily at all visits through month three (P≤0.05 for all comparisons, except P<0.0001 at month three). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were also observed at three month visit in patients receiving tofacitinib 5 mg twice daily (P<0.0001); however, the changes at two week and one month visits were not significantly different (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, changes from baseline in DAS28-4(ESR) were greater in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P=0.01 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater changes from baseline in DAS28-3(CRP) were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P<0.0001 for all comparisons). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three (P=0.0496 and P=0.0105, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) <2.6 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three (P≤0.05 and P<0.0001, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) ≤3.2 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month three were greater in tofacitinib 5 and 10 mg twice daily treatment groups than in those receiving placebo (−27.2 and −25.0 vs −8.3; P<0.0001 for both comparisons; P values not reported for all other visits). Improvements in FACIT-F at month three were greater in patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				tofacitinib 5 and 10 mg twice daily than in those receiving placebo (6.3 and 4.6 vs 1.1; P<0·0001 and P=0.0043, respectively; P values not reported for all other visits).
Van der Heijde et al[117] (ORAL Scan) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 mg or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving stable doses of	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and evidence of ≥3 joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs (if radiographic evidence of joint erosions was unavailable, presence of IgM rheumatoid factor positivity or antibodies to cyclic citrullinated peptide).	N=797 12 month	Primary: ACR20 response rate at month six, mean change from baseline in mTSS at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, DAS28-4(ESR) at all visits, changes from baseline in the ACR code disease activity measures at month six, rates of nonprogressors (≤0.5 unit change from baseline in mTSS or erosion score) at months	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (51.5 and 61.8% vs 25.3%; P=0.0001 for both comparisons). The least squares mean changes in mTSS at month six were 0.12 and 0.06 for patients receiving tofacitinib 5 and 10 mg twice daily, respectively, vs 0.47 for placebo (P=0.0792 and P≤0.05, respectively). The least squares mean changes in the HAQ-DI score at month three for tofacitinib at 5 and 10 mg twice daily were -0.40 and -0.54, respectively, vs -0.15 for placebo (P value not reported and P<0.0001, respectively). Proportions of patients achieving DAS28-ESR <2.6 at month six were 7.2% and 16.0% for tofacitinib at 5 and 10 mg twice daily, respectively, vs 1.6% for placebo (P value not reported and P<0.0001, respectively). Secondary: Compared to placebo at month six, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR50 (32.4 and 43.7 vs 8.4%; P<0.0001 for both comparisons) and ACR70 (14.6 and 22.3 vs 1.3%; P<0.0001 for both comparisons). At month 12, ACR20, ACR50, and ACR70 response rates were 48.5, 32.7, and 18.8%, respectively, for tofacitinib 5 mg and 57.0, 41.1, and 27.5%, respectively, for tofacitinib 10 mg. At month 12, the proportions of patients with DAS28-ESR <2.6 were 10.6 and 15.2% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively. At month six, the proportions of patients with DAS28-ESR ≤3.2 were 14.3 and 28.4% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively, compared to 3.1% of patients receiving placebo (P<0.0001 for both comparisons). At month 12, the rates of DAS28-ESR <3.2 for patients receiving tofacitinib at 5 and 10 mg twice daily increased

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MTX (15 to 25 mg weekly or <15 mg if there were safety issues at higher doses) for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) and NSAIDs were permitted. Prior use of biologic or nonbiologic DMARDs was permitted.			six, 12, and 24, changes from baseline in mTSS (at months 12 and 24), changes from baseline in erosion score and JSN score (at months six, 12, and 24), change from baseline in HAQ-DI score, the FACIT-F, and the patient's assessment of arthritis pain	to 23.4 and 30.7%, respectively. At month six, least squares mean changes from baseline in DAS28-ESR were greater for tofacitinib 5 and 10 mg twice daily compared to placebo (-2.1 and -2.5 vs -1.3; P<0.0001 for both comparisons); at month 12, least squares mean changes from baseline in DAS28-ESR were -2.3 and -2.5 for tofacitinib 5 and 10 mg twice daily, respectively. Compared to placebo a month six, statistically significant improvements from baseline were observed in all ACR core components in both tofacitinib 5 and 10 mg twice daily groups, including improvements in tender or painful joint count (P≤0.05 and P<0.01, respectively), swollen joint count (P<0.01 and P<0.0001, respectively), CRP (P<0.0001 for both comparisons), patient's global assessment of disease activity (P<0.0001 for both comparisons), physician's global assessment of disease activity (P<0.0001 for both comparisons), patient's assessment of pain (P<0.01 and P<0.0001, respectively), and HAQ-DI (P<0.0001 for both comparisons). The proportion of patients with no radiographic progression (≤0.5 unit increase from baseline in mTSS) at months six and 12 was similar in both tofacitinib treatment groups and significantly greater than in the placebo treatment group (P≤0.05 for both). At month six, the proportion of patients with no progression in erosion score (≤0.5 unit increase from baseline) was numerically greater, but not statistically significantly different, in the tofacitinib treatment groups compared to the placebo-treated group (P>0.05). The proportion of patients with no progression in erosion score at month 12 was significantly greater in both tofacitinib treatment groups compared to the placebo-treated group (P≤0.05). The plots of changes from baseline in mTSS, JSN score, and erosion score at months six and 12 for both tofacitinib-treated groups were very similar and were different from the plot for the placebo-treated group (P values not reported). Compared to placebo, greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits (P<0.001 for all comparisons, except P<0.01 for tofacitinib

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				5 mg vs placebo at one month visit). Improvements in FACIT-F from baseline to month six were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (5.6 and 6.9 vs 2.1; P<0.001 and P<0.0001, respectively; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month six were greater in 5 and 10 mg twice daily treatment groups than in those receiving placebo (-26.4 and -29.7 vs -15.70; P<0.01 and P<0.0001, respectively; P values not reported for all other visits).
Kremer et al[118] (ORAL Sync) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 or 10 mg twice daily.	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥4 tender or painful joints [68 joint count] and ≥4 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response to ≥1 stably dosed nonbiologic or biologic DMARDs	N=792 12 month	Primary: ACR20 response rate at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR), and FACIT-F score over time	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.44 and -0.53 vs -0.16; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). Secondary: Over time, statistically significant response rates were observed for ACR20 and ACR50 by week two in both tofacitinib groups compared to placebo (P≤0.001 for all comparisons) and for ACR70 by week two in the tofacitinib 10 mg group (P≤0.05 at week two and P≤0.001 at all visits thereafter) and one month in the tofacitinib 5 mg group (P≤0.001 for all comparisons). Mean treatment differences in changes from baseline in HAQ-DI, DAS28-4(ESR), and FACIT-F response rates for both tofacitinib groups compared to placebo were statistically significant over time (P≤0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving ≥1 nonbiologic DMARDs. Patients receiving MTX ≤25 mg weekly required ≥4 months of therapy at a stable dose for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) were permitted.				
He et al[119] Tofacitinib 1, 3, 5, 10, or 15 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo	MA, SR RCTs including patients ≥18 years of age with a diagnosis of RA	N=3,791 (8 trials) 12 to 24 weeks	Primary: ACR20 and ACR50 response rate at month three and six Secondary: Incidence of infections, immunological or hematological adverse events, incidence of withdrawal from the trials, changes in neutrophil	Primary: At month three, the differences in ACR20 response rates between tofacitinib 1 mg twice daily and placebo groups did not reach statistical significance (RR, 1.83; 95% CI, 1.00 to 3.32). Greater proportions of patients receiving tofacitinib 3 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.20 to 4.04). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.58 to 3.07) and (RR, 2.38; 95% CI, 1.81 to 3.14), respectively. The effect was maintained at month six for both 5 mg twice daily (RR, 1.94; 95% CI, 1.55 to 2.44) and 10 mg twice daily (RR, 2.20; 95% CI, 1.76 to 2.75) treatment groups. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily

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			count, hemoglobin and serum creatinine levels, incidence of ALT and AST more than one times upper limit of the normal range, and mean percentage changes of LDL and HDL	met the criteria for an ACR50 response at month three than those receiving placebo (RR, 2.91; 95% CI, 2.03 to 4.16) and (RR, 3.32; 95% CI, 2.33 to 4.72), respectively. Greater proportions of patients receiving tofacitinib 15 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.29; 95% CI, 1.19 to 4.41). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving adalimumab (RR, 1.65; 95% CI, 1.08 to 2.53) and (RR, 1.97; 95% CI, 1.32 to 2.92), respectively. At month six, there were no significant differences in ACR20 response rates in patients receiving tofacitinib vs adalimumab (P values not reported). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving adalimumab (RR, 1.95; 95% CI, 1.00 to 3.80) and (RR, 2.35; 95% CI, 1.26 to 4.38), respectively. Secondary: Compared to placebo, there were no statistically significant differences in the incidences of infections, neutropenia and withdrawal due to adverse events in patients receiving tofacitinib (P values not reported). However, significantly fewer patients withdrew from tofacitinib than placebo (RR, 0.60; 95% CI, 0.45 to 0.78). The withdrawal rate due to lack of efficacy was significantly lower in the patients receiving tofacitinib than placebo (RR, 0.18; 95% CI, 0.09 to 0.35). Compared to placebo, the mean neutrophil count significantly declined in patients receiving tofacitinib (P value not reported). The mean hemoglobin level was not significantly different in tofacitinib group compared to placebo group (P value not reported). Compared to placebo, the mean serum creatinine was found to be significantly higher for tofacitinib 10 mg twice daily (P value not reported). The risk ratios of the mean changes of ALT or AST exceeding one times upper limit of the normal range were statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant (P values not reported). Compared to placebo, the mean percentage change of HDL and LDL was significant higher in patients receiving tofacitinib (P values not reported).
Berhan et al[120] Tofacitinib 3, 5, 10, or 15 mg twice daily (with or without MTX) vs placebo	MA DB, RCT including patients with a diagnosis of active RA for ≥6 months who were on at least one of nonbiologic or biologic DMARD	N=3,260 (8 trials) 12 to 24 weeks	Primary: ACR20 response rate, change from baseline in HAQ-DI score Secondary: Safety	Primary: Compared to placebo, tofacitinib treated patients had higher odds of meeting the criteria for an ACR20 response (OR, 4.15; 95% CI, 3.23 to 5.32). With the exception of one study, ACR20 response rates for patients receiving tofacitinib dosages ≥3 mg twice daily was significantly greater than those who received placebo (P value not reported). The subgroup odds ratios in the subgroups of tofacitinib 10 mg twice daily (OR, 4.3; 95% CI, 3.023 to 6.376) and 15 mg twice daily (OR, 6.06; 95% CI, 2.383 to 15.428) was higher than 3 mg twice daily (OR, 4.06; 95% CI, 1.340 to 12.305) and 5 mg twice daily (OR, 3.55; 95% CI, 2.435 to 5.169) treated groups. A statistically significant improvement in HAQ-DI scores were seen in patients receiving tofacitinib than placebo treated patients (SMD, −0.62; 95% CI, -0.735 to -0.506). Patients treated with tofacitinib dosages ≥5 mg twice daily have shown a statistically significant reduction in HAQ-DI scores (P value not reported). Secondary: The proportion of infections was higher in the tofacitinib treated groups than in the placebo groups (SMD, 1.96, 95% CI, 1.428 to 2.676). In contrast to the subgroups of tofacitinib 10 mg (SMD, 3.08; 95% CI, 1.694 to 5.570) and 15 mg (SMD, 1.97; 95% CI, 1.088 to 3.558), the proportion of infections in the subgroups of tofacitinib 3 mg (SMD, 1.64; 95% CI, 0.858 to 3.142) and 5 mg (SMD, 1.52; 95% CI, 0.644 to 3.594) were not significantly different from placebo. There were significant increases from baseline in tofacitinib treated groups in the mean hemoglobin level (SMD, 0.11; 95% CI, 0.130 to 0.210), mean serum creatinine (SMD, 0.24; 95% CI, 0.112 to 0.372), HDL (SMD, 1.01;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95% CI, 0.332 to 1.682), and LDL (SMD, 0.95; 95% CI, 0.337 to 1.555). A significant number of patients with ALT (OR, 1.7; 95% CI, 1.29 to 2.46) and AST (OR, 2.19; 95% CI, 1.50 to 3.19) exceeding one times upper limit of the normal range were reported among tofacitinib treated groups. The rate of tofacitinib discontinuation due to adverse events was not significantly different from placebo (SMD, 1.27; 95% CI, 0.949 to 1.700).
Ulcerative Colitis				
Rutgeerts et al[121] (ACT 1 and ACT 2) Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks vs placebo	DB, MC, PC, RCT Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12) and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine (ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-aminosalicylates (ACT 2)	N=364 (ACT 1) N=364 (ACT 2) 30 weeks (ACT 2) 54 weeks (ACT1)	Primary: Clinical response at week eight Secondary: Clinical response or clinical remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal healing at weeks eight and 30 (ACT 1 and ACT 2) and week 54 (ACT 1), and clinical response at week eight in patients with a history of corticosteroid refractory disease	Primary: At week eight in ACT 1, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (69.4 and 61.5%) compared to the placebo group (37.2%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (64.5 and 69.2%) compared to the placebo group (29.3%; P<0.001 for both). Secondary: In ACT 1, the proportion of patients with clinical response at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (52.1 and 50.8%) compared to the placebo group (29.8%; P<0.001 and P=0.002, respectively). In ACT 2 at week 30, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (47.1 and 60.0%) compared to the placebo group (26.0%; P<0.001 for both). In ACT 1 at week 54, the clinical response rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 44.3 vs 19.8%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (38.8 and 32.0%) compared to the placebo group (14.9%; P<0.001 and P=0.002, respectively). In ACT 2 at week eight, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 27.5%) compared to the placebo group (5.7%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				36.9%) compared to the placebo group (15.7%; P=0.001 and P<0.001, respectively). In ACT 2 at week 30, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (25.6 and 35.8%) compared to the placebo group (10.6%; P=0.003 and P<0.001, respectively). In ACT 1 at week 54, the clinical remission rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (34.7 and 34.4 vs 16.5%; P=0.001 for both). In ACT 1 at week eight, the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (77.4 and 67.7 vs 35.3%; P<0.001 and P=0.010, respectively). In ACT 2 at week eight when compared to the placebo group (37.5%), the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 10 mg/kg (65.5%; P=0.011), but not 5 mg/kg group (63.3%; P=0.053). In ACT 1, the proportion of patients with mucosal healing at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (62.0 and 59.0%) compared to the placebo group (33.9%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (60.3 and 61.7%) compared to the placebo group (30.9%; P<0.001 for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (50.4 and 49.2%) compared to the placebo group (24.8; P<0.001 for both). In ACT 2 at week 30, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (46.3 and 56.7%) compared to the placebo group (30.1%; P=0.009 and P<0.001, respectively). In ACT 1 at week 54, the mucosal healing rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 46.7 vs 18.2%; P=0.001 for both).
Hyams et al[122] (abstract) Infliximab 5 mg/kg at	MC, OL, R Patients 6 to 17 years of age with	N=60 54 weeks	Primary: Clinical response at week eight (decrease from	Primary: At week eight, 73.3% of patients had a clinical response with infliximab (95% CI, 62.1 to 84.5). Clinical remission by Mayo score was achieved in 33.3% of patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks 0, 2 and 6 then 5 mg/kg every 8 weeks through week 46 vs infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 12 weeks through week 42	active ulcerative colitis (Mayo score 6 to 12, including endoscopic subscore ≥2) who failed to respond to or tolerate treatment with mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylates		baseline in Mayo score ≥30% and ≥3 points, with a decrease in rectal bleeding subscore of 0/1) compared to baseline Secondary: Not reported	At week 54, there was a greater proportion of patients achieving clinical remission with infliximab 5 mg/kg every eight weeks compared to infliximab 5 mg/kg every 12 weeks; though, this difference was not significant (P=0.146). Secondary: Not reported
Reinisch et al[123] Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA 160/80 group) vs Adalimumab 80 mg at week 0, 40 mg at weeks 2, 4 and 6 (ADA 80/40 group) vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis, (Mayo score of 6 to 12 with an endoscopy subscore of 2–3) who failed concurrent and stable treatment with oral corticosteroids and/or immunomodulators	N=390 8 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) compared to baseline Secondary: Proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or	Primary: At week eight, 18.5% of patients in the ADA 160/80 group (P=0.031 vs placebo) and 10.0% in the ADA 80/40 group (P=0.833 vs placebo) were in remission compared to placebo (9.2%). Secondary: At week eight, 54.6% of patients in the ADA 160/80 group (P vs placebo not reported), 51.5% in the ADA 80/40 group (P vs placebo not reported) and 44.6% in the placebo group had a clinical response. At week eight, 46.9% of patients in the ADA 160/80 group (P vs placebo not reported), 37.7% in the ADA 80/40 group (P vs placebo not reported) and 41.5% in the placebo group had mucosal healing. At week eight, 77.7% of patients in the ADA 160/80 group (P=0.038 vs placebo), 70.0% in the ADA 80/40 group (P vs placebo not reported) and 66.2% in the placebo group had a rectal bleeding subscore of ≤ 1. At week eight, 60.0% of patients in the ADA 160/80 group (P=0.035 vs placebo), 53.8% in the ADA 80/40 group (P vs placebo not reported) and 46.9% in the placebo group had a PGA subscore of ≤ 1 At week eight, 48.5% of patients in the ADA 160/80 group (P vs placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	not reported), 36.2% in the ADA 80/40 group (P vs placebo not reported) and 37.7% in the placebo group had a stool frequency subscore of ≤ 1
Sandborn et al[124] Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every other week vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis >3 months, (Mayo score of 6 to 12 with an endoscopy subscore >2) despite concurrent treatment with oral corticosteroids and/or azathioprine or 6-mercaptopurine.	N=494 52 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) at week 8 and 52 Secondary: Proportion of patients in remission at week 8 and 52; proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or	Primary: At week 8, 16.5% of patients in the adalimumab group were in remission compared to placebo (9.3%; P=0.019; 95% CI, 1.2 to 12.9). At week 52, 17.3% of patients in the adalimumab group were in remission compared to placebo (8.5%; P=0.004; 95% CI, 2.8 to 14.5). Secondary: At week 8 and 52, 8.5% of patients in the adalimumab group (P=0.47 vs placebo) and 4.1% in the placebo group were in sustained remission. At week 8, 50.4% of patients in the adalimumab group (P<0.001 vs placebo) and 34.6% in the placebo group had a clinical response. At week 52, 30.2% of patients in the adalimumab group and 18.3% in the placebo group had a clinical response. (P=0.002). At week 8 and 52, 23.8% of patients in the adalimumab group (P<0.001 vs placebo) and 12.2% in the placebo group were in sustained remission. Mucosal healing was achieved at week 8 in 41.1% of patients in the adalimumab group and 31.7% of patients receiving placebo (P=0.032). At week 52, 25% of patients in the adalimumab group and 15.4% of patients receiving placebo (P=0.009) had mucosal healing. Mucosal healing at week 8 and 52, 18.5% of patients in the adalimumab group (P<0.013 vs placebo)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients who discontinued corticosteroid; proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	and 10.6% in the placebo group. At week 8, 46.0% of patients in the adalimumab group (P=0.028 vs placebo) and 37.4% in the placebo group had a PGA subscore of ≤ 1. At week 8, 37.9% of patients in the adalimumab group (P=0.058 vs placebo) and 28.5% in the placebo group had a stool frequency subscore of ≤ 1. At week 8, 70.2% of patients in the adalimumab group (P=0.006 vs placebo) and 58.1% in the placebo group had a rectal bleeding subscore of ≤ 1. Proportion of patients that discontinued corticosteroid use before week 52 and achieved remission at week 52 was13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group. Proportion of patients that for ≥90 days before week 52 and achieved remission at week 52 was 13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group.
Sandborn et al[125] (PURSUIT-SC) Phase 2 (dose-finding): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2	2 DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-	Phase 2 N=169 Phase 3 N=774 6 weeks	Primary: Phase 2: Change in Mayo score from baseline to week six Phase 3: Clinical response at week six defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a rectal bleeding subscore of 0 to	Primary: In phase 2, median changes from baseline in the Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group (P=0.038, P=0.332 and P=0.038, respectively). In phase 3, the proportion of patients with clinical response at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons). Secondary: In phase 3, the proportion of patients in clinical remission at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (17.8 and 17.9 vs 6.4%; P≤0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(200 mg/100 mg) vs golimumab 100 mg subcutaneously at week 0 and 50 mg subcutaneously at week 2 (100 mg/50 mg) vs placebo Phase 3 (dose-confirming): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs placebo Patients were required to	mercaptopurine) or corticosteroid dependent		1 or a decrease from baseline in the rectal bleeding subscore ≥1 Secondary: Phase 2: Not reported Phase 3: Clinical remission defined as Mayo score ≤2 points, with no individual subscore >1, mucosal healing defined as a Mayo endoscopy subscore of 0 or 1, and IBDQ change from baseline, all at week 6	In phase 3, the proportion of patients achieving mucosal healing at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (42.3 and 45.1 vs 28.7%; P=0.0014 and P≤0.0001, respectively). In phase 3, the improvements from baseline in IBDQ score at week six were greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (mean 27.0±33.72 and 26.9±34.28 vs 14.8±31.25%; P<0.0001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX.				
Sandborn et al[126] (PURSUIT-M) Golimumab 50 mg SC every four weeks vs golimumab 100 mg SC every four weeks vs placebo Patients were required to maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX. After induction, patients in clinical response and receiving concomitant corticosteroids at baseline were required to	DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent who completed PURSUIT-IV or PURSUIT-SC studies	N=464 54 weeks	Primary: Clinical response through week 54 among golimumab-induction responders Secondary: Clinical remission at weeks 30 and 54, mucosal healing at weeks 30 and 54, clinical remission at both weeks 30 and 54 among patients who had clinical remission at baseline, and corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at baseline	Primary: The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Secondary: The proportion of patients in clinical remission at both weeks 30 and 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (27.8 and 23.2 vs 15.6%; P=0.004 and P=0.091, respectively); however, the difference was only statistically significant for golimumab 100 mg treatment group. The proportion of patients with mucosal healing at both weeks 30 and 54 was significantly greater for patients receiving golimumab 100 mg compared to placebo (42.4 vs 26.6%; P=0.002). The mucosal healing rate for patients receiving golimumab 50 mg was 41.7% (P value not reported). Greater proportions of patients who received golimumab 100 mg or 50 mg maintained clinical remission compared to placebo (40.4 and 36.5 vs 24.1%; P=0.073 and P=0.365, respectively); however, the differences were not statistically significant. Greater proportions of patients who received golimumab 100 mg or 50 mg were in corticosteroid-free clinical remission at week 54 compared to placebo (22.9 and 27.8 vs 18.4%; P=0.464 and P=0.299, respectively) ; however, the differences were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
taper corticosteroids (for dose of >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week; for dose of ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week) beginning at baseline.				
Feagan et al[127] (GEMINI-1) Vedolizumab 300 mg intravenous at weeks 0 and 2 (induction) followed by vedolizumab 300 mg intravenous every four or eight weeks (maintenance) vs placebo Patients could continue to take mesalamine, ≤30 mg of prednisone (or equivalent) per day or immunosuppressive agents at stable doses.	DB, MC, PC, RCT Patients 18 to 80 years of age with ulcerative colitis (Mayo Clinic score of 6 to 12) with a sigmoidoscopy subscore of ≥2 and disease that extended ≥15 cm from the anal verge. All patients had a lack of response or unacceptable adverse events with ≥1 glucocorticoid, immuno-suppresive agent or TNF antagonist.	N=895 52 weeks	Primary: Induction Clinical response at week six Maintenance Clinical remission at week 52 Secondary: Induction Clinical remission at week six Maintenance Durable clinical response (response at weeks 6 and 52), durable clinical remission (remission at weeks 6 and 52), glucocorticoid-free remission at week 52 in patients receiving	Primary: Induction In the double-blind cohort, clinical response at week six was achieved in 47.1 and 25.5% of patients treated with vedolizumab and placebo, respectively (95% CI, 11.6 to 31.7; P<0.001). In the open-label vedolizumab cohort, 44.3% achieved a clinical response and 19.2% achieved clinical remission. Maintenance A significantly greater proportion of patients treated with vedolizumab every four or eight weeks achieved clinical remission at week 52 compared to placebo (44.8 and 41.8% vs 15.9% respectively; 95% CI, 14.9 to 37.2; P<0.001). Secondary: Induction Clinical remission was achieved in 16.9 and 5.4% of patients treated with vedolizumab and placebo, respectively (P=0.001). Maintenance Rates of durable clinical response, durable clinical remission, mucosal healing and glucocorticoid-free remission were higher among patients in the vedolizumab group compared to placebo. There was no difference observed between vedolizumab regimens. In addition, concurrent treatment with glucocorticoids or immunosuppressants or previous treatment with TNF antagonists did not substantively affect the efficacy of vedolizumab.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			glucocorticoids at baseline	
Neonatal-Onset Multisystem Inflammatory Disease				
Sibley et al[128] Anakinra 1 to 5 mg/kg/day	OL Patients with NOMID with at least 2 of the following clinical manifestations: urticaria-like rash, CNS involvement (papilledema, cerebrospinal fluid CSF pleocytosis, or sensorineural hearing loss), or epiphyseal and/or patellar overgrowth on radiographs	N=43 60 months	Primary: Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, CHAQ scores, parent's/patient's pain scores, and inflammatory markers (CRP level, ESR, and SAA) Secondary: Reduction or elimination CNS organ inflammation and damage and the absence of leptomeningeal enhancement on MRI, and in the eyes as the absence of eye inflammation on examination. Other endpoints include improvements in	Primary: Scores for daily diaries, parent's and physician's global assessment of disease activity, parent's assessment of pain, and C-HAQ decreased significantly from baseline to 36 months (P=0.0016 for C-HAQ and P<0.001 for all other assessments). These parameters did not show significant change from month 36 to month 60. Significant decreases in inflammatory markers (CRP level, ESR, and SAA) were observed from baseline to 12 months and from baseline to 36 months (all P<0.001). These parameters did not show significant change from month 36 to month 60. Secondary: CNS inflammation, including CSF leukocyte count and elevated opening pressure, decreased significantly at the study end points 36 and 60 months compared to baseline (P=0.0026 and P=0.0076, respectively, for CSF WBC count and P=0.0012 and P<0.001, respectively, for opening pressure). These parameters did not show significant change from month 36 to month 60. The number of patients with leptomeningeal enhancement decreased to three of 26 patients at 36 months (P=0.039) and one of 20 patients at 60 months (P=0.016). Improvement in hearing occurred in 30% of ears, and progression of hearing loss was halted in the majority of the patients. Visual acuity and peripheral vision improved or stabilized in most patients over five years. One patient had worsening of visual acuity, and two other patients had worsening of peripheral vision in the absence of clinically detectable intraocular inflammation. (Note-All three of these patients had severely atrophic nerves at baseline).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hearing, vision, bone lesions and growth, and safety.	Bony overgrowth was present in 10 of 26 patients, and during the study period the volume of the bony lesions increased significantly; however, no new bone lesions developed in patients while they were receiving anakinra therapy. No dose-limiting toxicity was observed during the study. Upper respiratory infections (58 to 62%), rash (27 to 32%), malaise (17 to 19%) gastroenteritis (11 to 12%), and urinary tract infections (4 to 12%), nausea/vomiting (10 to 11%) injection site reactions (1 to 10%) were frequently observed.

*Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=alanine transaminase, AS=ankylosing spondylitis, ASAS=Assessment of Spondyloarthritis International Society criteria, AST=aspartate aminotransferase, AUC=area under the curve, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CDAI-100=Crohn's disease activity index decrease of ≥100 points from baseline, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=clinical remission, CR-100=clinical remission 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAS 28=Disease Activity Score in 28 joints, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL=electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI=Harvey-Bradshaw index, HCQ=hydroxychloroquine, HDL=high density lipoprotein, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JIA=juvenile idiopathic arthritis, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, LDL=low density lipoprotein, MCR=major clinical response, MRE=magnetic resonance enterography, MRI=magnetic resonance imaging, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA=serum amyloid A, SMD=standardized mean differences, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Special Populations

Table 5. Special Populations[3-14]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Abatacept	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children six years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Adalimumab	No evidence of overall differences in efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children four years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Anakinra	No evidence of overall differences in efficacy observed between elderly and younger	Renal dose adjustment is required; for creatinine	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	adult patients. Approved for use in children for the treatment of neonatal onset multisystem inflammatory disease. Safety and efficacy in the pediatric population have not been established for other indications.	clearances <30 mL/ minute, a dose of 100 mg for rheumatoid arthritis or 1 to 2 mg/kg for neonatal onset multisystem inflammatory disease every other day is recommend-ed.			
Certolizumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Etanercept	No evidence of overall differences in efficacy observed between elderly and younger adult patients. Approved for use in children two years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Golimumab	Simponi®: No evidence of overall differences in efficacy observed between elderly and younger adult patients. Safety and efficacy in the pediatric population have not been established. Simponi Aria®: Safety and efficacy in	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.				
Infliximab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients for the treatment of rheumatoid arthritis and psoriasis. Safety and efficacy in elderly patients have not been established for the treatment of ankylosing spondylitis, Crohn's disease, psoriatic arthritis or ulcerative colitis. Approved for use in children six years of age and older for the treatment of Crohn's disease and ulcerative colitis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Tocilizumab	Frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children two years of age and older for the treatment of systemic and polyarticular juvenile idiopathic arthritis. Safety and efficacy in	No dosage adjustment required in mild renal impairment. Not studied in patients with moderate to severe renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	the pediatric population have not been established for other indications.				
Tofacitinib	Frequency of serious infection and malignancy was higher in patients ≥65 years of age. Safety and efficacy in the pediatric population have not been established.	Renal dose adjustment is required; dose reduction to 5 mg once daily is recommended in moderate to severe renal impairment; not studied in patients with creatinine clearance <40 mL/minute.	Hepatic dose adjustment is required; dose reduction to 5 mg once daily is recommended in moderate hepatic impairment; not studied in patients with severe hepatic impairment.	C	Unknown
Ustekinumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Vedolizumab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Adverse Drug Events

The anti-tumor necrosis factor-α agents (adalimumab, certolizumab, etanercept, golimumab and infliximab) share similar adverse event profiles including risk of reactivation of latent tuberculosis, severe infection, heart failure, lupus-like syndrome, and lymphoma. Table 6 highlights the adverse drug events with a focus on those noted in ≥5% of study populations.

Table 6. Adverse Drug Events (%)[3-14,36,37]

Adverse Event	Abatacept	Adalimumab	Anakinra*	Certolizumab	Etanercept	Golimumab†	Infliximab	Tocilizumab	Tofacitinib	Ustekin-umab	Vedo-lizumab
Gastrointestinal											-
Abdominal pain	-	7	5	-	5 to 10	-	12	-	-	-	-
Diarrhea	-	-	7	-	8 to 16	-	12	-	-	-	-
Dyspepsia	6	-	-	-	4 to 11	-	10	-	-	-	-
Nausea	≥10	9	8	-	9 to 15	-	21	-	-	-	9
Vomiting	-	-	14‡	-	3 to 5	-	-	-	-	-	-
Laboratory Tests											-
Abnormal test	-	8	-	-	-	-	-	3 to 6	-	-	-
Alkaline phosphatase increased	-	5	-	-	-	-	-	-	-	-	-
Hematuria	-	5	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	6	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-	-	-	-
Respiratory											-
Bronchitis	5 to 13	-	-	3	-	-	10	-	-	-	-
Coughing	8	-	-	-	5 to 6	-	12	-	-	-	5
Flu syndrome	-	7	-	-	-	-	14	-	-	-	-
Nasopharyngitis	12	-	-	5	-	-	-	4 to 7	-	7 to 8	13
Non-upper respiratory infection	-	-	-	-	21 to 54	-	-	-	-	-	-
Pharyngitis	-	-	11.6‡	3	6 to 7	-	-	-	-	-	-
Respiratory disorder	-	-	-	-	5	-	-	-	-	-	-
Rhinitis	-	-	-	-	12 to 16	-	-	-	-	-	-
Sinusitis	5 to 13	11	7	-	3 to 5	-	14	-	-	-	-
Upper respiratory infection	≥10	17	14	6	38 to 65	13§ to 16	32	6 to 8	-	4 to 5	7
Skin											-
Pruritus	-	-	-	-	-	-	7	-	-	-	-
Rash	-	12	-	3	3 to 13	-	10	-	-	-	-
Other											-
Accidental injury	-	10	-	-	-	-	-	-	-	-	-
Alopecia	-	-	-	-	1 to 6	-	-	-	-	-	-
Arthralgia	-	-	6, 11.6‡	-	-	-	-	-	-	-	12
Asthenia	-	-	-	-	5 to 11	-	-	-	-	-	-
Back pain	7	6	-	4	-	-	8	-	-	-	-
Body pain	-	-	-	-	-	-	8	-	-	-	-

Adverse Event	Abatacept	Adalimumab	Anakinra*	Certolizumab	Etanercept	Golimumab†	Infliximab	Tocilizumab	Tofacitinib	Ustekin-umab	Vedo-lizumab
Dizziness	9	-	-	-	7 to 8	-	-	-	-	-	-
Fatigue	-	-	-	3	-	-	9	-	-	-	6
Fever	-	-	11.6‡	3	2 to 3	-	7	-	-	-	-
Flu like symptoms	-	-	6	-	-	-	-	-	-	-	-
Headache	18	12	12, 14‡	5	17 to 24	-	18	5 to 7	-	5	12
Hypertension	7	5	-	5	-	-	7	4 to 6	-	-	-
Infections (overall)	-	-	-	-	-	-	-	20	-	-	-
Injection site pain	-	12	-	-	-	-	-	-	-	-	-
Injection site reaction	-	8	16‡, 71	-	37 to 43	6	-	7.1‖ to 10.1‖	-	-	-
Moniliasis	-	-	-	-	-	-	5	-	-	-	-
Mouth ulcer	-	-	-	-	2 to 6	-	-	-	-	-	-
Peripheral edema	-	-	-	-	2 to 8	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	-	-	-	-	9
Urinary tract infection	6	8	-	-	-	-	8	-	-	-	-
Viral infection	-	-	-	-	-	5	-	-	-	-	-
Worsening of rheumatoid arthritis	-	-	19	-	-	-	-	-	-	-	-

-Event not reported or incidence <5%.
*Unless otherwise specified, adverse reaction observed in patients treated for rheumatoid arthritis.
†With or without disease modifying antirheumatic agents. Unless otherwise specified, adverse reaction observed in patients treated with subcutaneous formulation.
‡Neonatal-onset multisystem inflammatory disease during the first six months of therapy.
§Intravenous formulation (Simponi Aria®) only.
‖Subcutaneous formulation only.

Contraindications/Precautions

The immunomodulators are contraindicated in patients with a known hypersensitivity to any of the agents or to any component of the individual products.[3-12] Patients treated concomitantly with abatacept or anakinra and anti-tumor necrosis factor (TNF) agents experienced more infections than patients treated with TNF agents alone. There was no significant increase in efficacy with combination therapy; therefore, concomitant administration of abatacept or anakinra and TNF agents is not recommended.[3-8,10,12]

Serious and sometimes fatal infections have been reported with abatacept. Live vaccines should not be given concurrently or within three months of discontinuation with abatacept. Patients with chronic pulmonary obstructive disease treated with abatacept developed adverse reactions associated with worsening of their respiratory symptoms. Due to the inhibition of T-cell activation by abatacept, host defenses against infections and malignancies may be affected.[12]

Anakinra is contraindicated in patients with a known hypersensitivity to *Escherichia coli*-derived proteins. Serious infections have been associated with anakinra and should not be initiated in patients with active infections. In rheumatoid arthritis, discontinue use if serious infection develops. In neonatal-onset multisystem inflammatory disease (NOMID) patients, the risk of a NOMID flare when discontinuing anakinra treatment should be weighed against the potential risk of continued treatment. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have occurred with anakinra. Live vaccines are not recommended to be given concurrently with anakinra. Combination therapy with a TNF blocking agent is not recommended. Decreases in neutrophil count have been reported with anakinra.[9]

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. Additionally, viral reactivation, gastrointestinal perforations, and increased lipid levels were reported with tocilizumab. The impact of tocilizumab on demyelinating disorders is not known, although multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were rarely reported in clinical trials. Caution should be used when considering tocilizumab in patients with preexisting or recent onset demyelinating disorders. Treatment is not recommended in patients with an increased incidence of neutropenia, reduced platelets, increased transaminase levels, or in patients with active hepatic disease or hepatic impairment. Hypersensitivity reactions, including anaphylaxis reactions and death, have been reported with tocilizumab. Live vaccines are not recommended to be given concurrently with tocilizumab.[10]

Ustekinumab is associated with an increased risk of infections and reactivation of latent infections. In addition, serious infection requiring hospitalization have been reported in clinical trials, including diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with ustekinumab. Ustekinumab may increase the risk of malignancies. Live vaccines are not recommended to be given concurrently with ustekinumab.[11]

Serious and sometimes fatal infections have been reported in patients receiving tofacitinib, including pneumonia, cellulitis, herpes zoster, and urinary tract infection. Opportunistic infections included tuberculosis and other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, and cytomegalovirus. Some patients have presented with disseminated rather than localized disease and were often taking concomitant immunomodulating agents (e.g., methotrexate, corticosteroids). Treatment should not be initiated in patients with an active infection and should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. The risks and benefits of treatment should be considered prior to initiation in patients with chronic or recurrent infection, who have been exposed to tuberculosis, with a history of a serious opportunistic infection, who have resided or traveled in areas of endemic tuberculosis or mycoses or with underlying conditions that may predispose them to infection.[13]

In clinical trials, treatment with tofacitinib has resulted in viral reactivation, including cases of herpes virus reactivation. Screening for viral hepatitis should be performed before initiating tofacitinib.[13]

Malignancies were observed in clinical studies of tofacitinib. Risks and benefits of treatment should be considered prior to initiating therapy in patients with malignancy other than successfully treated non-melanoma skin cancer. Non-melanoma skin cancers have been reported in patients treated with tofacitinib. As such, periodic skin examination is recommended for patients at increased risk for skin cancer. Gastrointestinal perforation has been reported in clinical studies with tofacitinib; caution should be used in patients who may be at increased risk (e.g., history of diverticulitis). Treatment with tofacitinib is also associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Lymphocyte and neutrophil counts and hemoglobin level should be monitored at baseline and during treatment. Treatment with tofacitinib was associated with an increased incidence of neutropenia compared to placebo. As such, initiation of tofacitinib should be avoided in patients with a low neutrophil count. Treatment with tofacinib should be avoided in patients with a low hemoglobin level and treatment should be interrupted in patients who develop hemoglobin levels <8g/dL or whose hemoglobin level drops >2 g/dL on treatment. [13]

Treatment with tofacitinib is associated with an increased incidence of liver enzyme elevation compared to placebo, particularly with background disease modifying antirheumatic drug therapy. Monitoring of liver enzymes is recommended and treatment should be interrupted if drug-induced liver injury is suspected. [13]

Treatment with tofacitinib is associated with increases in lipid parameters including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Lipid parameters should be monitored approximately four to eight weeks following initiation of therapy.[13]

Patients should be brought up-to-date on vaccines in accordance with current vaccine guidelines prior to initiating tofacitinib.[13]

In clinical trials, hypersensitivity reactions occurred with vedolizumab, including a case of anaphylaxis in one patient. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing rash and increased blood pressure and heart rate have been observed. If serious allergic reactions or anaphylaxis occur, vedolizumab should be discontinued immediately and appropriate treatment should be initiated (e.g., epinephrine, antihistamines).[14]

Patients treated with vedolizumab are at increased risk for infection, with the most commonly reported infections in clinical trials involving the upper respiratory and nasal mucosa. Serious infections have also been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.[14]

Given that another integrin receptor antagonist had been associated with progressive multifocal leukoencephalopathy (PML), patients treated with vedolizumab in clinical trials were actively monitored for the development of PML. Although no cases of PML were identified over 24 months of exposure, the risk of PML cannot be ruled out.[14]

Treatment with vedolizumab has been associated with elevations of transaminase and/or bilirubin. vedolizumab should be discontinued in patients with jaundice or other signs of liver injury.[14]

Prior to initiating vedolizumab, patients should be brought up-to-date with all immunizations according to current guidelines. Although patients treated with vedolizumab may receive non-live vaccines, live vaccines should be administered only if the benefits outweigh the risks.[14]

Numerous precautions are associated with the TNF-blockers (adalimumab, certolizumab, etanercept, golimumab and infliximab), many of which are shared throughout the class and include:

- Infection, active or chronic (including localized), or history of recurrent infection; increased risk of developing a serious infection.
- Infections, serious (sepsis, tuberculosis, fungal, and other opportunistic infections); fatalities have been reported; discontinue if serious infection develops.

- Tuberculosis, history of latent or active; increased risk of developing infection; initiate treatment for latent tuberculosis before starting anti-TNF therapy.
- Tuberculosis, risk factors or potential exposure; infection should be ruled out prior to initiation of therapy.
- Central nervous system demyelinating disorder, preexisting or recent onset; risk for exacerbation.
- Close personal contact with person with active tuberculosis.
- Congestive heart failure; new-onset or worsening reported in patients with and without history.
- Hematologic abnormalities (e.g., pancytopenia, aplastic anemia) have been reported; discontinue if significant abnormalities develop.
- Hepatitis B virus carriers; risk of reactivation including after discontinuation of therapy, fatal outcomes have occurred; monitor for signs and symptoms of Hepatitis B virus infections during and for several months after adalimumab therapy and discontinue if Hepatitis B virus is reactivated.
- Live vaccine use or infectious agents such as live attenuated bacteria; not recommended.
- Malignancy; increased risk of lymphoma and possibly other malignancies such as breast, colon, prostate, lung, and melanoma.
- Lupus-like syndrome may occur secondary to autoantibodies[3-8]

Some of the immunomodulators are associated with boxed warnings, which are outlined below.

Black Box Warning for Adalimumab and Infliximab[3,8]

WARNING
Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with tumor necrosis factor blockers including Humira® and Remicade®. These cases have had a very aggressive disease course and have been fatal. All reported Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority was in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Humira® or Remicade® at or prior to diagnosis.

Black Box Warning for Tocilizumab[10]

WARNING
Serious Infections Patients treated with Actemra® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra® until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra® use and during therapy. Treatment for latent infection should be initiated prior to Actemra® use. • Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with Actemra® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra®, including the possible development of tuberculosis in patients who tested negative for infection prior to initiating therapy.

Black Box Warning for Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab[3-8]

WARNING

Serious Infections
Patients treated with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Cimzia®, Enbrel®, Humira®, Remicade® and Simponi® should be discontinued if a patient develops a serious infection or sepsis.
Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Cimzia®, Enbrel®, Remicade®, or Simponi® use and during therapy. Treatment for latent infection should be initiated prior to Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancy
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are members.

Black Box Warning for Tofacitinib[13]

WARNING

Serious Infections
Patients treated with Xeljanz® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Xeljanz® until the infection is controlled. Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease.
- Patients should be tested for latent tuberculosis before Xeljanz® use and during therapy.
- Treatment for latent infection should be initiated prior to Xeljanz® use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

WARNING

The risks and benefits of treatment with Xeljanz® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Xeljanz®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies
Lymphoma and other malignancies have been observed in patients treated with Xeljanz®. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz® and concomitant immunosuppressive medications.

Drug Interactions

Cytokines such as interleukin (IL)-6 have been shown to decrease the expression of CYP450 isoenzymes in patients with infections and inflammatory conditions such as rheumatoid arthritis. Inhibition of IL-6 signaling in rheumatoid arthritis patients treated with tocilizumab may restore CYP450 activities to normal levels which would have the potential to increase the metabolism of CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes (1A2, 2B6, 2C9, 2C19, 2D6, and 3A4). Upon initiation or discontinuation of tocilizumab it is recommended that therapeutic monitoring for any medication with a narrow therapeutic index be initiated and the dose of the medication be adjusted as needed.[10]

Table 7. Drug Interactions[37]

Generic Name	Interacting Medication or Disease	Potential Result
Abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, tocilizumab, ustekinumab	Live vaccines	Concomitant use may result in an increased risk of secondary transmission of infection by the live vaccine.
Adalimumab, anakinra, etanercept, golimumab, infliximab	Abatacept	Concurrent use may increase the risk of infections.
Adalimumab, certolizumab, etanercept, golimumab, infliximab	Anakinra	Concurrent use may increase the risk of infections.
Adalimumab, etanercept, infliximab	Rilonacept	Concurrent use may increase the risk of serious infections and neutropenia.
Anakinra	Etanercept	Concurrent use may increase the risk of serious infections and neutropenia.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing noncutaneous solid malignancies.
Infliximab	Tocilizumab	Concurrent use may increase immunosuppression and the risk of infections.
Tofacitinib	Biological DMARDs	Concurrent use may increase the risk of serious infections. Coadministration should be avoided.
Tofacitinib	CYP2C19 potent and CYP3A moderate inhibitors (e.g., fluconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.

Generic Name	Interacting Medication or Disease	Potential Result
Tofacitinib	CYP3A strong inhibitors (e.g., ketoconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inducers (e.g., rifampin)	Concurrent use may reduce tofacitinib concentrations, decreasing the clinical response. Coadminister with caution. Close clinical monitoring is warranted.
Tofacitinib	Immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus)	Concurrent use may increase the risk of added immunosuppression and serious infections. Coadministration of tofacitinib with potent immunosuppressants should be avoided.

DMARD=disease-modifying antirheumatic drug

Dosage and Administration

Table 8. Dosing and Administration[3-14]

Generic Name	Adult Dose	Pediatric Dose	Availability
Abatacept	Rheumatoid arthritis: Prefilled syringe and single use vial: initial (<60 kg), 500 mg IV over 30 minutes at weeks zero, two and four; (60 to 100 kg), 750 mg IV over 30 minutes at weeks zero, two and four; (>100 kg), 1,000 mg IV over 30 minutes at weeks zero, two and four; maintenance (<60 kg), 500 mg IV over 30 minutes every four weeks; (60 to 100 kg), 750 mg IV over 30 minutes every four weeks; (>100 kg), 1,000 mg IV over 30 minutes every four weeks or initial (<60 kg), 500 mg IV over 30 minutes followed by 125 mg SC within 24 hours; 750 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (>100 kg), 1,000 mg IV over 30 minutes followed by 125 mg SC within 24 hours; maintenance, 125 mg SC every four weeks	Juvenile idiopathic arthritis (six to 17 years of age): Prefilled syringe and single use vial: initial, (<75 kg),10 mg/kg IV over 30 minutes at weeks zero, two and four; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV over 30 minutes every four weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose	Prefilled syringe: 125 mg/mL Single use vial: 250 mg
Adalimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week Crohn's disease, ulcerative colitis: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as	Juvenile idiopathic arthritis (four to 17 years of age): 15 to <30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29) Plaque psoriasis: Prefilled pen and syringe, single use vial: initial, 80 mg SC; maintenance, 40 mg SC every other week starting one week after the initial dose Rheumatoid arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate	week There is limited data in pediatric patients with a weight <15 kg.	Single use vial: 40 mg/0.8 mL
Anakinra	Neonatal-onset multisystem inflammatory disease: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily Rheumatoid arthritis: Prefilled syringe: initial, 100 mg SC daily; maintenance, 100 mg SC daily	Neonatal-onset multisystem inflammatory disease: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, maximum of 8 mg/kg daily	Prefilled syringe: 100 mg/0.67 mL
Certolizumab	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks two and four; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every four weeks Crohn's disease: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 400 mg SC (as two SC injections of 200 mg) once every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg
Etanercept	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled autoinjector and syringe and vial: initial/maintenance, 50 mg SC weekly Plaque psoriasis: Prefilled autoinjector and syringe and vial: initial, 50 mg SC twice weekly for three months; maintenance, 50 mg SC weekly	Juvenile idiopathic arthritis (two to 17 years of age): Prefilled autoinjector and syringe and vial: initial and maintenance (<63 kg), 0.8 mg/kg SC weekly; (≥63 kg), 50 mg SC weekly	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder

Generic Name	Adult Dose	Pediatric Dose	Availability
			for injection): 25 mg
Golimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly; maintenance, 50 mg SC once monthly Rheumatoid arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly in combination with methotrexate; maintenance, 50 mg SC once monthly in combination with methotrexate Vial (Simponi Aria®): initial, 2 mg/kg IV over 30 minutes at weeks zero and four; maintenance, 2 mg/kg IV over 30 minutes every eight weeks; all in combination with methotrexate Ulcerative colitis: Prefilled autoinjector and syringe: initial, 200 mg SC once, followed by 100 mg SC at week two; maintenance, 100 mg SC once every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial (Simponi Aria®): 50 mg/4 mL
Infliximab	Ankylosing spondylitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every six weeks Crohn's disease: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg in patients who respond and then lose response Plaque psoriasis, psoriatic arthritis, ulcerative colitis : Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks Rheumatoid arthritis: Vial: initial, 3 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 3 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg IV over two hours every eight weeks or 3 mg/kg IV over two hours every four weeks if incomplete response; all in combination with methotrexate	Crohn's disease, ulcerative colitis (six years of age and older): Vial: initial, 5 mg/kg IV over two hours at weeks zero, two and six; maintenance, 5 mg/kg IV over two hours every eight weeks	Single use vial: 100 mg
Tocilizumab	Rheumatoid arthritis: Prefilled syringe: initial and maintenance (<100 kg), 162 mg SC every other week, followed by	Polyarticular juvenile idiopathic arthritis (two years	Prefilled syringe: 162 mg/0.9

Generic Name	Adult Dose	Pediatric Dose	Availability
	162 mg SC every week; (≥100 kg), 162 mg SC every week Vial: initial, 4 mg/kg IV every four weeks as a 60 minute infusion; maintenance, dose may be increased to 8 mg/kg IV every four weeks; maximum, 800 mg/infusion	of age and older): Vial: initial and maintenance (<30 kg), 10 mg/kg IV every four weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every four weeks as a 60 minute infusion Systemic juvenile idiopathic arthritis (two years of age and older): Vial: initial and maintenance (<30 kg), 12 mg/kg IV every two weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every two weeks as a 60 minute infusion	mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL
Tofacitinib	Rheumatoid arthritis: Tablet: 5 mg twice daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 5 mg
Ustekinumab	Plaque psoriasis (with or without psoriatic arthritis): Prefilled syringe and single use vial: initial (≤100 kg), 45 mg SC followed by 45 mg four weeks later; (>100 kg), 90 mg SC followed by 90 mg SC four weeks later; maintenance (≤100 kg), 45 mg SC every 12 weeks; (>100 kg), 90 mg SC every 12 weeks Psoriatic arthritis: Prefilled syringe and single use vial: initial, 45 mg SC followed by 45 mg four weeks later; maintenance, 45 mg SC every 12 weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL
Vedolizumab	Crohn's disease: Injection: initial, 300 mg IV at zero, two and six weeks; maintenance, 300 mg IV every eight weeks. Ulcerative colitis: Injection: initial, 300 mg IV at zero, two and six weeks; maintenance, 300 mg IV every eight weeks.	Safety and efficacy in the pediatric population have not been established.	Single use vial: 300 mg/20 mL

IV=intravenously, SC=subcutaneously

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[15]	• Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. • Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. • Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. • Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. • Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. • Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. • Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence. • There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. • Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in

Clinical Guideline	Recommendations
	AS. • Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.
Assessment of Spondyloarthritis International Society: **2010 Update of the International Assessment of Spondyloarthritis International Society Recommendations for the Use of Anti-Tumor Necrosis Factor Agents in Patients with Axial Spondyloarthritis (2010)**[16]	• All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a four-week period in total at a maximum recommended dose unless contraindicated. • Patients with pure axial manifestations do not have to take DMARDs before TNF-α inhibitor treatment can be started. • Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate, and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine. • Patients with symptomatic enthesitis must have failed appropriate local treatment.
National Institute for Health and Clinical Excellence: **Adalimumab, Etanercept and Infliximab for Ankylosing Spondylitis (2008)**[17]	• Adalimumab or etanercept are recommended as treatment options for adults with severe active AS only if all of the following criteria are fulfilled: o The patient's disease satisfies the modified New York criteria for diagnosis of AS. o There is confirmation of sustained active spinal disease, demonstrated by: a score of at least four units on the Bath AS Disease Activity Index and at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (these should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment). o Conventional treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended dosage for four weeks has failed to control symptoms. • It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should only be continued in the presence of an adequate response. • Infliximab is not recommended for the treatment of AS; patients currently receiving infliximab for the treatment of AS should have the option to continue therapy until they and their clinicians consider it appropriate to stop. • Golimumab was not incorporated into the guidelines at last publication due to the recent Food and Drug Administration (FDA) approval (April 24, 2009).
National Institute for Health and Clinical Excellence: **Golimumab for the treatment of Ankylosing Spondylitis (2011)**[18]	• Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if it is used as described for adalimumab and etanercept in NICE Guideline (2008) 'Adalimumab, etanercept and infliximab for ankylosing spondylitis'.

Clinical Guideline	Recommendations
American College of Gastroenterology: **Management of Crohn's Disease in Adults (2009)**[19]	Mild to moderate active disease • Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2 to 4.0 g daily or sulfasalazine for ileocolonic or colonic disease as 3 to 6 g daily in divided doses. • Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared to placebo and less effective than budesonide or conventional corticosteroids. • Alternatively, metronidazole at a dose of 10 to 20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine. • Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon. • Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with Crohn's disease. Moderate to severe disease • Patients with moderate to severe disease are treated with prednisone 40 to 60 mg daily until resolution of symptoms and resumption of weight gain (generally seven to 28 days). • Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). • Elemental diets are less effective than corticosteroids, but can avoid corticosteroid-induced toxicities. • Azathioprine and 6-mercaptopurine are effective for maintaining a steroid induced remission, and parenteral methotrexate at a dose of 25 mg/week is effective for steroid-dependent and steroid-refractory Crohn's disease. • The TNF-α inhibitors, adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active Crohn's disease in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. • Infliximab monotherapy and infliximab in combination with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Adalimumab, certolizumab, and infliximab may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. • The anti-alpha 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active Crohn's disease who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies and TNF-α inhibitor therapy. Severe/fulminant disease • Because of the acuteness and diversity of presentation of patients with severe Crohn's disease and the potential for development of complications, the management decisions for these patients are based more on practicality than controlled trial evidence. • Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an TNF-α inhibitor (adalimumab or infliximab), or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. • Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass.

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	• An abdominal mass should be evaluated through transabdominal ultrasound, magnetic resonance imaging scan. • Once the presence of an abscess has been excluded or if the patient has been receiving oral corticosteroids, parenteral corticosteroids equivalent to 40 to 60 mg of prednisone daily or its equivalent are administered in divided doses or as a continuous infusion. • There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after five to seven days, for patients who are unable to maintain adequate nutritional requirements. <u>Perianal and fistulizing disease</u> • Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons. • Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives or infliximab. <u>Maintenance therapy</u> • Mesalamine and sulfasalazine have not had consistent maintenance benefits after medical inductive therapy. • Conventional corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. • Budesonide at a dose of 6 mg/day reduces the time to relapse in ileal and/or right colonic disease, but does not provide significant maintenance benefits after six months. • Azathioprine/6-mercaptopurine and methotrexate have demonstrable maintenance benefits after inductive therapy with corticosteroids. • Azathioprine can maintain remissions induced by infliximab in steroid-naive patients. • Maintenance therapy with adalimumab, certolizumab, and infliximab is effective. • Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Maintenance therapy with natalizumab is effective. • Infliximab, mesalamine, metronidazole or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence, whereas conventional corticosteroids and budesonide at a dose of 6 mg/day are not effective.

National Institute for Health and Clinical Excellence: **Crohn's Disease Management in Adults, Children and Young People (2012)**[20]	<u>Monotherapy</u>
	• Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.
	• Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for:
	  o Children in whom there is concern about growth or side effects.
	  o Young people in whom there is concern about growth.
	• In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first

Clinical Guideline	Recommendations
	presentation or a single inflammatory exacerbation in a 12-month period. • In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. • Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. • Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. <u>Combination therapy</u> • Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. • Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). • Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. <u>Infliximab and adalimumab</u> • Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. • Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. • People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again. <u>Remission maintenance</u> • For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications. • Consider methotrexate to maintain remission only in patients who: o Needed methotrexate to induce remission. o Did not tolerate azathioprine or mercaptopurine for maintenance. o Contraindicated to azathioprine or mercaptopurine.

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	• Do not offer conventional glucocorticosteroids or budesonide to maintain remission. Remission maintenance following surgery • After surgery ,consider azathioprine or mercaptopurine to maintain remission in people with factors such as: o More than one resection. o Previously complicated or debilitating disease (e.g. abscess, involvement of adjacent structures, fistulising or penetrating disease). • Consider 5-ASA treatment to maintain remission after surgery. • Do not offer budesonide or enteral nutrition to maintain remission after surgery.
American College of Rheumatology: **Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features (2011)**[21]	General considerations • Recommendations for the treatment of juvenile idiopathic arthritis (JIA) are divided into five treatment groups that were developed by the core expert panel responsible for the literature review in the recommendation development. The treatment groups are as follows: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features (and without active arthritis) and systemic arthritis with active arthritis (and without active systemic features). • Glucocorticoid joint injections for active arthritis are recommended regardless of concurrent therapy (no DMARD, nonbiologic DMARD, biologic DMARD) or JIA treatment group. Due to its "superior" efficacy, triamcinolone hexacetonide should be used. • When initiating a TNF-α inhibitor (etanercept or adalimumab), continuation of methotrexate is recommended for patients that had a partial previous response. History of arthritis in four or fewer joints • For patients with low disease activity, no joint contractures and without features of poor prognosis, initiation of therapy with NSAID monotherapy is recommended as a treatment option. Therapy with an NSAID without additional therapy is not recommended longer than two months. • For all patients regardless of disease activity level, prognostic features or joint contractures, initiation of intra-articular joint injections (with or without additional therapy is recommended. • For patients with high disease activity and poor prognostic features, methotrexate is recommended as initial treatment (without prior therapy). For patients with high disease activity without poor prognostic features or with moderate disease activity and poor prognostic features, methotrexate is recommended after initial joint injection. For patients with low disease activity and poor prognostic features or moderate disease activity without poor prognostic features, methotrexate is recommended after repeated joint injections. • For patients with enthesitis-related arthritis category of JIA with moderate or high disease activity with and without poor prognostic features, sulfasalazine is recommended after glucocorticoid injections or an adequate trial of NSAIDs. • Initiation of a TNF-α inhibitor is recommended for patients with moderate or high disease activity with poor prognostic features after receiving glucocorticoid joint injections and three months of methotrexate at

Clinical Guideline	Recommendations
	maximum tolerated dose. Initiation of a TNF-α inhibitor is also recommended in patients with high disease activity without poor prognostic features after receiving glucocorticoid joint injections and six months of methotrexate. For patients with enthesitis-related arthritis category of JIA and moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving glucocorticoid joint injections and an adequate trial of sulfasalazine (without prior methotrexate). History of arthritis of five or more joints • Initial treatment with methotrexate is recommended in patients with high disease activity with or without poor prognostic features and in patients with moderate disease activity and poor prognostic features. For patients with low disease activity and poor prognostic features, methotrexate therapy is recommended after one month of therapy with NSAIDs. In patients with moderate disease activity without poor prognostic features, methotrexate is recommended after one to two months of therapy with NSAIDs. • Leflunomide is a treatment alternative to methotrexate as initial therapy in patients with high disease activity and poor prognostic features. In patients with high disease activity without poor prognostic features or moderate disease activity with poor prognostic features, leflunomide is a treatment alternative after a brief trial with NSAIDs. • For patients with moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for three months at the maximum tolerated typical doses. For patients with low disease activity with or without poor prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for six months. • For patients with moderate or high disease activity regardless of prognostic features, switching from one TNF-α inhibitor to another is recommended as a treatment option after receiving four months of therapy with current TNF-α inhibitor. • Abatacept is recommended as a treatment option after receiving four months of therapy with a TNF-α inhibitor in patients with high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features. For patients with moderate or high disease activity regardless of prognostic features or patients with low disease activity with features of poor prognosis, abatacept is recommended as a treatment option after receiving more than one TNF-α inhibitor sequentially. • Switching to a TNF-α inhibitor is recommended as a treatment option in patients that received abatacept for three months and have high disease activity with poor prognostic features and in patients that received abatacept for six months and have moderate to high disease activity with or without features of poor prognosis. Active sacroiliac arthritis • For patients with high disease activity and features of poor prognosis, TNF-α inhibitors are recommended after receiving an adequate trial of NSAIDs. • A TNF-α inhibitor is recommended in patients with high disease activity regardless of prognostic features or moderate disease activity with

Clinical Guideline	Recommendations
	features of poor prognosis that have received three months of methotrexate, or in patients with moderate disease without poor prognosis that received six months of methotrexate. • A TNF-α inhibitor is recommended in patients with moderate or high disease activity regardless of prognostic features that have received three months of sulfasalazine, or in patients with low disease with poor prognosis that received six months of sulfasalazine. Systemic arthritis with active systemic features • NSAID monotherapy is appropriate during clinical evaluation for possible systemic arthritis. NSAID monotherapy is not recommended for patients with active fever and physician global assessment of overall disease activity ≥7 of 10. In patients with active fever, continuation of NSAID monotherapy longer than one month is not appropriate. • Initial therapy with systemic glucocorticoids (with or without additional concurrent therapy) is recommended for patients with active fever and physician global assessment of seven or greater. For all patients with active fever, systemic glucocorticoids are recommended following up to two weeks of NSAIDs. • Anakinra is recommended for all patients with active fever and poor prognostic features, regardless of current therapy. For patients that sustain or develop fever while receiving systemic glucocorticoid, anakinra is recommended. Systemic arthritis with active arthritis • NSAID monotherapy (with or without glucocorticoid joint injections) for up to one month is recommended for patients with low disease activity without features of poor prognosis. • For all patients with active arthritis, regardless of prognostic features, methotrexate is recommended after one month or less of NSAID monotherapy (with or without glucocorticoid injections). • After three months of methotrexate, anakinra is recommended for patients with moderate or high disease activity with or without poor prognostic features. Anakinra is recommended for patients with high or moderate disease activity, regardless of prognostic features, and have received methotrexate and a TNF-α inhibitor or methotrexate and abatacept. Initiation of anakinra later in the disease course may be less appropriate compared to nearer to the onset of disease. • For patients with moderate or high disease activity with or without poor prognosis features, TNF-α inhibitors are recommended after receiving three months of methotrexate. Switching from anakinra to TNF-α inhibitors may be appropriate for patients with moderate to high disease activity regardless of prognostic features. • Abatacept is recommended for patients that received methotrexate and a TNF-α inhibitor and have high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features.
American College of Rheumatology: **2013 Update of the 2011 American College of Rheumatology Recommendations**	Initial treatment of systemic JIA with active systemic features and varying degrees of synovitis • Anakinra is recommended as one initial treatment option for patients with a physician global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or an MD global <5 and an AJC >0. • Systemic glucocorticoid monotherapy (oral or intravenous) is recommended for a maximum period of two weeks for patients with an

Clinical Guideline	Recommendations
for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications (2013)[22]	MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC. • Initiating NSAID monotherapy in a patient without prior treatment is recommended as one approach for patients with an MD global <5 irrespective of the AJC. <u>Treatment of systemic JIA with active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended only in patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of abatacept for patients with an AJC of zero irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is uncertain. • Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD global ≥5 and an AJC <4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of abatacept for patients with an MD global ≥5 and an AJC >4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Anakinra is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy. • Use of a calcineurin inhibitor is recommended only for patients with an MD global ≥5 and an AJC of zero after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Canakinumab is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy, methotrexate or leflunomide, anakinra, or tocilizumab irrespective of the MD global and AJC. • Canakinumab is also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy. • Glucocorticoid monotherapy is recommended as a treatment option after failure of NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC. Adjunct glucocorticoid therapy at any point is appropriate to consider.

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	• Intraarticular glucocorticoid injection is recommended as adjunct therapy at any time. • Methotrexate or leflunomide is recommended for patients with an MD global <5 and an AJC >0 after treatment with glucocorticoid monotherapy, an IL-1 inhibitor, or tocilizumab. Methotrexate or leflunomide is recommended for patients with an MD global ≥5 and an AJC >0, only after a trial of an IL-1 inhibitor or tocilizumab. • Initiation of a TNF-α inhibitor is recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab. Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). • Use of a TNF-α inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Use of a TNF-α inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. • Tocilizumab is recommended as a treatment option for patients with continued disease activity following glucocorticoid monotherapy, methotrexate or leflunomide, or anakinra irrespective of the MD global and AJC. • Tocilizumab is also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy. <u>Initial treatment of systemic JIA without active systemic features and varying degrees of synovitis</u> • Intraarticular glucocorticoid injection is recommended as an initial treatment for patients with an AJC ≤4. The utility of repeating injections in the same joint(s) as the only intervention is uncertain. • Initiation of methotrexate or leflunomide is recommended for patients with an AJC >4. • Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of one month is recommended as one treatment approach for patients with an AJC >0. Continuing NSAID monotherapy for longer than two months for patients with continued disease activity is inappropriate. <u>Treatment of systemic JIA without active systemic features and varying degrees of synovitis in patients with continued disease activity</u> • Use of abatacept is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. • Anakinra is recommended as a treatment option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy. Use of anakinra is also recommended for patients with an AJC >0 following treatment with methotrexate or leflunomide. • Initiation of canakinumab is recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab, a DMARD plus a TNF-α inhibitor, or abatacept. • Use of methotrexate or leflunomide is recommended as a treatment option for an AJC >0 following treatment with intraarticular injection, NSAID monotherapy, an IL-1 inhibitor, or tocilizumab.

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	• Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. • Initiation of tocilizumab is recommended for an AJC >0 following treatment with anakinra or methotrexate or leflunomide. Initial treatment of systemic JIA with features concerning for macrophage activation syndrome (MAS) • Use of anakinra is recommended as one treatment option for patients with features concerning for MAS. • Use of a calcineurin inhibitor is recommended as one therapeutic option for patients with features concerning for MAS. • Use of systemic glucocorticoid monotherapy (administered by oral or intravenous route) is also recommended as a therapeutic option for patients with features concerning for MAS. • Continuing glucocorticoid monotherapy for longer than two weeks is inappropriate.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[23]	Recommendations for treatment • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage. • In patients with active psoriatic arthritis and clinically relevant psoriasis, a DMARD that also improves psoriasis, such as methotrexate, should be preferred. • Local corticosteroid injections should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution. • In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as methotrexate, therapy with a TNF-α inhibitor should be commenced. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or steroid injections, a TNF-α inhibitor may be considered. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF-α inhibitor should be considered. • A TNF-α inhibitor might be considered for a very active patient treatment naïve to DMARDs (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement). • In patients who fail to respond adequately to one TNF-α inhibitor, switching to another TNF-α inhibitor should be considered. • When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.
National Psoriasis Foundation: **Consensus Guidelines for the Management of Plaque Psoriasis**	Oral therapies • Acitretin is the only antipsoriatic retinoid available for systemic use in the United States. The use of acitretin is limited due to its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene or biological therapy or phototherapy may increase rates of clearance. Acitretin is

Clinical Guideline	Recommendations
(2012)[24]	especially useful in patients with severely sun-damaged skin, in which it may suppress actinic keratoses and even invasive malignant neoplasms. • Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects, hypertension and hyperglycemia. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term treatment agent to control a flare of psoriasis, after which therapy is switched for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity. • Methotrexate is directly anti-inflammatory because of its effects on T-cell gene expression patterns. Compared to cyclosporine, methotrexate has a more modest effect on psoriasis severity, but can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver. <u>Biologic agents</u> • Adalimumab may be used as first-line systemic treatment of plaque psoriasis and has a higher efficacy and lower rate of adverse effects compared to methotrexate. • Etanercept is commonly used as a first-line systemic drug for chronic plaque psoriasis. • Infliximab is administered via intravenous infusion, is a fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis • Ustekinumab is associated with favorable results when compared to etanercept in terms of efficacy and safety. It may be used as first-line systemic treatment for chronic plaque psoriasis. • Alefacept is generally used for intermittent use. There is little evidence to support use to achieve full clearance, and it is often used in combination regimens. It may be used as first-line systemic drug for chronic plaque psoriasis.
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3 and 4 (2008-2009)**[25-27]	<u>Topical therapies</u> • Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include anthralin, coal tar, nonmedicated topical moisturizers, pimecrolimus, salicylic acid, tacrolimus, tazarotene, vitamin D analogues, and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid however the agent is typically used in combination with other topical therapies.

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	Systemic therapies • Although biologics are often less toxic and not teratogenic, traditional systemic therapies (acitretin, cyclosporine, methotrexate) are still used more often due to oral route of administration and low cost. • Used more than 50 years ago, methotrexate is most commonly prescribed for severe, recalcitrant, disabling psoriasis when used in a weekly, single low-dose regimen for its effect on the immune system; concurrent folate supplementation may be warranted. • Though highly effective and known for its rapid effects, cyclosporine is associated with nephrotoxicity and hypertension; its use is restricted to one and two years in the United States and United Kingdom, respectively. • When used in conjunction with ultraviolet radiation B or psoralen and ultraviolet radiation A phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression; effects are dose-dependent and response is observed after three to six months. • Agents not FDA-indicated but used in psoriasis with limited supporting evidence include: azathioprine, fumarates (not approved in the United States), leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine. Biologics • Three TNF-α inhibitors are FDA-approved for the treatment of psoriatic arthritis; adalimumab, etanercept, and infliximab (please note that the publication of these guidelines was before FDA-approval of golimumab). • Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy associated with psoriasis that if left untreated can lead to persistent inflammation with progressive joint damage that can result in severe physical limitations and disability. • NSAIDs and/or intra-articular injections of corticosteroids may be appropriate treatment options in patients with milder, localized disease. • Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with methotrexate, TNF-α inhibitors, or both. These treatment options are considered the standard of care. • Other DMARDs which may be used in the treatment of psoriatic arthritis include leflunomide and sulfasalazine. Antimalarials, cyclosporine, and gold are used less frequently due to the evidence for their efficacy being less convincing than for leflunomide, methotrexate, and sulfasalazine. • Although expensive, there are potential long-term cost savings and benefits associated with the use of biologics in the treatment of psoriatic arthritis, including reduced need for joint replacement surgery; reduced demands on medical, nursing, and therapy services; reduced needs for concomitant medicines; reduced demands on social services and careers; improved quality of life; improved prospect of remaining in the work force; and increased life expectancy. • Because the clinical trial efficacy data (primary endpoint of American College of Rheumatology 20% improvement) with all three FDA-approved TNF-α inhibitors are roughly equivalent, the choice of which agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration.

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	• Adalimumab and infliximab both demonstrated significant benefit for the treatment of psoriatic arthritis in clinical trials, while etanercept demonstrated significant improvements in signs and symptoms of psoriatic arthritis.
American College of Rheumatology: **2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)[28]**	Initiating and switching among DMARDs • If a patient deteriorates from low to moderate/high disease activity after three months of DMARD monotherapy (in patients without poor prognostic features), then methotrexate, hydroxychloroquine, or leflunomide should be added. • Add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD if the patient still experiences moderate or high disease activity following three months of methotrexate or methotrexate/DMARD combination therapy. Switching from DMARDs to biologic agents • For patients with continued moderate or high disease activity following three months of methotrexate monotherapy or DMARD combination therapy, an alternative to DMARD therapy is adding or changing therapy to a TNF-α inhibitor, abatacept or rituximab. • Add or switch to a TNF-α inhibitor if a patient continues to have moderate or high disease activity, following three months of intensified DMARD combination therapy or after a second DMARD has been tried. Switching among biologic agents due to lack of benefit or loss of benefit • In patients with moderate or high disease activity despite three months of TNF-α inhibitor therapy due to a lack or loss of benefit, switching to another TNF-α inhibitor or a non-TNF-α inhibitor biologic is recommended. • In patients with moderate or high disease activity despite six months of a non-TNF-α inhibitor biologic and the failure is due to a lack or loss of benefit, the patient should switch to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Switching among biologic agents due to harms/adverse events • Patients with high disease activity following treatment failure of a TNF-α inhibitor due to a serious adverse event, an attempt should be made to switch to a non-TNF-α inhibitor biologic. • In patients with moderate or high disease activity after failing an TNF-α inhibitor because of a nonserious adverse event, switch to another anti-TNF-α inhibitor or a non-TNF-α inhibitor biologic. • Patients with moderate or high disease activity after failing a non-TNF-α inhibitor biologic because of an adverse event (serious or nonserious) should be switched to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Biologic use in Hepatitis B or C • Etanercept could potentially be used in rheumatoid arthritis patients with hepatitis C requiring rheumatoid arthritis treatment; however, biologic agents should not be used in rheumatoid arthritis patients with untreated chronic hepatitis B and in rheumatoid arthritis patients with treated chronic hepatitis B with Child-Pugh class B and higher. Malignancies

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	• Patients treated for solid malignancies more than five years ago or who have been treated for nonmelanoma skin cancer more than five years ago, treatment with a biologic agent may be initiated or continued if the patient would otherwise qualify for biologic therapy. • Rituximab should only be started or initiated in rheumatoid arthritis patients with a previously treated solid malignancy within the last five years, a previously treated nonmelanoma skin cancer within the last five years, a previously treated melanoma skin cancer, or a previously treated lymphoproliferative malignancy. • Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past five years. Congestive heart failure • Anti-TNF biologic in rheumatoid arthritis patients with congestive heart failure is not recommended in those with a New York Heart Association class III or IV and who have an ejection fraction of 50% or less.
European League Against Rheumatism: **Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying Antirheumatic Drugs: 2013 Update (2013)**[15]	• Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. • Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. • Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. • Treatment should be aimed at reaching a target of remission or low disease activity in every patient. • Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis. • If methotrexate is contraindicated or is not tolerated, treatment with sulfasalazine or leflunomide should be considered. • In DMARD-naïve patients, treatment with conventional synthetic DMARD monotherapy or combination therapy of conventional synthetic DMARDs is recommended. • Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible. • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another conventional synthetic DMARD strategy should be considered; when poor prognostic factors are present, addition of a biologic DMARD should be considered. • In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF-α inhibitors, abatacept or tocilizumab) should be commenced with methotrexate; treatment with rituximab may be considered in the patients with recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a tuberculosis-endemic region, or a previous history of demyelinating disease. • If a first biologic DMARD has failed, patients should be treated with another biologic DMARD; if a first TNF-α inhibitor therapy has failed, patients may receive another TNF-α inhibitor or a biological agent with a different mechanism of action. • Given the paucity of clinical experience and long-term safety data, tofacitinib should primarily be used when biological treatment has failed; additional clinical experience and safety data from registries, with a

Clinical Guideline	Recommendations
	particular focus on serious infections, herpes zoster and malignancies, will be needed before the place of tofacitinib in the treatment sequence can be clarified. • If a patient is in persistent remission after having tapered glucocorticoids, tapering of biologic DMARDs can be considered, especially if this treatment is combined with a conventional synthetic DMARD. • In cases of sustained long-term remission, cautious reduction of the conventional synthetic DMARD dose could be considered, as a shared decision between patient and physician.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis National Clinical Guideline for Management and Treatment in Adults (2009)**[29]	• In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. • In people with recent-onset rheumatoid arthritis receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. • In people with newly diagnosed rheumatoid arthritis for which combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. • In people with established rheumatoid arthritis whose disease is stable, cautiously reduce dosages of disease modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. • When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. • In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. • Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy. • Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. • Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. • Oral NSAIDs or COX-2 inhibitors should be used at the lowest effective

Clinical Guideline	Recommendations
	dose for the shortest possible period of time. • When offering treatment with an oral NSAID or COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost. • All oral NSAIDs or COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. • If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient. • If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen. • The TNF-α inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. • TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy. • Treatment with TNF-α inhibitors should be continued only if there is an adequate response at six months following initiation of therapy. An adequate response is defined as an improvement in DAS 28 of 1.2 points or more. • After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. • An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy provided the risks and benefits have been fully discussed with the patient and documented. • Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended. • Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. • Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. • Initiation of TNF-α inhibitors and follow-up of treatment response and

Clinical Guideline	Recommendations
	adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.
National Institute for Health and Clinical Excellence: **Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After the Failure of a Tumor Necrosis Factor Inhibitor (2010)**[30]	• Rituximab in combination with methotrexate is recommended as an option in adult patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor. • Treatment with rituximab should be given no more frequently that every six months and should be continued only if an adequate response is maintained at this dosing interval. • Abatacept, adalimumab, etanercept and infliximab each in combination with methotrexate, are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with rituximab. • Adalimumab and etanercept monotherapy are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with methotrexate. • Treatment with abatacept, adalimumab, etanercept and infliximab should be continued only if there is an adequate response six months after therapy. • Abatacept, adalimumab, etanercept, infliximab and rituximab should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.
National Institute for Health and Clinical Excellence: **Golimumab for the Treatment of Rheumatoid Arthritis After the Failure of Previous Disease-Modifying Antirheumatic Drugs (2011)**[31]	• Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only, including methotrexate, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. • Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
American College of Gastroenterology, Practice Parameters Committee:	Management of mild-moderate distal colitis • Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates. • The combination of oral and topical agents is “superior” to each agent

Clinical Guideline	Recommendations
Ulcerative Colitis Practice Guidelines in Adults (2010)[32]	used alone. • Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-analysis demonstrated topical mesalamine to be "superior" to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. • Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. • Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. <u>Maintenance of remission in distal disease</u> • Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. • Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. • Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. • When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. <u>Management of mild-moderate extensive colitis: active disease</u> • Oral sulfasalazine is considered first line. • Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. • 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. • Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. <u>Maintenance of remission for mild-moderate extensive colitis</u> • Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses. • 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. • Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. <u>Management of severe colitis</u> • If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent hospitalization is not required. • Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. • Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence).

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	• Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.

Conclusions

Immunomodulators inhibit the pro-inflammatory response involved in the pathophysiology of several chronic inflammatory diseases. The immunomodulators interfere with this inflammatory pathway through slightly different mechanisms.[3-14] Few head-to-head trials have been performed amongst these agents, making it difficult to compare the efficacy, although all have been shown to be efficacious compared to placebo for their respective Food and Drug Administration (FDA)-approved indication(s).[38-128] Current clinical guidelines do not generally distinguish among the different agents for any indication for which the specific agent is approved.[14-32] Given the paucity of clinical experience and long-term safety data, guidelines recommend that tofacitinib be reserved for patients in whom biological treatment has failed.[15] The adverse event profiles are similar across the class. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class; however, several other agents have recently gained additional indications.[3-14]

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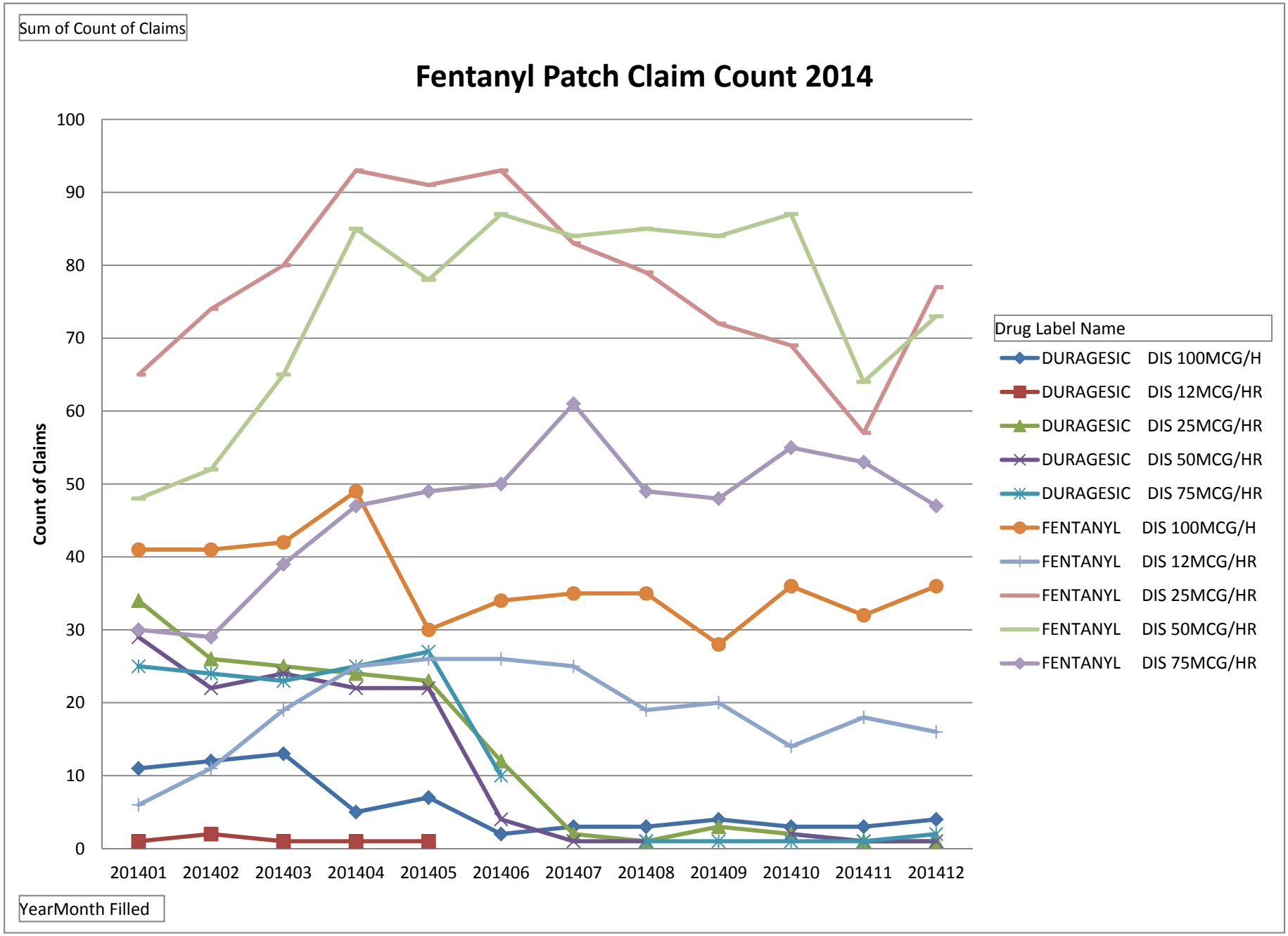
YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201401	DURAGESIC DIS 100MCG/H	11	11	110	293	$ 10,981.37
201401	DURAGESIC DIS 12MCG/HR	1	1	15	30	$ 386.59
201401	DURAGESIC DIS 25MCG/HR	34	18	164	480	$ 5,004.05
201401	DURAGESIC DIS 50MCG/HR	29	24	255	735	$ 13,972.77
201401	DURAGESIC DIS 75MCG/HR	25	17	187	482	$ 15,637.64
201401	FENTANYL DIS 100MCG/H	41	29	358	843	$ 2,200.96
201401	FENTANYL DIS 12MCG/HR	6	5	45	135	$ 429.02
201401	FENTANYL DIS 25MCG/HR	65	50	503	1,403	$ 1,807.35
201401	FENTANYL DIS 50MCG/HR	48	45	482	1,369	$ 2,603.85
201401	FENTANYL DIS 75MCG/HR	30	26	277	774	$ 1,756.50
201402	DURAGESIC DIS 100MCG/H	12	10	106	276	$ 12,111.45
201402	DURAGESIC DIS 12MCG/HR	2	2	25	60	$ 645.90
201402	DURAGESIC DIS 25MCG/HR	26	13	129	371	$ 3,960.33
201402	DURAGESIC DIS 50MCG/HR	22	18	184	514	$ 10,444.38
201402	DURAGESIC DIS 75MCG/HR	24	14	159	419	$ 13,742.53
201402	FENTANYL DIS 100MCG/H	41	30	340	837	$ 2,831.53
201402	FENTANYL DIS 12MCG/HR	11	10	90	270	$ 853.28
201402	FENTANYL DIS 25MCG/HR	74	61	595	1,648	$ 1,732.05
201402	FENTANYL DIS 50MCG/HR	52	51	517	1,439	$ 3,117.35
201402	FENTANYL DIS 75MCG/HR	29	28	290	840	$ 1,914.45
201403	DURAGESIC DIS 100MCG/H	13	11	115	304	$ 13,135.28
201403	DURAGESIC DIS 12MCG/HR	1	1	15	30	$ 386.59
201403	DURAGESIC DIS 25MCG/HR	25	12	124	354	$ 3,730.87
201403	DURAGESIC DIS 50MCG/HR	24	19	213	604	$ 12,083.53
201403	DURAGESIC DIS 75MCG/HR	23	17	185	496	$ 15,966.32
201403	FENTANYL DIS 100MCG/H	42	31	380	882	$ 3,905.09
201403	FENTANYL DIS 12MCG/HR	19	15	128	364	$ 995.29
201403	FENTANYL DIS 25MCG/HR	80	65	578	1,648	$ 1,936.88
201403	FENTANYL DIS 50MCG/HR	65	61	636	1,812	$ 4,849.78
201403	FENTANYL DIS 75MCG/HR	39	34	334	959	$ 2,430.90
201404	DURAGESIC DIS 100MCG/H	5	5	55	150	$ 6,280.54
201404	DURAGESIC DIS 12MCG/HR	1	1	15	30	$ 386.59
201404	DURAGESIC DIS 25MCG/HR	24	10	100	280	$ 3,187.71
201404	DURAGESIC DIS 50MCG/HR	22	14	161	468	$ 9,151.89
201404	DURAGESIC DIS 75MCG/HR	25	15	165	451	$ 14,261.57
201404	FENTANYL DIS 100MCG/H	49	37	462.01	1,004	$ 5,691.22
201404	FENTANYL DIS 12MCG/HR	25	19	155	412	$ 1,288.06
201404	FENTANYL DIS 25MCG/HR	93	68	664.06	1,815	$ 2,290.62
201404	FENTANYL DIS 50MCG/HR	85	77	756.1	2,131	$ 6,172.53
201404	FENTANYL DIS 75MCG/HR	47	42	458	1,294	$ 3,492.42
201405	DURAGESIC DIS 100MCG/H	7	7	75	210	$ 8,565.24
201405	DURAGESIC DIS 12MCG/HR	1	1	10	30	$ 259.31
201405	DURAGESIC DIS 25MCG/HR	23	11	101	304	$ 3,071.65
201405	DURAGESIC DIS 50MCG/HR	22	17	156	425	$ 8,870.92
201405	DURAGESIC DIS 75MCG/HR	27	14	169	447	$ 14,613.91

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201405	FENTANYL DIS 100MCG/H	30	24	295	656	$ 3,442.64
201405	FENTANYL DIS 12MCG/HR	26	17	188	522	$ 1,317.87
201405	FENTANYL DIS 25MCG/HR	91	70	636.11	1,796	$ 2,902.80
201405	FENTANYL DIS 50MCG/HR	78	68	666.06	1,847	$ 5,346.36
201405	FENTANYL DIS 75MCG/HR	49	41	439	1,182	$ 4,069.18
201406	DURAGESIC DIS 100MCG/H	2	2	20	60	$ 2,284.70
201406	DURAGESIC DIS 25MCG/HR	12	4	29	86	$ 498.69
201406	DURAGESIC DIS 50MCG/HR	4	3	18	54	$ 685.22
201406	DURAGESIC DIS 75MCG/HR	10	3	20	60	$ 935.00
201406	FENTANYL DIS 100MCG/H	34	31	393	869	$ 5,075.22
201406	FENTANYL DIS 12MCG/HR	26	19	160	438	$ 1,623.36
201406	FENTANYL DIS 25MCG/HR	93	69	637.16	1,771	$ 3,157.05
201406	FENTANYL DIS 50MCG/HR	87	77	787	2,223	$ 6,699.97
201406	FENTANYL DIS 75MCG/HR	50	47	503	1,400	$ 5,542.94
201407	DURAGESIC DIS 100MCG/H	3	3	30	90	$ 3,427.05
201407	DURAGESIC DIS 25MCG/HR	2	2	20	60	$ 624.22
201407	DURAGESIC DIS 50MCG/HR	1	1	10	30	$ 566.70
201407	FENTANYL DIS 100MCG/H	35	30	341	840	$ 4,279.25
201407	FENTANYL DIS 12MCG/HR	25	19	181.01	463	$ 1,904.53
201407	FENTANYL DIS 25MCG/HR	83	71	688.1	1,936	$ 3,408.09
201407	FENTANYL DIS 50MCG/HR	84	75	724	2,044	$ 6,080.63
201407	FENTANYL DIS 75MCG/HR	61	52	620	1,732	$ 6,798.49
201408	DURAGESIC DIS 100MCG/H	3	3	30	88	$ 3,427.05
201408	DURAGESIC DIS 25MCG/HR	1	1	10	30	$ 312.11
201408	DURAGESIC DIS 50MCG/HR	1	1	10	10	$ 566.70
201408	DURAGESIC DIS 75MCG/HR	1	1	10	30	$ 861.89
201408	FENTANYL DIS 100MCG/H	35	30	346	903	$ 4,653.68
201408	FENTANYL DIS 12MCG/HR	19	15	130.07	365	$ 1,685.56
201408	FENTANYL DIS 25MCG/HR	79	68	660.07	1,784	$ 2,753.23
201408	FENTANYL DIS 50MCG/HR	85	74	750	2,071	$ 6,161.88
201408	FENTANYL DIS 75MCG/HR	49	42	453	1,263	$ 5,085.71
201409	DURAGESIC DIS 100MCG/H	4	4	31	91	$ 3,540.81
201409	DURAGESIC DIS 25MCG/HR	3	3	24	61	$ 747.16
201409	DURAGESIC DIS 75MCG/HR	1	1	10	30	$ 861.89
201409	FENTANYL DIS 100MCG/H	28	25	277	715	$ 4,980.94
201409	FENTANYL DIS 12MCG/HR	20	15	150.01	395	$ 1,687.62
201409	FENTANYL DIS 25MCG/HR	72	64	613.2	1,707	$ 2,596.65
201409	FENTANYL DIS 50MCG/HR	84	71	765	2,157	$ 5,971.04
201409	FENTANYL DIS 75MCG/HR	48	43	486	1,307	$ 5,161.17
201410	DURAGESIC DIS 100MCG/H	3	3	30	90	$ 3,427.05
201410	DURAGESIC DIS 25MCG/HR	2	2	20	60	$ 624.22
201410	DURAGESIC DIS 50MCG/HR	2	2	11	31	$ 622.89
201410	DURAGESIC DIS 75MCG/HR	1	1	10	30	$ 861.89
201410	FENTANYL DIS 100MCG/H	36	34	369	923	$ 6,346.73
201410	FENTANYL DIS 12MCG/HR	14	13	114	343	$ 1,248.87

YearMonth Filled	Drug Label Name	Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201410	FENTANYL DIS 25MCG/HR	69	64	661	1,817	$ 2,942.79
201410	FENTANYL DIS 50MCG/HR	87	75	784	2,203	$ 6,279.35
201410	FENTANYL DIS 75MCG/HR	55	45	518.075	1,406	$ 5,692.01
201411	DURAGESIC DIS 100MCG/H	3	3	30	90	$ 3,427.05
201411	DURAGESIC DIS 25MCG/HR	1	1	10	30	$ 312.11
201411	DURAGESIC DIS 50MCG/HR	1	1	10	30	$ 566.70
201411	DURAGESIC DIS 75MCG/HR	1	1	10	30	$ 861.89
201411	FENTANYL DIS 100MCG/H	32	28	352	853	$ 6,013.44
201411	FENTANYL DIS 12MCG/HR	18	16	149	446	$ 1,003.46
201411	FENTANYL DIS 25MCG/HR	57	52	532	1,460	$ 2,199.09
201411	FENTANYL DIS 50MCG/HR	64	58	585	1,622	$ 4,664.09
201411	FENTANYL DIS 75MCG/HR	53	46	537	1,454	$ 5,595.62
201412	DURAGESIC DIS 100MCG/H	4	3	40	120	$ 4,569.40
201412	DURAGESIC DIS 25MCG/HR	1	1	10	30	$ 312.11
201412	DURAGESIC DIS 50MCG/HR	1	1	10	30	$ 566.70
201412	DURAGESIC DIS 75MCG/HR	2	2	20	60	$ 1,723.78
201412	FENTANYL DIS 100MCG/H	36	31	316	828	$ 5,779.17
201412	FENTANYL DIS 12MCG/HR	16	14	145	415	$ 1,345.47
201412	FENTANYL DIS 25MCG/HR	77	65	764	2,077	$ 3,189.82
201412	FENTANYL DIS 50MCG/HR	73	65	710	1,993	$ 5,814.43
201412	FENTANYL DIS 75MCG/HR	47	42	447	1,245	$ 5,532.76


Sum of Count of Claims
Fentanyl Patch Claim Count 2014
Count of Claims
100
90
80
70
60
50
40
30
20
10
0
201401
201402
201403
201404
201405
201406
201407
201408
201409
201410
201411
201412
YearMonth Filled
Drug Label Name
DURAGESIC DIS 100MCG/H
DURAGESIC DIS 12MCG/HR
DURAGESIC DIS 25MCG/HR
DURAGESIC DIS 50MCG/HR
DURAGESIC DIS 75MCG/HR
FENTANYL DIS 100MCG/H
FENTANYL DIS 12MCG/HR
FENTANYL DIS 25MCG/HR
FENTANYL DIS 50MCG/HR
FENTANYL DIS 75MCG/HR

F. Duragesic® (fentanyl transdermal) Patches

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: July 30, 2009

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy, or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following two criteria in order to gain prior authorization approval:

a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteriodal analgesics, or PRN dosing with short-acting opioid.

b. Patient requires continuous opioid administration.

c. The Prescriber has checked the Nevada State Board of Pharmacy PMP system for possible abuse

d. If transitioning from another opioid, daily morphine equivalent doses are used to calculate the appropriate fentanyl patch dose

- Morphine 60—134 mg/day PO: Initial Duragesic dose 25 mcg/hr.
- Morphine 135—224 mg/day PO: Initial Duragesic dose 50 mcg/hr.
- Morphine 225—314 mg/day PO: Initial Duragesic dose 75 mcg/hr.
- Morphine 315—404 mg/day PO: Initial Duragesic dose 100 mcg/hr.
- Morphine 405—494 mg/day PO: Initial Duragesic dose 125 mcg/hr.
- Morphine 495—584 mg/day PO: Initial Duragesic dose 150 mcg/hr.
- Morphine 585—674 mg/day PO: Initial Duragesic dose 175 mcg/hr.

•Morphine 675—764 mg/day PO: Initial Duragesic dose 200 mcg/hr.

•Morphine 765—854 mg/day PO: Initial Duragesic dose 225 mcg/hr.

•Morphine 855—944 mg/day PO: Initial Duragesic dose 250 mcg/hr.

•Morphine 945—1034 mg/day PO: Initial Duragesic dose 275 mcg/hr.

•Morphine 1035—1124 mg/day PO: Initial Duragesic dose 300 mcg/hr.

In addition the following guideline applies:

c. ~~Do not authorize if on long-acting narcotics. If recipient is switching to fentanyl and has a prior authorization for a long-acting narcotic, discontinue the prior authorization for the long-acting narcotic and inform the prescriber.~~

1. Prior Authorizations

Prior approval will be given for a ~~six~~ twelve month time

period. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

F. Duragesic® (fentanyl transdermal) Patches

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: July 30, 2009

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy, or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following two criteria in order to gain prior authorization approval:

a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteriodal analgesics, or PRN dosing with short-acting opioid.

b. Patient requires continuous opioid administration.

In addition the following guideline applies:

c. Do not authorize if on long-acting narcotics. If recipient is switching to fentanyl and has a prior authorization for a long-acting narcotic, discontinue the prior authorization for the long-acting narcotic and inform the prescriber.

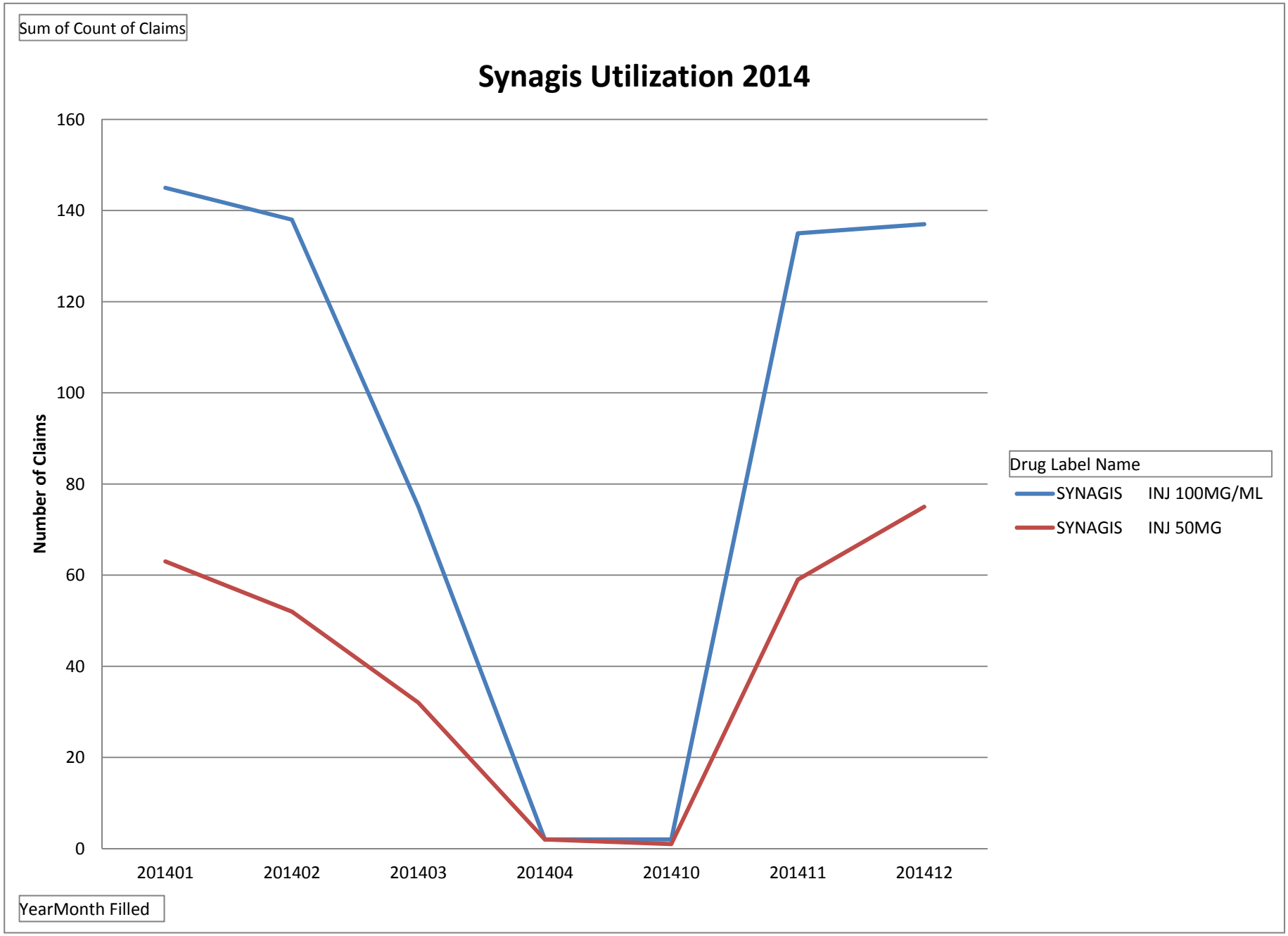
1. Prior Authorizations

Prior approval will be given for a six month time period.

Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Synagis Utilization 2014

YearMonth Filled	Drug Label Name		Count of Claims	Count of Members	Qty Disp	Days Supply	Due Amt
201401	SYNAGIS	INJ 100MG/ML	145	123	201	4,071	$ 506,814.05
201401	SYNAGIS	INJ 50MG	63	52	34	1,772	$ 89,875.59
201402	SYNAGIS	INJ 100MG/ML	138	132	189	3,827	$ 474,420.94
201402	SYNAGIS	INJ 50MG	52	52	27.5	1,443	$ 69,605.66
201403	SYNAGIS	INJ 100MG/ML	75	73	99	2,127	$ 247,116.62
201403	SYNAGIS	INJ 50MG	32	32	18	914	$ 44,178.47
201404	SYNAGIS	INJ 100MG/ML	2	2	2	58	$ 5,045.62
201404	SYNAGIS	INJ 50MG	2	2	1	58	$ 2,676.54
201410	SYNAGIS	INJ 100MG/ML	2	2	3	60	$ 20.12
201410	SYNAGIS	INJ 50MG	1	1	0.5	30	$ -
201411	SYNAGIS	INJ 100MG/ML	135	105	165	3,754	$ 394,663.93
201411	SYNAGIS	INJ 50MG	59	46	29.5	1,668	$ 75,556.83
201412	SYNAGIS	INJ 100MG/ML	137	108	174	3,824	$ 410,398.50
201412	SYNAGIS	INJ 50MG	75	63	37.5	2,120	$ 95,712.11


Sum of Count of Claims
Synagis Utilization 2014
160
140
120
100
80
60
40
20
0
Number of Claims
201401
201402
201403
201404
201410
201411
201412
YearMonth Filled
Drug Label Name
SYNAGIS INJ 100MG/ML
SYNAGIS INJ 50MG

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Synagis® (palivizumab) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

No Changes proposed at this time.

Y. Synagis® Palivizumaub

Therapeutic Class: Antiviral Monoclonal Antibodies
Last Reviewed by the DUR Board: August 13, 2014

Synagis® (palivizumab) injections are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

For consideration outside these guidelines, a prior authorization may also be submitted with supporting medical necessity documentation.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Recipients younger than 12 months of age at the start of Respiratory Syncytial Virus (RSV) season, must meet one of the following criteria:

1. The recipient was born at 28 weeks, six days of gestation or earlier; or

2. The recipient has a diagnosis of chronic lung disease (CLD) of prematurity; or

3. The recipient has hemodynamically significant congenital heart disease; or

4. The recipient has congenital abnormalities of the airways or neuromuscular disease; or

5. The recipient has a diagnosis of cystic fibrosis; and

a. The recipient has clinical evidence of CLD and/or nutritional compromise.

b. Recipients younger than two years of age at the start of RSV season must meet one of the following criteria:

1. The recipient has a diagnosis of CLD of prematurity; and

a. The recipient has required medical therapy (e.g., bronchodilator, diuretics, oxygen, coritcosteroids) within six months to the start of RSV season; or

2. The recipient has had a cardiac transplant; or

3. The recipient is severely immunocompromised (solid organ or hematopoietic stem cell transplant, chemotherapy, or other conditions) during the RSV season; or

4. The recipient has had a cardiopulmonary bypass and continues to require prophylaxis after surgery or at the conclusion of extracorporeal membrane oxygenation; or

5. The recipient has a diagnosis of cystic fibrosis; and

   a. The recipient has had manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persists when stable) or weight for length less than the tenth percentile.

2. Prior Authorization Guidelines

   a. Prior Authorization approval will be up to five doses per RSV season for recipients meeting criteria.

   b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

Therapeutic Class Overview
Palivizumab

Therapeutic Class

- **Overview/Summary:** Respiratory syncytial virus (RSV) causes seasonal outbreaks throughout the world with usual occurrence from November to April in the northern hemisphere. RSV causes acute respiratory tract illness in individuals of all ages with almost all children infected by two years of age.[1] In the United States, 75,000 to 125,000 children under one year of age are hospitalized due to RSV every year. Most healthy individuals recover from RSV infection in one to two weeks; however, the infection can be severe in certain high-risk individuals.[2] The only agent that is approved by the Food and Drug Administration for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection is palivizumab (Synagis®). Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Safety and efficacy of palivizumab have not been established for treatment of RSV disease. Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity. Palivizumab acts by binding the RSV envelope fusion protein on the surface of the virus and blocking a critical step in the membrane fusion process; palivizumab also prevents cell-to-cell fusion of RSV-infected cells. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] This review only includes the clinical evidence evaluating the safety and efficacy of palivizumab in high-risk individuals.

  The most recent consensus guidelines are published by the American Academy of Pediatrics (AAP) for the prevention of RSV infections with palivizumab in certain high-risk groups. The AAP recommends that palivizumab be administered once monthly beginning in November, up to a maximum of five doses for infants and young children <2 years of age with chronic lung disease of prematurity and for infants and young children <1 year of age who have congenital heart disease or preterm birth before 29 weeks (≤28 weeks, six days) of gestation. The use of palivizumab can be considered for several other high-risk infants as outlined in the AAP guidelines. Furthermore, according to the AAP guidelines, infants born ~~at~~ at 29 weeks, 0 days gestation or later are not universally recommended to receive palivizumab prophylaxis. ~~between 32 and 35 weeks of gestation should receive palivizumab prophylaxis only until they reach three months of age or up to a maximum of three doses~~. This was a change from the ~~2006~~ 2012 AAP guideline, which ~~allowed~~ recommended ~~five doses in~~ infants of this gestational age receive palivizumab prophylaxis.~~category until their 6th month birthday.~~ There are several cases in which infants in their second year of life may receive palivizumab prophylaxis, however, it is recommended that no adults or children >2 years should receive palivizumab. In addition, it is recommended that palivizumab be discontinued in any young child that has a breakthrough RSV hospitalization while being treated prophylactically. Due to a cumulative effect on serum concentration, the fifth palivizumab dose administered in March should provide immunologic protection through April.[8]

Table 1. Current Medications Available in the Therapeutic Class[3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Palivizumab (Synagis®)	Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus in children with high risk of respiratory syncytial virus disease	Single-dose solution vials for injection: 50 mg/0.5 mL 100 mg/1 mL	-

Evidence-based Medicine

- Placebo-controlled, randomized controlled clinical trials have demonstrated that palivizumab prophylaxis is effective in reducing hospitalizations due to respiratory syncytial virus (RSV).[4,5]
- Meta-analyses and systematic reviews also concluded effectiveness of palivizumab prophylaxis in reducing RSV-related hospitalizations; however, there was no difference in relative risk reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo.[6,7]

Key Points within the Medication Class

- According to the American Academy of Pediatrics consensus guidelines for the prevention of respiratory syncytial virus (RSV) infections, it is appropriate to provide palivizumab prophylaxis in the following high-risk groups:[8]

Patient Age	Indication	APP Recommended Action
Patient <12 months of age at the start of the RSV season	• Born at 28 weeks, six days' gestation or earlier	Recommended
	• Diagnosis of chronic lung disease of prematurity	Recommended
	• Diagnosis of hemodynamically significant congenital heart disease	Recommended
	• Diagnosis of congenital abnormalities of the airways or neuromuscular disease	Consideration
	• Diagnosis of cystic fibrosis and who have clinical evidence of CLD and/or nutritional compromise	Consideration
Patient <2 years of age at the start of the RSV season	• Diagnosis of chronic lung disease of prematurity and has required medical therapy within six months to the start of the RSV season	Recommended
	• Patient has had a cardiac transplant	Consideration
	• Patient is severely immunocompromised	Consideration
	• Patient has had cardiopulmonary bypass and continues to require prophylaxis after surgery or at the conclusion of extracorporeal membrane oxygenation	Consideration

- Other Key Facts:
  - Palivizumab prophylaxis is not recommended for otherwise healthy children born at or after 29 weeks, 0 days' gestation, in the second year of life on the basis of a history of prematurity alone, or for the prevention of health care-associated RSV disease.[8]
  - The most frequently adverse events of palivizumab were fever and rash.[3-7]
  - Only available as brand palivizumab and is associated with significant acquisition costs.
  - Monthly prophylaxis should be discontinued with a breakthrough RSV hospitalization[8]

References

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3. Synagis® [package insert]. Gaithersburg (MD): MedImmune, LLC; 2014 Mar.
4. The IMpact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in infants at high risk. Pediatrics. 1998 Sep;102(3 Pt 1):531-7.
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6. Checchia PA, Nalysnyk L, Fernandes AW, Mahadevia PJ, Xu Y, Fahrbach K, et al. Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: a systematic literature review and meta-analysis. Pediatr Crit Care Med. 2011 Sep;12(5):580-8.
7. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013 Apr 30;4:CD006602.
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Therapeutic Class Review
Palivizumab

Overview/Summary

Respiratory syncytial virus (RSV) causes seasonal outbreaks throughout the world and has usual occurrence from November to April in the northern hemisphere. RSV causes acute respiratory tract illness in individuals of all ages with almost all children infected by two years of age.[1] In the United States, 75,000 to 125,000 children under one year of age are hospitalized due to RSV every year. Most healthy individuals recover from RSV infection in one to two weeks; however, the infection can be severe in certain high-risk individuals.[2] The only medication that is approved by the Food and Drug Administration for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection is palivizumab (Synagis®). Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Safety and efficacy of palivizumab have not been established for treatment of RSV disease. Palivizumab is a recombinant humanized monoclonal antibody with anti-RSV activity. Palivizumab acts by binding the RSV envelope fusion protein on the surface of the virus and blocking a critical step in the membrane fusion process; palivizumab also prevents cell-to-cell fusion of RSV-infected cells. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] This review only includes the clinical evidence evaluating the safety and efficacy of palivizumab in high-risk infants and children. Given the limitations in comparing one cost-effectiveness study to another cost-utility evaluation, pharmacoeconomic analyses were not included as part of this review. Nonetheless, palivizumab therapy is associated with significant acquisition costs.

The most recent consensus guidelines are published by the American Academy of Pediatrics (AAP) for the prevention of RSV infections with palivizumab. According to the AAP recommendations, palivizumab prophylaxis is recommended in the following high-risk groups: patients <12 months of age at the onset of the RSV season who were born at 28 weeks, six days' gestation or earlier, who have a diagnosis of chronic lung disease of prematurity, or who have a diagnosis of hemodynamically significant congenital heart disease; palivizumab is also recommended for patients <2 years of age at the onset of the RSV season who have a diagnosis of chronic lung disease of prematurity and who required medical therapy within six months to the start of the RSV season. In addition the AAP makes a case for several indications where palivizumab prophylaxis can be considered and may be appropriate. These include patients <12 months old at the start of the RSV season who have a diagnosis of congenital abnormalities of the airways or neuromuscular disease, and for patients <2 years of age at the start of the RSV season who have diagnosis of cystic fibrosis, patients who have had a cardiac transplant, patients that are severely immunocompromised during the RSV season, and patients who have had cardiopulmonary bypass. The AAP recommends that palivizumab be administered once monthly beginning in November, up to a maximum of five doses for infants and young children with the appropriate indications. Due to a cumulative effect on serum concentration, the fifth palivizumab dose administered in March should provide immunologic protection through April. If a patient has a breakthrough hospitalization due to RSV infection, the AAP recommends discontinuing prophylaxis with palivizumab as the risk for a second infection is very low.[8]

Medications

Table 1. Medications Included Within Class Review[3,9]

Generic Name (Trade name)	Medication Class	Generic Availability
Palivizumab (Synagis®)	Monoclonal antibody (RSV F protein inhibitor)	-

Indications

Table 2. Food and Drug Administration-Approved Indications[3]

Generic Name	Prevention of Serious Lower Respiratory Tract Disease caused by Respiratory Syncytial Virus in Children with High Risk of Respiratory Syncytial Virus Disease
Palivizumab	✔

Pharmacokinetics

Table 3. Pharmacokinetics[3]

Generic Name	Serum Half-Life (days)
Palivizumab	18 (adults); 20 (children <24 months old)

Clinical Trials

The safety and efficacy of palivizumab was evaluated in two randomized, double-blind, placebo-controlled trials (N=2,789) of respiratory syncytial virus (RSV) infection prophylaxis in children at high-risk of an RSV-related hospitalization. In both studies, patients received palivizumab 15 mg/kg or placebo intramuscularly every month for five total doses. The patients were followed for 150 days from randomization.[3-5] The study by Connor et al (N=1,502) was conducted in children less than or equal to 24 months of age with bronchopulmonary dysplasia or infants less than or equal to six months of age with premature birth at less than or equal to 35 weeks gestation during one RSV season. Palivizumab therapy was associated with 55% reduction in hospitalization (4.8% children in palivizumab group vs 10.6% children in placebo group; 95% confidence interval [CI], 38 to 72; *P*=0.00004). Significant reductions were observed in both, children with bronchopulmonary dysplasia and premature children without bronchopulmonary dysplasia. Palivizumab was associated with significant reduction in RSV hospitalizations in infants >5 kg (51%; *P*=0.014) and ≤5 kg (57%; *P*=0.001) and in infants <32 weeks gestational age (47%; *P*=0.003) and 32 through 35 weeks gestational age (80%; *P*=0.002).[4] The study by Feltes et al (N=1,287) was conducted in children less than or equal to 24 months of age with hemodynamically significant congenital heart disease over four consecutive seasons. RSV hospitalization rates was 5.3% in the palivizumab group compared to 9.7% in the placebo group (*P*=0.003).[5]

Meta-analysis and systematic literature review conducted by Checchia et al evaluated the impact of palivizumab prophylaxis on all-cause mortality and RSV-related mortality in infants at high-risk such as ≤35 weeks of gestation, chronic lung disease or congenital heart disease. All-cause mortality during the RSV season occurred in 0.19% of infants with prophylaxis compared to 0.53% of infants without prophylaxis (Peto odds ratio, 0.30; 95% CI, 0.17 to 0.55). Majority of the studies did not report RSV-related deaths. The number needed to treat with palivizumab to prevent one all-cause death for the various subgroups ranged from 113 to 1,736.[6] A Cochrane review by Andabaka et al included seven clinical trials evaluating effectiveness and safety of palivizumab prophylaxis against placebo, no prophylaxis or motavizumab (agent not available in the United States). The authors found that children receiving palivizumab had a statistically significant 51% relative risk reduction in RSV hospitalizations compared to patients receiving placebo (relative risk [RR], 0.49; 95% CI, 0.37 to 0.64). There was no difference in relative risk reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo (RR, 0.69; 95% CI, 0.42 to 1.15). Patients in the palivizumab group had a statistically non-significant 36% relative increase in the risk of hospitalization due to RSV infection, when compared to motavizumab group (RR, 1.36; 95% CI, 0.97 to 1.90). Patients receiving palivizumab had a statistically non-significant 26% relative risk reduction in all-cause mortality compared to motavizumab patients (RR, 0.74; 95% CI, 0.38 to 1.43). This systematic review also included 34 studies evaluating cost-effectiveness or cost-utility and the authors concluded that the cost-effectiveness of palivizumab prophylaxis depends on threshold set by each country's healthcare sector as well as consumption of resources taken into account in each study.[7]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Andabaka et al[7] Palivizumab 15 mg/kg prophylaxis vs placebo or no prophylaxis or another type of prophylaxis in reducing the risk of complications in high-risk infants and children (motavizumab*)	SR RCTs comparing palivizumab prophylaxis with a placebo, no prophylaxis or another type of prophylaxis in preventing serious lower respiratory tract disease caused by RSV in high-risk infants and children were included (children with cystic fibrosis were excluded); cost-effectiveness analyses and cost-utility analyses comparing palivizumab prophylaxis with no prophylaxis were included	7 trials for effectiveness and safety; 34 trials for cost-effectiveness (or cost-utility) 150 days after randomization (30 days after last dose)	Primary: Effectiveness and safety of palivizumab prophylaxis compared to placebo, or another type of prophylaxis, in reducing the risk of complications (hospitalization due to RSV infection); assess cost-effectiveness (or cost-utility) of palivizumab prophylaxis compared to no prophylaxis in infants and children in different risk groups Secondary: Not reported	Primary: Of the seven trials included in the review, three RCTs compared palivizumab to placebo and four compared motavizumab to palivizumab. Thirty-four economic evaluation studies were included. Patients receiving palivizumab had a statistically significant 51% RR reduction in RSV hospitalizations compared to patients receiving placebo (RR, 0.49; 95% CI, 0.37 to 0.64). Patients receiving palivizumab also had a statistically significant 50% RR reduction in admissions to the ICU (RR, 0.50; 95% CI, 0.30 to 0.81). The number of patients requiring mechanical ventilation for RSV infection seemed similar between the two groups (RR, 1.10; 95% CI, 0.20 to 6.09). There was no difference in RR reduction in all-cause mortality with monthly prophylaxis with palivizumab compared to placebo (RR, 0.69; 95% CI, 0.42 to 1.15). Patients in the palivizumab group had a 12% RR reduction in any serious adverse event compared to placebo (RR, 0.88; 95% CI, 0.80 to 0.96) and had a statistically non-significant risk reduction in serious adverse event related to study drug (RR, 0.14; 95% CI, 0.01 to 2.80). Patients in the palivizumab group had a statistically non-significant 36% relative increase in the risk of hospitalization due to RSV infection, when compared to motavizumab recipients (RR, 1.36; 95% CI, 0.97 to 1.90). The risk of outpatient medically attended lower respiratory tract infections specific for RSV infection in the palivizumab group was twice that of the motavizumab group (RR, 1.98; 95% CI, 1.25 to 3.13). Patients receiving palivizumab had a statistically non-significant 68% RR increase in admission to the ICU compared to motavizumab patients (RR, 1.68; 95% CI, 0.89 to 3.19), as well as a statistically non-significant 49% RR increase in incidence of supplemental oxygen therapy for RSV infection (RR, 1.49; 95% CI, 0.98 to 2.26). The risk of mechanical ventilation in the palivizumab group was almost four times that of the motavizumab group (RR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				3.79; 95% CI, 1.26 to 11.42). Patients receiving palivizumab had a statistically non-significant 26% RR reduction in all-cause mortality compared to motavizumab patients (RR, 0.74; 95% CI, 0.38 to 1.43). No significant differences were found in the proportion of children with any adverse event (RR, 1.00; 95% CI, 0.99 to 1.02), with adverse event related to study drug (RR, 0.98; 95% CI, 0.73 to 1.32), with any serious adverse event (RR, 1.04; 95% CI, 0.96 to 1.13), or with serious adverse event related to study drug (RR, 0.88; 95% CI, 0.32 to 2.43) between patients receiving palivizumab and motavizumab. The overall quality of economic evaluations was good. There were considerable variations in modelling approaches across the studies and this resulted in differences in cost-effectiveness results. The cost-effectiveness of palivizumab prophylaxis depends on threshold set by each country's healthcare sector as well as consumption of resources taken into account in each study. Secondary: Not reported
Checchia et al[6] Palivizumab prophylaxis vs placebo (no prophylaxis)	MA, SR Included trials had to report ten or more patients per study group, age up to 24 months at enrollment and noting any of the following outcomes: all-cause mortality and RSV-related	N=~15,000 (10 trials) Duration varied	Primary: All-cause mortality and RSV-related mortality Secondary: RSV hospitalizations, emergency department and ICU admissions, hospital and ICU length of stay,	Primary: Seven out of ten trials reported mortality outcomes. The mortality rate for all causes occurring during the first RSV season for the preterm group with prophylaxis was 0.19% and for the preterm group without prophylaxis was 0.53% (Peto OR, 0.30; 95% CI, 0.17 to 0.55). Mortality rates for the different subgroups of the preterm cohort were 1) CLD: prophylaxis, 0.22%; with no prophylaxis, 0.34% (Peto OR, 0.83; 95% CI, 0.13 to 5.25); 2) preterm ≤32 weeks gestational age with prophylaxis, 0.23%; preterm ≤32 weeks gestational age with no prophylaxis, 0.99% (Peto OR, 0.25; 95% CI, 0.13 to 0.49); 3) preterm 32 to 35 weeks gestational age with prophylaxis, 0.09%; preterm 32 to 35 weeks gestational age with no prophylaxis, 0.13% (Peto OR, 0.22; 95% CI, 0.03 to 1.89); 4) CHD with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	mortality, RSV hospitalizations, emergency department and ICU admissions, hospital and ICU length of stay, oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation		oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation	prophylaxis, 3.29%; and CHD with no prophylaxis, 4.17% (Peto OR, 0.78; 95% CI, 0.44 to 1.39). A sensitivity analysis comparing RCTs vs non RCTs showed that all-cause mortality in the premature cohort was similarly reduced, non RCT had an OR of 0.32 (95% CI, 0.15 to 0.58) and RCT had an OR of 0.32 (95% CI, 0.09 to 1.20). The results were not statistically significant for the RCT groups. The number needed to treat with palivizumab to prevent one all-cause death for the various subgroups were as follows: 1) all preterm, 270; 2) CLD, 1,736; 3) preterm ≤32 weeks gestational age, 136; 4) preterm 32 to 35 weeks gestational age, 987; 5) mixed preterm gestational categories, not available; 6) CHD, 113. Secondary: Emergency department and ICU admissions, hospital and ICU length of stay, oxygen requirements, apnea episodes, outpatient visits, and use of mechanical ventilation were not included in the MA as not all studies had this information and as a result, a formal MA was not conducted for these endpoints. In the two RCTs of preterm infants in which hospitalizations were the primary end points, palivizumab resulted in a significant reduction of RSV hospitalizations (OR, 0.42; 95% CI, 0.27 to 0.64). The results were similar when RCTs were excluded from analyses (OR, 0.33; 95% CI, 0.22 to 0.48). The number needed to treat with palivizumab to prevent one RSV hospitalization for the various subgroups were as follows: 1) all preterm, 16; 2) CLD, 11; 3) preterm ≤32 weeks gestational age, 14; 4) preterm 32 to 35 weeks gestational age, 18; 5) mixed preterm gestational categories, 24; 6) CHD, 23.
Connor et al[4] Impact-RSV Palivizumab 15 mg/kg	DB, MC, PC, RCT Children six months of age or	N=1,502 (1,002 in the palivizumab group and 500	Primary: Hospitalization with confirmed RSV infection; safety	Primary: Palivizumab therapy was associated with 55% reduction in hospitalization (4.8% children in palivizumab group vs 10.6% children in placebo group; 95% CI, 38% to 72%; *P*=0.00004). Significant reductions were observed in both,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
intramuscularly every 30 days for five doses vs placebo 15 mg/kg intramuscularly every 30 days for five doses	younger with prematurity (≤ 35 weeks of gestation) or ≤24 months old with a clinical diagnosis of bronchopulmonary dysplasia (or chronic lung disease of prematurity) requiring ongoing medical treatment (i.e., supplemental oxygen, steroids, bronchodilators, or diuretics within the past six months); children with CHD were excluded, except for those with a patent ductus arteriosus or a septal defect that was uncomplicated and hemodynamically insignificant	in the placebo group) 150 days (30 days after the last scheduled study injection)	Secondary: Compare the effect of monthly palivizumab prophylaxis with placebo on characteristics of RSV hospitalization: total RSV days with supplemental oxygen, incidence and total RSV-associated days in the ICU, and incidence and total days of RSV-associated mechanical ventilation; compare the effect of monthly palivizumab prophylaxis with placebo on the incidence and total days of hospitalization for non-RSV respiratory disease and respiratory disease and hospitalizations for any cause;	children with bronchopulmonary dysplasia (7.9% children in palivizumab group vs 12.8% children in placebo group; 39% reduction, 95% CI, 20 to 58; *P*=0.038), and premature children without bronchopulmonary dysplasia (1.8% children in palivizumab group vs 8.1% children in placebo group; 78% reduction, 95% CI, 66 to 90; *P*<0.001). Palivizumab was associated with significant reduction in RSV hospitalizations in infants >5 kg (51%; *P*=0.014) and ≤5 kg (57%; *P*=0.001) and in infants <32 weeks gestational age (47%; *P*=0.003) and 32 through 35 weeks gestational age (80%; *P*=0.002). When included in the logistic regression analysis, gestational age was not a significant predictor of RSV hospitalization and the palivizumab effect remained statistically significant (*P*<0.001). The proportion of children with adverse events judged by the blinded investigator to be related to the study drug was similar between the two groups. Overall, 1.8% of the placebo group and 2.7% of the palivizumab group reported adverse events related to the injection site. Secondary: Children randomized to palivizumab had significantly fewer total days (per 100 children) of RSV hospitalization (62.6 placebo days vs 36.4 palivizumab days; *P*<0.001), days with increased oxygen (50.6 days vs 30.3 days; *P*<0.001), and days with an lower respiratory infection score of 3 or greater (47.4 days vs 29.6 days; *P*<0.001). Three percent of placebo patients and 1.3% of palivizumab recipients had RSV ICU admissions (*P*=0.026); total days were 12.7 and 13.3, respectively (*P*=0.023). There was no significant differences in incidence of mechanical ventilation (0.2 vs 0.7%; *P*=0.280) or total days of mechanical ventilation (1.7 vs 8.4 days; *P*=0.210) between the two groups. Palivizumab recipients had significant reductions in the incidence (31 vs 24%; *P*=0.011) and total days per 100 children (242 vs 191 days; *P*=0.005) of all hospitalizations and the incidence (22 vs 16%; *P*=0.008) and total days per 100 children (180 vs 124 days; *P*=0.004) of respiratory hospitalizations.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			compare the effect of palivizumab prophylaxis with placebo on the incidence of otitis media	These differences were attributable to the observed reduction of RSV hospitalizations, because no significant differences were observed in the incidence (14 vs 13%; *P*=0.470) or total days per 100 children (118 vs 88 days; *P*=0.369) of respiratory hospitalizations unrelated to RSV. The proportion of children with at least one episode of otitis media was similar in both placebo and palivizumab group (40 vs 42%; *P*=0.505).
Feltes et al[5] Palivizumab 15 mg/kg intramuscularly every 30 days for five doses vs placebo 15 mg/kg intramuscularly every 30 days for five doses	DB, MC, PC, RCT Children ≤24 months of age at time of randomization with documented hemodynamically significant unoperated or partially corrected CHD as determined by clinical (e.g., prescriptions for cardiac medications) and echocardiographic assessment by the investigator; patients were excluded if they had simple atrial septal defects, ventricular septal defects, patent ductus arteriosus, or unstable cardiac	N=1,287 150 days (30 days after the last scheduled study injection)	Primary: Compare the safety, tolerance, and efficacy of palivizumab with placebo for the reduction of the incidence of RSV hospitalization among children with hemodynamically significant CHD Secondary: Compare the effects of treatment on RSV hospitalization outcomes as measured by total days of RSV hospitalization, total RSV hospital days with increased oxygen requirement,	Primary: RSV hospitalization rates was 5.3% in the palivizumab group compared to 9.7% in the placebo group (*P*=0.003). Treatment with palivizumab remained significant when logistic regression analysis was performed with predefined variables of age, sex and cardiac strata (*P*=0.004). The proportion of children with adverse events, adverse events that required medical intervention and adverse events judged by the blinded investigator to be related to the study drug was similar between the two groups. There were some adverse events that were reported at an absolute incidence ≥1% higher in the palivizumab group compared to the placebo group including fever (27.1% in palivizumab group vs 23.9% in placebo group), infection (5.6% in palivizumab group vs 2.9% in placebo group), study drug injection site reaction (3.4% in palivizumab group vs 2.2% in placebo group), upper respiratory infection (47.4% in palivizumab group vs 46.1% in placebo group), conjunctivitis (11.3% in palivizumab group vs 9.3% in placebo group), arrhythmia (3.1% in palivizumab group vs 1.7% in placebo group), and cyanosis (9.1% in palivizumab group vs 6.9% in placebo group). The most common injection site reactions were redness, swelling and bruising and none were serious. The incidence of serious adverse events was significantly lower in the palivizumab group compared to the placebo group (55.4 vs 63.1%; *P*=0.005). Secondary: Children randomly assigned to palivizumab had significantly fewer total days of RSV hospitalization per 100 children (56% reduction; 57.4 days in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or respiratory status		incidence and total days of RSV-associated intensive care, and incidence and total days of RSV-associated mechanical ventilation; to describe the effect of cardiac bypass on serum palivizumab concentrations; and to determine palivizumab trough concentrations before the second and fifth doses	palivizumab group vs 129.0 days in placebo group; *P*=0.003). Children randomly assigned to palivizumab had significantly fewer RSV hospital days with increased oxygen requirement per 100 children (73% reduction; 27.9 days in palivizumab group vs 101.5 days in placebo group; *P*=0.014). The incidence of RSV-associated intensive care was lower in the palivizumab group (46% reduction; 13 children in palivizumab group vs 24 children in placebo group; *P*=0.094). The total number of days of RSV-associated intensive care per 100 children was also lower in the palivizumab group (78% reduction; 15.9 days in palivizumab group vs 71.2 days in placebo group; *P*=0.080). The incidence of RSV-associated mechanical ventilation was lower in the palivizumab group (41% reduction; eight children in palivizumab group vs 14 children in placebo group; *P*=0.282), and days of RSV-associated mechanical ventilation per 100 children was also lower in the palivizumab group (88% reduction; 6.5 days in palivizumab group vs 54.7 days in placebo group; *P*=0.224). Prolonged RSV hospitalization (≥14 days) occurred in five children in the palivizumab group compared to 16 children in the placebo group. Paired serum was available before and after cardiac bypass for 139 children who had received palivizumab. Before and after cardiopulmonary bypass, the mean ± SD serum palivizumab concentrations were 98.0 ± 52 µg/mL and 41.4 ± 33 µg/mL, respectively (58% reduction in serum palivizumab concentration after bypass; *P*=0.0001). Mean ± SD serum palivizumab concentrations before the second and fifth doses were 55.5 ± 19 µg/mL and 90.8 ± 35 µg/mL in the palivizumab group and 0.4 ± 5 µg/mL and 0.1 ± 2 µg/mL in the placebo group.

*Drug not available in the United States.
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial, SR=systematic review
Miscellaneous: CHD=congenital heart disease, CI=confidence interval, CLD=chronic lung disease of maturity, ICU=intensive care unit, OR=odds ratio, RR=relative risk, RSV=respiratory syncytial virus, SD=standard deviation

Special Populations

Table 5. Special Populations[3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Palivizumab	Safety and efficacy in children greater than 24 months of age at the start of dosing have not been established.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	C	Unknown; not indicated for adult use.

Adverse Drug Events

Table 6. Adverse Drug Events[3]

Adverse Event	Palivizumab
Acute hypersensitivity reactions	✔
Anaphylaxis	✔
Fever	✔
Injection site reactions*	✔
Rash	✔
Severe thrombocytopenia*	✔

*Postmarketing experience.

Contraindications/Precautions

Table 7. Contraindications[3]

Contraindication(s)	Palivizumab
Previous significant hypersensitivity reaction to palivizumab	✔

Table 8. Warnings and Precautions[3]

Warning(s)/Precaution(s)	Palivizumab
Anaphylactoid/hypersensitivity reactions: there have been reports of very rare cases of anaphylaxis; rare cases of severe acute hypersensitivity reactions have also been reported; caution is recommended with mild hypersensitivity reaction and for severe hypersensitivity reaction, the medication should be permanently discontinued	✔
Appropriate use: the single-dose vial does not contain a preservative; administration should occur immediately after dose withdrawal from the vial; the vial should not be re-entered and any unused portion should be discarded	✔
Bleeding disorders: use with caution in patients with a history of bleeding disorders (including thrombocytopenia); bleeding/hematoma may occur from intramuscular administration.	✔
Respiratory syncytial virus: safety and efficacy have not been demonstrated in the treatment of established respiratory syncytial virus disease	✔
Respiratory syncytial virus diagnostic test interference: interference (false negatives) with immunological-based respiratory syncytial virus diagnostic tests (antigen detection) and viral culture assays has been reported; reverse-transcriptase-polymerase chain reaction-based assays and clinical findings should be relied upon	✔

Drug Interactions

There are no formal drug-drug interaction studies conducted with palivizumab. In one of the clinical trials, there was no incremental increase in adverse reactions seen in patients who also received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids.[3,10]

Dosage and Administration

Table 9. Dosing and Administration[3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Palivizumab	Safety and efficacy in adults have not been established.	Prevention of serious lower respiratory tract disease caused by RSV in children with high risk of RSV disease: Injection: 15 mg/kg of body weight intramuscularly prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season* Max: 5 injections per season	Single-dose solution vials for injection: 50 mg/0.5 mL 100 mg/1 mL

RSV=respiratory syncytial virus
*Children undergoing cardio-pulmonary bypass should receive an additional dose of palivizumab as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly as scheduled.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Pediatrics: **Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased risk of Hospitalization for Respiratory Syncytial Virus Infection (2014)**[8]	Prevention of respiratory syncytial virus (RSV) infections: • Palivizumab is the only licensed product available to reduce the risk of RSV lower respiratory tract disease in infants and children with chronic lung disease of prematurity, with a history of preterm birth (less than 29 weeks' gestation), or with congenital heart disease. • Palivizumab is administered intramuscularly at a dose of 15 mg/kg once every 30 days for a maximum of five injections per RSV season. • Maintaining compliance with monthly administration of palivizumab is important. • The five recommended doses of palivizumab will provide more than 6 months (>24 weeks) of serum palivizumab concentrations above the desired level for most children. For this reason, administration of more than the five monthly doses are not recommended. • Additional doses of palivizumab should not be given to any patient with a history of a severe allergic reaction following a previous dose. • Palivizumab is not effective in treatment of RSV disease and is not recommended for this indication. • Palivizumab is not recommended for any patients >2 years old at the onset of the RSV season Cost considerations: • Immunoprophylaxis with palivizumab is an effective, although costly, intervention that reduces RSV hospitalization rates • Optimal cost benefit from palivizumab immunoprophylaxis is achieved during peak outbreak months when most RSV hospitalizations occur. • No prospective, randomized clinical trial has demonstrated a significant decrease in the rate of mortality attributable to RSV or in the rate of

Clinical Guideline	Recommendations
	recurrent wheezing following RSV infection among infants who receive prophylaxis with palivizumab. Initiation and termination of immunoprophylaxis: • Peak RSV activity in North America typically occurs begins in October or November and continues until April or early May of the following year. • The median peak activity over six seasons (2007 to 2013) ranged from mid-December to early February. • Results from clinical trials indicate that palivizumab trough serum concentrations more than 30 days after the fifth dose will be well above the protective concentration for most infants. Five monthly doses of palivizumab will provide more than 20 weeks of protective serum antibody concentration. • In the continental United States, a total of five monthly doses for infants and young children with congenital heart disease, chronic lung disease of prematurity, or preterm birth before 29 weeks' gestation (28 weeks, six days' and younger) will provide an optimal balance of benefit and cost, even with variation in season onset and end. • For infants who qualify for five doses, initiation of immunoprophylaxis in November and continuation for a total of five monthly doses will provide protection into April and is recommended for most areas of the United States. If prophylaxis is initiated in October, the fifth and final dose should be administered in February. • Infants and children with congenital heart disease or chronic lung disease of prematurity or preterm infants born at or before 28 weeks, six days' gestation who initiate palivizumab prophylaxis after start of the RSV season will not require all five doses. Eligibility criteria for prophylaxis of high-risk infants and young children: • Infants with chronic lung disease of prematurity (birth <32 weeks, 0 days' gestation and requirement for >21% oxygen for at least 28 days after birth): o Recommended for patients <12 months of age at the onset of the RSV season. o Recommended for patients <2 years of age at the start of the RSV season if, and only if, the patient has required medical therapy within six months prior to the start of the RSV season ▪ supplemental oxygen ▪ bronchodilator ▪ diuretic therapy ▪ chronic corticosteroid therapy. o These patients should receive a maximum of five doses. o Data are limited regarding the effectiveness of palivizumab during the second year of life. Individual patients may benefit from decisions made in consultation with neonatologists, pediatric intensivists, pulmonologists, or infectious disease specialists. • Infants born prematurely before 29 weeks' (≤28 weeks, 6 days') gestation: o Recommended for patients <12 months of age at the start of the RSV season. Available data for infants born at 29 weeks, 0 days' gestation or later do not identify a clear gestational age

Clinical Guideline	Recommendations
	cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days' gestation or later are not universally recommended to receive palivizumab prophylaxis. • Infants born prematurely on or after 29 weeks' gestation: o Available data does not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear, as such palivizumab prophylaxis is not recommended for preterm infants born on or after 29 weeks, 0 days' gestation. • Several considerations are outlined for other high-risk patients where the data is limited and a recommendation cannot be made. The decision to use palivizumab prophylaxis should be made on an individual basis by the specialized prescriber. o Patients who have a diagnosis of congenital abnormalities of the airways or neuromuscular disease and are <12 months of age at the start of the RSV season, o Patients who have a diagnosis of cystic fibrosis who have clinical evidence of chronic lung disease and/or nutritional compromise and are <12 months of age at the start of the RSV season, o Patients who have a diagnosis of cystic fibrosis who have had manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest radiography or chest computed tomography that persists when stable) and are <2 years of age at the start of the RSV season, o Patients who have had a cardiac transplant and are <2 years of age at the start of the RSV season, o Patients who are severely immunocompromised (solid organ or hematopoietic stem cell transplant, chemotherapy, or other conditions) during the RSV season and are <2 years of age at the start of the RSV season, o Patients who have had cardiopulmonary bypass and continues to require prophylaxis after surgery or at the conclusion of extracorporeal membrane oxygenation and are <2 years of age at the start of the RSV season. • Special situations: o Hospitalized infants who qualify for prophylaxis during the RSV season should receive the first dose of palivizumab 48 to 72 hours before discharge or promptly after discharge. o Infants who have begun palivizumab prophylaxis earlier in the season and are hospitalized on the date when the next monthly dose is due should receive that dose as scheduled while they remain in the hospital. o Patients who experience an RSV-related hospitalization should discontinue use of palivizumab as the likelihood of a second infection in a single season is <0.5%. o Because a mean decrease in palivizumab serum concentration of 58% was observed after surgical procedures that use cardiopulmonary bypass, for children who still require prophylaxis, a postoperative dose of palivizumab (15 mg/kg) should be considered as soon as the patient is medically stable; then continue on with regular injections monthly until finished

Clinical Guideline	Recommendations
	with the course of therapy o No data exist to support palivizumab use in controlling outbreaks of health care-associated disease, and palivizumab use is not recommended for this purpose. Palivizumab does not interfere with response to vaccines. o Data for patients with Down syndrome is lacking. It is recommended these patients only receive palivizumab prophylaxis if they meet the other criteria already outlined in the guidelines. o Palivizumab is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.

Conclusions

Respiratory syncytial virus (RSV) causes acute respiratory tract illness in individuals of all ages and the infection can be severe in certain high-risk individuals.[2] Currently, one agent, palivizumab (Synagis®), has been approved by the Food and Drug Administration and is commercially available in the United States for the prevention of serious lower respiratory tract infection caused by RSV in pediatric patients at high risk of RSV infection. Safety and efficacy of palivizumab were established in infants with a history of premature birth (≤35 weeks gestational age), children with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease. Palivizumab is not approved for the treatment of RSV disease. The recommended dose of palivizumab is 15 mg/kg of body weight injected intramuscularly once monthly throughout the RSV season.[3] The most frequently occurring adverse events in clinical trials in patients using palivizumab were fever and rash.[3-7] According to available clinical evidence, palivizumab therapy reduces hospital and intensive care unit admission rates, but it does not effectively reduce either the incidence of RSV or RSV mortality.[4-7] The consensus guidelines published by the American Academy of Pediatrics establishes eligibility criteria for prophylaxis of high-risk infants and young children for the prevention of RSV infections with palivizumab.[8] Currently, palivizumab is only available as a branded agent.

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Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Acetaminophen	19367	35096
Ibuprofen	6442	8699
Lisinopril	6126	11927
Insulin	5873	10626
Fluticasone	5515	8925
Metformin	4528	8842
Hydrochlorothiazide	4407	8400
Amlodipine	4272	9053
Levothyroxine	4027	8887
Metoprolol	2971	6275
Trazodone	2880	6282
Citalopram	2843	6285
Oxycodone	2836	7604
Sertraline	2571	5686
Quetiapine	2333	6186
Aspirin	2320	4681
Promethazine	2230	3070
Naproxen	2096	3117
Fluoxetine	2073	4506
Ciprofloxacin	2069	2354
Risperidone	2048	5341
Estradiol	1909	3606
Codeine	1857	2177
Esomeprazole	1842	3840
Diclofenac	1780	2950
Losartan	1772	3457
Aripiprazole	1722	4079
Meloxicam	1654	2981
Morphine	1626	4462
Carvedilol	1610	3432
Famotidine	1557	3023
Iron	1522	3070
Budesonide	1507	2645
Clindamycin	1449	1662
Atenolol	1355	2884
Bupropion	1351	2820
Amphetamine	1292	2997
Lamotrigine	1272	3178
Clopidogrel	1252	2649
Metronidazole	1172	1299
Glipizide	1153	2285
Baclofen	1128	2350
Amitriptyline	1075	2352
Levofloxacin	974	1126
Methylphenidate	922	2242
Olanzapine	862	2223

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Paroxetine	856	1866
Lidocaine	853	1333
Duloxetine	763	1830
Lisdexamfetamine	711	1624
Penicillin	700	802
Chlorhexidine	670	771
Medroxyprogesterone	637	743
Mirtazapine	613	1379
Prenatal	572	817
Ziprasidone	569	1447
Methadone	568	1503
Glimepiride	548	1011
Propranolol	544	1169
Carbamazepine	521	1265
Venlafaxine	489	1215
Hydrocodone	484	595
Phenytoin	483	1133
Lurasidone	468	1045
Neomycin	456	496
Diltiazem	435	912
Lithium	430	1044
Hydromorphone	429	1049
Ketoconazole	422	596
Metoclopramide	419	725
Conjugated	400	809
Enalapril	398	764
Ofloxacin	383	441
Atomoxetine	372	848
Paliperidone	362	960
Benazepril	340	655
Tobramycin	335	394
Glyburide	329	624
Valsartan	324	656
Fentanyl	323	737
Timolol	322	587
Polymyxin	302	321
Haloperidol	293	660
Varenicline	293	448
Rivaroxaban	279	597
Methotrexate	251	558
Hydroxychloroquine	237	483
Dexmethylphenidate	235	547
Linaclotide	229	441
Bacillus	224	393
Amiodarone	220	440
Pioglitazone	215	432

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Lansoprazole	210	426
Cyclosporine	204	382
Labetalol	203	430
Nortriptyline	203	410
Indomethacin	201	309
Gentamicin	192	243
Emtricitabine	190	442
Desvenlafaxine	188	425
Enoxaparin	174	425
Formoterol	171	299
Testosterone	160	282
Doxepin	159	319
Buprenorphine	157	483
Prochlorperazine	157	229
Etodolac	155	256
Moxifloxacin	153	194
Ritonavir	152	357
Canagliflozin	145	305
Ketorolac	145	171
Asenapine	144	342
Celecoxib	142	282
Bacitracin	137	170
Oxymorphone	136	372
Bisoprolol	135	262
Nabumetone	132	225
Mycophenolate	131	294
Drospirenone	113	245
Liraglutide	113	231
Linagliptin	108	224
Ramipril	100	176
Fluphenazine	97	253
Tacrolimus	96	262
Tamoxifen	95	205
Tretinoin	88	111
Collagenase	87	170
Abacavir	84	210
Chlorpromazine	84	184
Clozapine	80	367
Efavirenz	78	176
Phenylephrine	76	94
Progesterone	72	124
Raloxifene	68	143
Midodrine	67	165
Piroxicam	66	104
Imipramine	64	161
Liothyronine	64	138

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Cilostazol	62	126
Etanercept	61	137
Cobicistat	58	132
Nadolol	57	118
Hydroxyurea	56	97
Bumetanide	53	111
Milnacipran	52	104
Dabigatran	51	104
Minoxidil	50	128
Apixaban	48	103
Flurbiprofen	48	76
Azathioprine	46	92
Adalimumab	44	107
Valproic	44	123
Iloperidone	41	103
Olmesartan	41	76
Ribavirin	41	81
Vilazodone	41	88
Leflunomide	39	75
Omalizumab	37	88
Fluvoxamine	36	89
Prasugrel	36	78
Perphenazine	35	93
Felbamate	34	98
Captopril	33	78
Exenatide	33	61
Loxapine	33	92
Interferon	32	77
Levomilnacipran	28	57
Tapentadol	26	65
Lamivudine	25	61
Salmeterol	24	41
Fluorouracil	23	23
Phytonadione	23	40
Sotalol	23	51
Clomipramine	22	49
Tenofovir	22	45
Antihemophilic	21	88
Misoprostol	21	31
Sulindac	21	36
Disulfiram	20	36
Dronedarone	19	42
Ketoprofen	19	29
Nevirapine	19	60
Capecitabine	18	55
Irbesartan	18	28

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Isoniazid	18	38
Epoetin	17	71
Flecainide	16	32
Sirolimus	16	35
Ticagrelor	16	33
Deferasirox	15	33
Oxaprozin	15	24
Trifluoperazine	15	41
Quinidine	14	61
Thioridazine	14	39
Ganciclovir	13	22
Propylthiouracil	12	23
Aliskiren	11	21
Desipramine	11	18
Perampanel	11	34
Thiothixene	11	27
Vortioxetine	11	20
Bismuth	10	10
Dapagliflozin	10	18
Propafenone	10	17
Telmisartan	10	20
Everolimus	9	24
Zidovudine	9	20
Ambrisentan	8	23
Estropipate	8	16
Isotretinoin	8	15
Mexiletine	8	16
OnabotulinumtoxinA	8	10
Pimozide	8	18
Arformoterol	7	19
Bosentan	7	15
Immune	7	48
Quinine	7	16
Salsalate	7	15
Vigabatrin	7	17
Amiloride	6	15
Azilsartan	6	15
Natalizumab	6	16
Pimecrolimus	6	11
Tinidazole	6	7
Amprenavir	5	15
Becaplermin	5	7
Certolizumab	5	8
Dihydroergotamine	5	8
Entecavir	5	14
Mestranol	5	10

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Quinapril	5	7
Teriflunomide	5	10
Tofacitinib	5	12
Dofetilide	4	6
Selegiline	4	16
Teriparatide	4	12
Tetrabenazine	4	11
Alogliptin	3	5
Dantrolene	3	7
Didanosine	3	10
Dienogest	3	4
Eltrombopag	3	6
Factor	3	12
Infliximab	3	5
Maraviroc	3	7
Nefazodone	3	10
Phenelzine	3	6
Tocilizumab	3	4
Trandolapril	3	8
Trastuzumab	3	7
Caffeine	2	2
Darbepoetin	2	3
Deferiprone	2	7
Esterified	2	5
Ezogabine	2	17
Fondaparinux	2	10
Idursulfase	2	6
Mefenamic	2	2
Ospemifene	2	4
Oxymetholone	2	4
Terbutaline	2	3
Ticlopidine	2	5
AbobotulinumtoxinA	1	1
Bevacizumab	1	2
Candesartan	1	1
Cytarabine	1	2
Danazol	1	2
Disopyramide	1	1
Ethacrynic	1	3
Fosinopril	1	1
Golimumab	1	3
Indacaterol	1	4
Itraconazole	1	1
Lindane	1	3
Lomitapide	1	3
Macitentan	1	3

Black Box Warning Medications

GPI Name	Count of Member	Count of Claim
Maprotiline	1	1
Moexipril	1	3
Pazopanib	1	3
Pentazocine	1	1
Pindolol	1	3
Riociguat	1	3
Rituximab	1	4
Rosiglitazone	1	3
Stavudine	1	2
Sunitinib	1	1
Umeclidinium	1	1
Vismodegib	1	1

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
ACETAMINOPHEN W/ CODEINE				
201401	469	438	29256.276	4693
201402	438	401	31468	4170
201403	464	434	31649	4235
201404	499	457	32413	4905
201405	453	411	30768.5	4384
201406	445	406	27745.5	4364
201407	471	429	28641.5	4687
201408	432	409	25819	4509
201409	430	395	27473.5	4404
201410	679	625	39403	6869
201411	607	561	35960	6167
201412	608	557	35882.5	6428
ALFENTANIL				
201402	2	2	4	2
201403	3	3	6	3
201406	1	1	2	1
201407	1	1	2	1
201408	2	2	4	2
201410	1	1	2	1
BUPRENORPHINE				
201401	14	14	56	400
201402	19	15	64	427
201403	14	13	60	394
201404	17	15	66	464
201405	16	15	59	416
201406	18	16	64	452
201407	13	12	50	340
201408	15	14	60	424
201409	13	13	52	366
201410	16	16	61	429
201411	14	13	56	396
201412	14	12	56	394
BUPRENORPHINE HCL				
201401	8	7	404	203
201402	4	4	190	109
201403	9	8	435	215
201404	13	11	743	321
201405	12	8	524	211
201406	12	8	472	232
201407	9	7	242	159
201408	7	7	339	172
201409	9	6	329	170
201410	5	4	119	101
201411	5	5	157	121
201412	9	4	200	145
BUPRENORPHINE HCL-NALOXONE				
201401	87	53	2407	1569

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201402	83	52	2258	1350
201403	94	66	2921	1703
201404	98	64	2777	1715
201405	116	76	3259	2054
201406	109	86	3244	2160
201407	144	95	4198	2651
201408	134	90	3809	2370
201409	154	92	4179	2500
201410	166	104	4235	2726
201411	115	78	3503	2239
201412	141	90	4395	2622
BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE				
201401	49	45	3233	736
201402	49	45	3117	754
201403	52	45	3435	833
201404	57	47	3905	955
201405	69	60	4874	1129
201406	66	57	4446	1170
201407	77	65	4699	1218
201408	75	64	5048	1217
201409	73	61	4416	1025
201410	73	62	4603	1276
201411	66	58	4230	1087
201412	59	48	3906	1085
BUTALBITAL-ASPIRIN-CAFFEINE W/COD				
201401	19	19	1760	414
201402	14	13	1250	283
201403	22	22	2090	458
201404	16	16	1500	350
201405	22	22	2110	488
201406	21	21	1960	371
201407	26	19	2385	437
201408	29	23	2290	487
201409	30	25	2668	488
201410	24	21	1933	382
201411	29	22	2245	495
201412	23	18	1625	382
BUTORPHANOL TARTRATE				
201401	14	13	60.5	239
201402	13	12	59.5	190
201403	13	13	52	237
201404	14	14	60	328
201405	16	12	66	238
201406	16	13	52.5	251
201407	15	14	47	316
201408	12	12	47	252
201409	12	11	41	221
201410	20	16	70	297
201411	10	7	37.5	181
201412	14	12	56	283

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
CODEINE SULFATE				
201401	2	2	560	60
201402	4	4	591	71
201403	2	2	80	35
201404	3	3	125	64
201405	1	1	40	20
201406	2	2	72	34
201407	3	3	270	90
201408	3	3	151	61
201409	4	3	161	38
201410	2	1	84	2
201411	2	2	102	31
201412	1	1	60	30
FENTANYL				
201401	290	216	2396	6544
201402	294	223	2495	6684
201403	331	253	2708	7453
201404	376	269	2991.17	8035
201405	354	253	2735.17	7419
201406	318	241	2567.16	6961
201407	294	238	2614.11	7195
201408	273	222	2399.14	6544
201409	260	215	2356.21	6463
201410	269	232	2517.075	6903
201411	231	200	2335	6045
201412	259	215	2612	6852
FENTANYL CITRATE				
201401	1	1	112	28
201402	1	1	112	28
201403	1	1	112	28
201404	1	1	112	28
201405	1	1	112	28
201406	1	1	112	28
201407	1	1	112	28
201408	1	1	112	28
201409	1	1	112	28
201410	1	1	112	28
201411	1	1	60	15
HYDROCODONE BITARTRATE				
201405	1	1	60	30
201406	1	1	60	30
201407	1	1	60	30
201408	4	4	208	104
201409	2	2	65	60
HYDROCODONE-ACETAMINOPHEN				
201401	9160	7600	699404	168006
201402	8487	7332	648124.53	154872
201403	9519	7990	704511.51	169144
201404	10218	8442	737630.54	176422
201405	9971	8178	732186.68	174104

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201406	9834	8249	710632.94	170599
201407	10187	8375	742442.04	178653
201408	9603	8071	696073.32	166823
201409	9576	8017	694493.11	168426
201410	8307	7101	615588.43	148763
201411	6740	6053	518913.42	127277
201412	7590	6560	590645.05	145585
HYDROCODONE-IBUPROFEN				
201401	58	51	3178	827
201402	59	53	3066	843
201403	57	53	3350	907
201404	46	43	3295	911
201405	47	43	3181	800
201406	40	37	2819	740
201407	54	47	3543	954
201408	57	49	3680	916
201409	48	45	3512	962
201410	50	44	3116	841
201411	42	40	2584	716
201412	36	34	2557	735
HYDROMORPHONE HCL				
201401	1237	850	30700.5	7907
201402	1233	871	27495	6855
201403	1373	982	27837.5	7184
201404	1187	816	31540	7613
201405	1106	778	30499	7433
201406	1104	782	27073	6904
201407	1115	780	26964	6746
201408	1112	801	26844	6672
201409	982	732	28117	6655
201410	1075	777	28598.458	7213
201411	726	558	24685.5	6257
201412	819	606	28456	6900
MEPERIDINE HCL				
201401	64	50	357.5	215
201402	47	37	342.5	142
201403	53	46	518.5	216
201404	62	50	736	277
201405	60	51	602	254
201406	57	48	364.5	175
201407	67	55	265.5	151
201408	51	40	296	142
201409	35	27	282	137
201410	46	39	371	149
201411	36	30	313	147
201412	30	26	336.75	134
METHADONE HCL				
201401	578	499	79656.3	15033
201402	555	489	73181.75	14000
201403	596	519	78027.1	15117

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201404	640	529	85642.4	15644
201405	690	551	83274.5	15737
201406	658	545	80175.2	14913
201407	663	526	83034.8	15468
201408	614	503	76044.94	14345
201409	588	497	74676.5	13996
201410	557	476	72286.5	14117
201411	509	451	65702	13032
201412	512	450	69079	13926
MORPHINE SULFATE				
201401	2400	1845	115257.54	45023
201402	2367	1890	104725.25	41410
201403	2447	1909	108396.6	42289
201404	2781	2124	111553.64	44254
201405	2788	2087	108686.94	43378
201406	2701	2111	106730.76	41949
201407	2876	2126	111250.3	45585
201408	2620	2008	101860.71	41035
201409	2490	1914	94257.5	38991
201410	2322	1780	105300.893	43313
201411	1868	1491	90407.8	37000
201412	1875	1466	99672.8	41053
MORPHINE SULFATE BEADS				
201401	3	3	90	90
201402	3	3	90	90
201403	3	3	90	90
201404	1	1	30	30
201405	1	1	30	30
201406	1	1	30	30
201407	1	1	30	30
201409	1	1	30	30
201410	2	2	60	60
NALBUPHINE HCL				
201402	1	1	200	20
201403	4	3	440	42
201404	3	2	410	36
201405	3	2	410	54
201406	11	8	722	99
201407	6	5	246	63
201408	10	7	691	89
201409	7	4	441	92
201410	6	4	460	74
201411	6	5	261	52
201412	3	2	22	35
OXYCODONE HCL				
201401	2746	2149	272942	64938
201402	2584	2135	254212.505	60207
201403	2810	2216	269564.01	63543
201404	2976	2282	282457.01	66840
201405	3014	2290	284174.615	66946

Opioid Utilization 2014

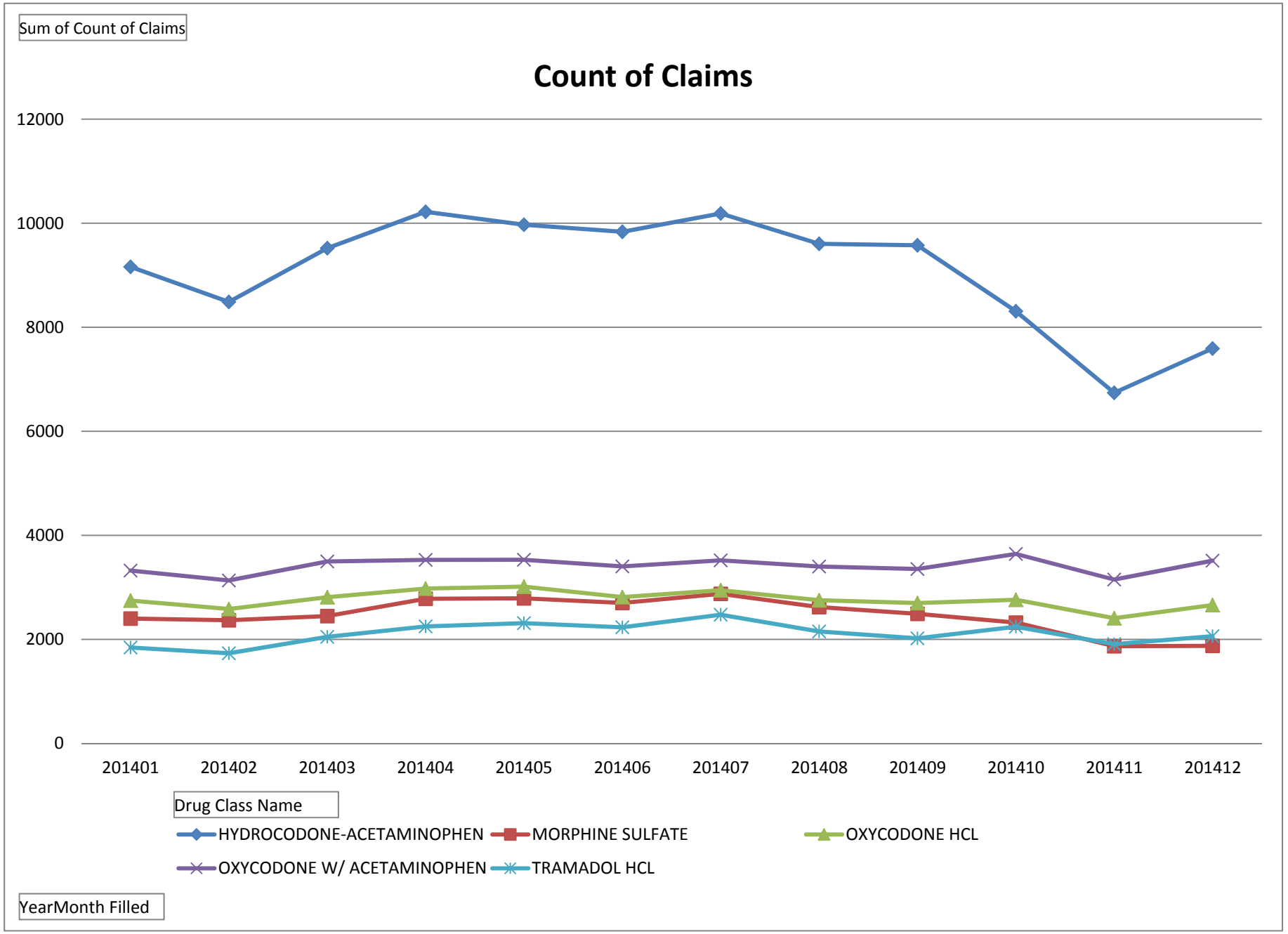
Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201406	2812	2274	275197.31	65320
201407	2945	2327	286016.79	68299
201408	2753	2243	334716.779	64782
201409	2699	2224	266310.139	64043
201410	2760	2221	275183.005	66220
201411	2406	2059	241824.51	58181
201412	2660	2147	270224	65101
OXYCODONE W/ ACETAMINOPHEN				
201401	3323	2712	230126.5	54106
201402	3133	2639	213289	49653
201403	3498	2904	236004	55879
201404	3527	2878	239587.9	56270
201405	3530	2924	241906.56	57377
201406	3402	2825	231130	54048
201407	3520	2875	243964.649	57714
201408	3401	2850	234175.104	55382
201409	3353	2817	231748.104	54903
201410	3642	3056	256213.944	61704
201411	3150	2773	230320.736	55432
201412	3513	2934	262223	63563
OXYCODONE-ASPIRIN				
201401	5	5	540	128
201402	3	3	450	90
201403	4	4	237	46
201404	3	3	330	90
201405	4	4	390	80
201406	4	4	286	87
201407	3	3	136	45
201408	2	2	120	45
201409	3	3	136	42
201410	3	3	160	63
201412	1	1	60	30
OXYCODONE-IBUPROFEN				
201412	1	1	50	8
OXYMORPHONE HCL				
201401	115	93	8201	3250
201402	97	89	6385	2726
201403	121	102	7541	3393
201404	125	105	8334.3	3546
201405	121	105	8148	3481
201406	106	92	7202	3101
201407	123	91	7976	3438
201408	120	94	7952.8	3263
201409	104	89	6967	2990
201410	138	103	9880	3939
201411	112	97	8335	3256
201412	132	102	9782	3839
PENTAZOCINE W/ NALOXONE				
201401	1	1	120	20
201403	2	2	31	6

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201406	1	1	30	5
201408	1	1	60	15
201412	1	1	30	5
REMIFENTANIL HCL				
201402	1	1	1	1
201403	1	1	2	1
201404	3	3	3	3
201405	4	4	2.35	4
201406	2	1	1.2	2
201407	1	1	0.15	1
201408	5	5	0.943	5
201409	1	1	1	1
201410	4	4	2.71	4
201411	1	1	0.05	1
201412	2	2	0.6	2
TAPENTADOL HC				
201401	20	18	1980	540
201402	21	20	1890	622
201403	25	24	2258	655
201404	26	21	2046	588
201405	31	22	2545	728
201406	29	24	2165	637
201407	19	17	1950	543
201408	23	20	2088	588
201409	19	18	1720	508
201410	21	21	2130	615
201411	23	21	2201	623
201412	22	19	2505	615
TRAMADOL HCL				
201401	1842	1634	145386	36866
201402	1733	1584	139627	35465
201403	2048	1839	160761	40896
201404	2249	2006	172355.6	43622
201405	2311	2026	172752	43805
201406	2231	1932	166277	41771
201407	2473	2140	185389.574	46827
201408	2152	1917	156355.462	39906
201409	2019	1815	145724.5	36794
201410	2242	2003	163915	41309
201411	1907	1745	138543	35441
201412	2062	1826	151354	39154
TRAMADOL-ACETAMINOPHEN				
201401	89	79	5273	1160
201402	89	82	6136	1568
201403	91	80	6291	1321
201404	91	86	5665	1344
201405	85	79	6032	1366
201406	82	78	5057	1170
201407	105	92	7005	1448
201408	86	78	5198	1101

Opioid Utilization 2014

Row Labels	Sum of Count of Claims	Sum of Count of Members	Sum of Qty	Sum of Days Supply
201409	79	77	4732	946
201410	74	69	4793	998
201411	73	71	4004	919
201412	93	87	5281	1190
Grand Total	**274995**	**227433**	**19440143.72**	**4919481**


Sum of Count of Claims
Count of Claims
12000
10000
8000
6000
4000
2000
0
201401
201402
201403
201404
201405
201406
201407
201408
201409
201410
201411
201412
Drug Class Name
HYDROCODONE-ACETAMINOPHEN
MORPHINE SULFATE
OXYCODONE HCL
OXYCODONE W/ ACETAMINOPHEN
TRAMADOL HCL
YearMonth Filled

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
ANTIANXIETY AGENTS	**26**	**26**	**34**	**36**	**31**	**45**	**47**	**110**	**55**	**74**	**84**	**101**	**142**	**122**	**132**	**136**	**169**	**184**	**1554**
ALPRAZOLAM CON 1 MG/ML																		1	**1**
ALPRAZOLAM TAB 0.25MG								4			1			1	4	7	3	3	**23**
ALPRAZOLAM TAB 0.5MG											1	4		2	6	5	5	3	**26**
ALPRAZOLAM TAB 0.5MG OD													1						**1**
ALPRAZOLAM TAB 1MG													1	6	1	4	8	8	**28**
ALPRAZOLAM TAB 1MG ER															1				**1**
ALPRAZOLAM TAB 2MG																		7	**7**
BUSPIRONE TAB 10MG												2	3	9	11	7	18	15	**65**
BUSPIRONE TAB 15MG											1	4		3	6	3	7	16	**40**
BUSPIRONE TAB 30MG										5	4								**9**
BUSPIRONE TAB 5MG										4	2			5	4	6		2	**23**
BUSPIRONE TAB 7.5MG																		4	**4**
CLORAZ DIPOT TAB 3.75MG													5	3					**8**
CLORAZ DIPOT TAB 7.5MG														3				2	**5**
DIAZEPAM CON 5MG/ML				1		2							1						**4**
DIAZEPAM SOL 1MG/ML	2	10	8	1	16	10	5	13	12		4	10	22	1	12	5		4	**135**
DIAZEPAM TAB 10MG												3	4	5		5	14	2	**33**
DIAZEPAM TAB 2MG				1	1	1	6	9		11	5	6	1	2	8	6	11	4	**72**
DIAZEPAM TAB 5MG						1		6		2	10	1	10	9	12	3		2	**56**
HYDROXYZ HCL SOL 10MG/5ML	2	5	5	7	2	4	7	17	5	4	1		3	5	1	1	1	2	**72**
HYDROXYZ HCL SYP 10MG/5ML	2		4	11	7	15	10	31	1	5	2	2	7				1		**98**
HYDROXYZ HCL TAB 10MG								9	15	5	5	6	3	8	11	3	1	3	**69**
HYDROXYZ HCL TAB 25MG							2	1	2	10	10	18	7	6	8	13	18	27	**122**
HYDROXYZ HCL TAB 50MG							3	1	5	4	4	2	2	6	4	6		12	**49**
HYDROXYZ PAM CAP 100MG												2	3			2	1		**8**
HYDROXYZ PAM CAP 25MG						2	6	9	8	12	20	13	36	21	15	17	18	1	**178**
HYDROXYZ PAM CAP 50MG						7	1	4	2	6	2	9	9	20	11	24	40	33	**168**
LORAZEPAM CON 2MG/ML	19	2	5	3	1	1			1	2			1					4	**39**
LORAZEPAM INJ 2MG/ML			1				1					2	2			2		1	**9**
LORAZEPAM TAB 0.5MG	1	9	5	5	4	2	6	5	4	4	11	8	7	3	5	14	14	14	**121**
LORAZEPAM TAB 1MG			6	7				1			1	9	13	4	9	3	9	9	**71**
LORAZEPAM TAB 2MG													1		3			5	**9**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
ANTIDEPRESSANTS				**23**	**7**	**44**	**182**	**234**	**305**	**450**	**446**	**725**	**653**	**940**	**1101**	**1078**	**1105**	**1247**	**8540**
AMITRIPTYLIN TAB 100MG																		12	**12**
AMITRIPTYLIN TAB 10MG					3	6	17	14	13	9	4	22	12	11	21	34	15	17	**198**
AMITRIPTYLIN TAB 25MG						5	4	7		3	3	2	17	1	13	6	9	2	**72**
AMITRIPTYLIN TAB 50MG											1			2		6	10	1	**20**
AMITRIPTYLIN TAB 75MG																	9		**9**
BRINTELLIX TAB 10MG														1					**1**
BUPROPION TAB 100MG										1			1	1	8		3	5	**19**
BUPROPION TAB 100MG SR								1	12	11	10	3	13	26	20	23	35	25	**179**
BUPROPION TAB 150MG SR								5	4				11	22	42	25	20	29	**158**
BUPROPION TAB 200MG ER												2				1			**3**
BUPROPION TAB 200MG SR								1	2	5		5	8	9	12	16	25	7	**90**
BUPROPION TAB 75MG											1		1	21	5	8	8	2	**46**
BUPROPN HCL TAB 150MG XL								6	5	4	8	4	3	17	25	32	9	76	**189**
BUPROPN HCL TAB 300MG XL								3	4	1	1	4	10	9	28	25	29	37	**151**
CITALOPRAM SOL 10MG/5ML														1					**1**
CITALOPRAM TAB 10MG						2		4	13	25	34	17	39	31	31	21	43	61	**321**
CITALOPRAM TAB 20MG								7	3	1	19	26	13	26	63	39	62	72	**331**
CITALOPRAM TAB 40MG												1	11	22	14	29	28	52	**157**
CLOMIPRAMINE CAP 25MG											4	8					3		**15**
CYMBALTA CAP 20MG												2				2		1	**5**
CYMBALTA CAP 30MG																1	5	2	**8**
CYMBALTA CAP 60MG																3		1	**4**
DESIPRAMINE TAB 10MG																		4	**4**
DOXEPIN HCL CAP 10MG													1				2		**3**
DOXEPIN HCL CAP 25MG															3				**3**
DOXEPIN HCL CON 10MG/ML				2															**2**
DULOXETINE CAP 20MG												6							**6**
DULOXETINE CAP 30MG														7			4		**11**
DULOXETINE CAP 60MG															9			1	**10**
ESCITALOPRAM SOL 5MG/5ML						2	8					8		2					**20**
ESCITALOPRAM TAB 10MG										2	2	16	12	43	8	28	17	19	**147**
ESCITALOPRAM TAB 20MG											9	7		19	18	16	11	24	**104**
ESCITALOPRAM TAB 5MG							11		5	8	1	6	2	5		7	7	5	**57**
FETZIMA CAP 40MG																		1	**1**
FLUOXETINE CAP 10MG							8	16	26	20	17	37	27	47	48	52	45	39	**382**
FLUOXETINE CAP 20MG							1	5	15	25	18	50	23	84	116	81	73	89	**580**
FLUOXETINE CAP 40MG							2	6				8	8	32	25	48	24	24	**177**
FLUOXETINE SOL 20MG/5ML						1		1	6	13	3	12	13		1	1	13	3	**67**
FLUOXETINE TAB 10MG									8	42	15	35	38	25	27	24	16	49	**279**
FLUOXETINE TAB 20MG										6		13	10	8	18	20	17	7	**99**
FLUVOXAMINE CAP 150MG ER									1	3									**4**
FLUVOXAMINE TAB 100MG									1	1								4	**6**
FLUVOXAMINE TAB 25MG							2					3	10	2	3				**20**
FLUVOXAMINE TAB 50MG											1	1		3	7			9	**21**
IMIPRAM HCL TAB 10MG				2		1	6		4	13	7	2		5		2		8	**50**
IMIPRAM HCL TAB 25MG						2	27	21	20	6	19	22	20	11	5	7			**160**
IMIPRAM HCL TAB 50MG								14	7	3	7	14	9	15		6			**75**
IMIPRAM PAM CAP 100MG														2	3				**5**
IMIPRAM PAM CAP 75MG																1			**1**
MIRTAZAPINE TAB 15MG							10	15	1	27	7	25	25	24	19	13	38	47	**251**
MIRTAZAPINE TAB 15MG ODT												9			1				**10**
MIRTAZAPINE TAB 30MG											1		6	5	14	8	15	7	**56**
MIRTAZAPINE TAB 30MG ODT								3	3										**6**
MIRTAZAPINE TAB 45MG															3	3		1	**7**
MIRTAZAPINE TAB 45MG ODT								2	2										**4**
MIRTAZAPINE TAB 7.5MG												1						1	**2**
NORTRIPTYLIN CAP 10MG														3			1	4	**8**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
NORTRIPTYLIN CAP 25MG																	1	2	**3**
NORTRIPTYLIN CAP 50MG																	3	9	**12**
PAROXETINE TAB 10MG						1	1					3	1			2	1	11	**20**
PAROXETINE TAB 20MG										3				3	1	1	5	6	**19**
PAROXETINE TAB 30MG														1					**1**
PAROXETINE TAB 40MG															4		2	2	**8**
PRISTIQ TAB 100MG													7						**7**
PRISTIQ TAB 50MG												3	2			3	5	7	**20**
PROZAC CAP 20MG																	5		**5**
PROZAC CAP 40MG																2	1		**3**
SERTRALINE CON 20MG/ML				9			10	5			22	7	13	4				2	**72**
SERTRALINE TAB 100MG							1				11	43	44	61	93	133	145	80	**611**
SERTRALINE TAB 25MG						7	21	30	45	50	16	36	24	35	38	50	31	22	**405**
SERTRALINE TAB 50MG						1	8	25	22	50	41	52	63	89	118	114	126	116	**825**
TOFRANIL TAB 25MG												1							**1**
TRAZODONE TAB 100MG							3	2	1	17	31	63	50	87	71	54	75	88	**542**
TRAZODONE TAB 150MG							2			4	3	16	25	28	29	21	15	27	**170**
TRAZODONE TAB 300MG															6				**6**
TRAZODONE TAB 50MG				10	4	16	40	41	82	97	128	122	81	88	131	101	85	102	**1128**
VENLAFAXINE CAP 150MG ER																5	4	4	**13**
VENLAFAXINE CAP 37.5 ER											1	7				4	1		**13**
VENLAFAXINE CAP 37.5MG												1							**1**
VENLAFAXINE CAP 75MG ER											1			2			3	15	**21**
VENLAFAXINE TAB 100MG																	1		**1**
VENLAFAXINE TAB 75MG																		2	**2**
VIIBRYD TAB 40MG																		4	**4**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
ANTIPSYCHOTICS/ANTIMANIC AGENTS			**5**	**32**	**101**	**333**	**575**	**854**	**1095**	**1144**	**1379**	**1403**	**1439**	**1381**	**1399**	**1279**	**1327**	**1292**	**15038**
ABILIFY SOL 1MG/ML				8	5	9	14	10	6	23	25	18	6	7	9	6	7	2	**155**
ABILIFY TAB 10MG					1	22	38	60	110	82	98	114	124	119	111	98	113	68	**1158**
ABILIFY TAB 15MG					4	1	14	36	30	42	47	57	81	86	79	63	61	69	**670**
ABILIFY TAB 20MG						1	11	2	16	7	25	22	39	36	37	47	30	11	**284**
ABILIFY TAB 2MG					3	28	72	55	68	49	55	61	40	35	37	32	21	22	**578**
ABILIFY TAB 30MG										13	12	4	8	21	30	17	18	37	**160**
ABILIFY TAB 5MG				2	12	32	96	111	172	131	134	145	155	118	107	83	106	62	**1466**
ABILIFY DISC TAB 10MG							3		9			1							**13**
ABILIFY MAIN INJ 300MG															2				**2**
ABILIFY MAIN INJ 400MG																5			**5**
CHLORPROMAZ TAB 100MG												1		2	2		1	10	**16**
CHLORPROMAZ TAB 200MG															6	2		2	**10**
CHLORPROMAZ TAB 25MG									7	2	2	2	2		1		2		**18**
CHLORPROMAZ TAB 50MG														10	3	1	5	2	**21**
CLOZAPINE TAB 100MG																2		8	**10**
EQUETRO CAP 300MG																		1	**1**
FANAPT TAB 8MG																	12	8	**20**
GEODON CAP 80MG																6	2		**8**
HALOPER LAC INJ 5MG/ML													2				1		**3**
HALOPERIDOL TAB 0.5MG																8	8	1	**17**
HALOPERIDOL TAB 10MG																2		12	**14**
HALOPERIDOL TAB 1MG														20	5		4	3	**32**
HALOPERIDOL TAB 2MG														8			1	6	**15**
HALOPERIDOL TAB 5MG													2	2	3	6	8	13	**34**
INVEGA TAB 1.5MG						1	1			6	14			2	5				**29**
INVEGA TAB 3MG							2	1	3	10	16	26	10	12	16	15	2		**113**
INVEGA TAB 6MG										7	19	9	3	18	14	11	3	4	**88**
INVEGA TAB 9MG									5					3	12	7	6	1	**34**
INVEGA SUST INJ 156MG/ML																2		3	**5**
INVEGA SUST INJ 234/1.5																		1	**1**
INVEGA SUST INJ 39/0.25																		1	**1**
LATUDA TAB 120MG												1		2	7	6	17	3	**36**
LATUDA TAB 20MG					5	5	1	7	4	8		4	1	1	1	6	8	11	**62**
LATUDA TAB 40MG						3	1	2	3	5	8	17	12	19	6	7	7	18	**108**
LATUDA TAB 60MG						2	5	1	1	1	5	6	9	5	9	2	6	5	**57**
LATUDA TAB 80MG											3	5	9	4	4	10	23	20	**78**
LITHIUM CARB CAP 150MG							3	8	11	6	17	3	8	9	5	13	15		**98**
LITHIUM CARB CAP 300MG							2	12	10	8	28	12	16	12	37	17	29	55	**238**
LITHIUM CARB CAP 600MG													7		2	11	12	9	**41**
LITHIUM CARB TAB 300MG									1	9	1	2	4	18	9	11	4	2	**61**
LITHIUM CARB TAB 300MG ER								6	1		1	18		11	10	11	5	7	**70**
LITHIUM CARB TAB 450MG ER										1		13	2	16	31	13	21	31	**128**
LITHIUM CITR SOL 8MEQ/5ML				1															**1**
LOXAPINE CAP 10MG																		3	**3**
OLANZAPINE TAB 10MG									1	6	4	2	15	12	9	15	20	48	**132**
OLANZAPINE TAB 10MG ODT											1	4		3				1	**9**
OLANZAPINE TAB 15MG							1			5	3	12	3	2	2	2	9	4	**43**
OLANZAPINE TAB 15MG ODT																3	7		**10**
OLANZAPINE TAB 2.5MG				1		3	3		5	12	17	7	13	4	18	6	1		**90**
OLANZAPINE TAB 20MG							1					9	3	2			1	4	**20**
OLANZAPINE TAB 5MG							1	2	1	11	26	19	18	8	15	6	17	36	**160**
OLANZAPINE TAB 5MG ODT				2		4			1	8		1	6		1		1	7	**31**
OLANZAPINE TAB 7.5MG											2		9	1	6	2			**20**
PERPHENAZINE TAB 8MG																		5	**5**
QUETIAPINE TAB 100MG							7	12	25	14	42	79	93	90	68	83	65	51	**629**
QUETIAPINE TAB 200MG							3	2		6	10	15	33	28	21	40	55	51	**264**
QUETIAPINE TAB 25MG					3	3	9	13	20	16	27	45	17	16	32	24	21	2	**248**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
QUETIAPINE TAB 300MG							9		22	5	5	2	22	33	16	21	33	48	**216**
QUETIAPINE TAB 400MG									9	16	1		7	7	9	5	11	43	**108**
QUETIAPINE TAB 50MG							2	26	12	29	19	47	74	61	68	69	55	49	**511**
RISPERDAL INJ 25MG																		1	**1**
RISPERDAL INJ 50MG																	4	1	**5**
RISPERIDONE SOL 1MG/ML			5	13	54	61	39	30	44	51	61	13	34	21	15	7	2	12	**462**
RISPERIDONE TAB 0.25 ODT								1				2							**3**
RISPERIDONE TAB 0.25MG					4	39	49	90	81	77	38	48	32	45	20	13	20	1	**557**
RISPERIDONE TAB 0.5MG				4	4	59	92	146	169	195	192	137	144	96	114	69	90	60	**1571**
RISPERIDONE TAB 0.5MG OD					3	12		10	7	12	1	5	1				2	11	**64**
RISPERIDONE TAB 1MG				1	3	44	64	110	118	146	187	192	157	107	136	119	118	85	**1587**
RISPERIDONE TAB 1MG ODT							1		1	7	5	17	2	9	1	8		1	**52**
RISPERIDONE TAB 2MG						1	9	24	31	49	109	52	59	49	55	55	46	54	**593**
RISPERIDONE TAB 2MG ODT							1						12	5					**18**
RISPERIDONE TAB 3MG							1	10	18	11	8	24	8	24	19	14	7	7	**151**
RISPERIDONE TAB 3MG ODT							1	3											**4**
RISPERIDONE TAB 4MG										2	5	5	3	10		6	10	3	**44**
SAPHRIS SUB 10MG								14	2	7	20	14	14	19			8	7	**105**
SAPHRIS SUB 5MG								12	2	3	7	9	15	11		7	3		**69**
SEROQUEL TAB 100MG																		1	**1**
SEROQUEL TAB 50MG												4							**4**
SEROQUEL XR TAB 150MG							2	1	11	4	5	11	17	14	15	17	13	11	**121**
SEROQUEL XR TAB 200MG										5	2	7	5	17	25	14	4	8	**87**
SEROQUEL XR TAB 300MG										1	2	15	17	20	10	40	24	22	**151**
SEROQUEL XR TAB 400MG														5	9	8	8	16	**46**
SEROQUEL XR TAB 50MG						3	10	17	32	11	11	9	15	20	30	27	21	15	**221**
ZIPRASIDONE CAP 20MG							1	13	16	8	23	15	11	10	25	26	13	9	**170**
ZIPRASIDONE CAP 40MG							2	6	4	7	21	22	6	7	19	20	20	43	**177**
ZIPRASIDONE CAP 60MG							4	1		5	9	3	22	6	13	9	36	35	**143**
ZIPRASIDONE CAP 80MG									6	5	6	16	12	23	28	24	24	29	**173**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
HYPNOTICS	**70**	**70**	**74**	**42**	**46**	**47**	**12**	**42**	**15**	**16**	**48**	**53**	**48**	**44**	**41**	**27**	**64**	**33**	**792**
MIDAZOLAM INJ 5MG/ML						1													**1**
PHENOBARB ELX 20MG/5ML	28	46	56	33	29	14		22		6		7	21	7	4		2	9	**284**
PHENOBARB SOL 20MG/5ML	30	19	14	5	11	17			5	1	11	10	9	4	2		2	1	**141**
PHENOBARB TAB 15MG				1															**1**
PHENOBARB TAB 16.2MG		1	1	3									5	3					**13**
PHENOBARB TAB 30MG	1						10	4							9		8		**32**
PHENOBARB TAB 32.4MG	11	4	3		4	9	1	16	8		27	25	9			5	6		**128**
PHENOBARB TAB 64.8MG									2	5		9		13	9	2		4	**44**
PHENOBARB TAB 97.2MG															4	3			**7**
TEMAZEPAM CAP 15MG											6	1		4	5	1	9		**26**
TEMAZEPAM CAP 30MG							1								2	9	15		**27**
TEMAZEPAM CAP 7.5MG										4	1		4	5		5	1	3	**23**
TRIAZOLAM TAB 0.25MG											1				2				**3**
ZALEPLON CAP 5MG																		2	**2**
ZOLPIDEM TAB 10MG					2	5								7	4	1	15	7	**41**
ZOLPIDEM TAB 5MG						1					2	1		1		1	6	7	**19**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
ADHD/ANTI-NARCOLEPSY	**1**			**18**	**121**	**568**	**1197**	**2204**	**2415**	**2984**	**2833**	**2834**	**2699**	**2024**	**2009**	**1423**	**1181**	**889**	**25400**
ADDERALL TAB 10MG												3	2						**5**
ADDERALL TAB 15MG											1								**1**
ADDERALL TAB 20MG									1										**1**
ADDERALL TAB 5MG											1								**1**
ADDERALL XR CAP 10MG					8	11	55	107	138	99	57	61	62	34	16	18	8	12	**686**
ADDERALL XR CAP 15MG					6	17	24	60	75	100	76	59	72	32	56	16	18	7	**618**
ADDERALL XR CAP 20MG						4	11	78	61	93	110	134	143	109	106	70	74	88	**1081**
ADDERALL XR CAP 25MG							1	5	31	40	39	36	36	36	26	34	39	7	**330**
ADDERALL XR CAP 30MG						4	6	14	4	36	75	39	109	52	73	75	57	60	**604**
ADDERALL XR CAP 5MG						22	16	48	35	35	17	9	12	10	14	9	5	4	**236**
AMPHETAMINE CAP 10MG ER					1		9	11	9	7	4	4	1		2	2	4		**54**
AMPHETAMINE CAP 15MG ER						1	3	2	5	3	6	5	17	2	4	1	1		**50**
AMPHETAMINE CAP 20MG ER									12	11	5	8	17	10	3	2	10	5	**83**
AMPHETAMINE CAP 25MG ER									1	4		1	7					1	**14**
AMPHETAMINE CAP 30MG ER							8				1	5	8	11	4	13	5	5	**60**
AMPHETAMINE CAP 5MG ER						1	3	2	2	5									**13**
AMPHETAMINE TAB 10MG					3	5	33	48	89	147	115	96	93	67	42	45	44	43	**870**
AMPHETAMINE TAB 12.5MG											1								**1**
AMPHETAMINE TAB 15MG							5	12	16	14	19	8	51	13	13	16	17	12	**196**
AMPHETAMINE TAB 20MG							2	6	23	36	37	42	27	22	60	49	24	31	**359**
AMPHETAMINE TAB 30MG							6		1	7	4	1	4	21	4	5	7	12	**72**
AMPHETAMINE TAB 5MG					8	34	70	53	85	65	59	38	25	5	7	10	6	6	**471**
AMPHETAMINE TAB 7.5MG					2	1	1	14	7	7	12	12		1					**57**
CAFFEINE CIT INJ 60MG/3ML	1																		**1**
CLONIDINE TAB 0.1MG ER					3	11	27	73	81	53	61	71	17	28	17	25	15	12	**494**
CONCERTA TAB 18MG								1	2		3								**6**
CONCERTA TAB 27MG							1		1	2		1	4			5			**14**
CONCERTA TAB 36MG									2	8	14	1	1	4	1		9	1	**41**
CONCERTA TAB 54MG								4	5		1	1	1	9		2			**23**
DAYTRANA DIS 10MG/9HR						1		7			7	1		1					**17**
DAYTRANA DIS 15MG/9HR							1			13			8						**22**
DAYTRANA DIS 20MG/9HR										21	7	12	8		20	4			**72**
DAYTRANA DIS 30MG/9HR										1		1	4	18	35	8	8	5	**80**
DEXEDRINE CAP 15MG CR													1					1	**2**
DEXMETHYLPH CAP 15MG ER									1	7		13	5						**26**
DEXMETHYLPH CAP 30MG ER														1	2		3		**6**
DEXMETHYLPH CAP 40MG ER												1	1						**2**
DEXMETHYLPH TAB 10MG							2	6	9	21	20	14	6	5	22	4	11	6	**126**
DEXMETHYLPH TAB 2.5MG					2		1			2	4								**9**
DEXMETHYLPH TAB 5MG						2	12	23	9	20	12	16	6	5	5	3		6	**119**
DEXTROAMPHET CAP 10MG ER						8	10	10	6	29	13	10	6	18	8	10	1	3	**132**
DEXTROAMPHET CAP 15MG ER								14	12	8	4	20	9	5	1	4	9	2	**88**
DEXTROAMPHET CAP 5MG ER							3		2	1	1	3	1	1					**12**
DEXTROAMPHET TAB 10MG								4	14	30	6	2		1	3	3	2		**65**
DEXTROAMPHET TAB 5MG						1	13	20	10	8	1		5	12					**70**
FOCALIN TAB 10MG									1										**1**
FOCALIN TAB 2.5MG						1													**1**
FOCALIN XR CAP 10MG				1	1	20	17	36	19	53	44	33	38	12	16	6	24	10	**330**
FOCALIN XR CAP 15MG						2	24	30	26	40	29	33	11	2	20	11	18	1	**247**
FOCALIN XR CAP 20MG							2	23	33	38	62	52	63	41	20	13	12	24	**383**
FOCALIN XR CAP 25MG								6	11	9	6		3	19	7	11	4		**76**
FOCALIN XR CAP 30MG								7	4	4	4	19	11	25	7	7	3	9	**100**
FOCALIN XR CAP 35MG												6	5	6	4				**21**
FOCALIN XR CAP 40MG										1	6		4	5	12	7	3		**38**
FOCALIN XR CAP 5MG				6	2	6	1	16	12	12	9	6	1	6	5		8		**90**
GUANFACINE TAB 1MG ER								1					3	1					**5**
GUANFACINE TAB 2MG ER								2	1	1	2		1	1					**8**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
GUANFACINE TAB 3MG ER												1	3	1	1	1		1	**8**
GUANFACINE TAB 4MG ER									1	1					1				**3**
INTUNIV TAB 1MG					12	101	120	109	95	139	120	157	95	78	45	32	18	11	**1132**
INTUNIV TAB 2MG					12	85	139	223	179	184	182	165	156	68	65	77	37	44	**1616**
INTUNIV TAB 3MG					3	18	43	133	123	170	99	164	143	135	114	53	42	25	**1265**
INTUNIV TAB 4MG							5	38	38	61	80	102	98	101	102	69	49	29	**772**
KAPVAY TAB 0.1 MG							3		1		1								**5**
METADATE CD CAP 30MG												1							**1**
METADATE CD CAP 50MG												1							**1**
METHYLPHENID CAP 10MG					1	3		4		1	1	1	1		2				**14**
METHYLPHENID CAP 20MG						1		22	9	6	6	15	8	2	8				**77**
METHYLPHENID CAP 20MG ER											4	2	5	2	1				**14**
METHYLPHENID CAP 30MG							2	2	7	5	2	5	9	9					**41**
METHYLPHENID CAP 30MG ER							2	3	1			2	8	13	1				**30**
METHYLPHENID CAP 40MG							3	2	3	4	6		1	5	5		8	4	**41**
METHYLPHENID CAP 40MG ER								5				2			1				**8**
METHYLPHENID CAP 50MG												8	9	12	15	3	4		**51**
METHYLPHENID CAP 60MG														2	6	2	4		**14**
METHYLPHENID SOL 10MG/5ML						2		4	4	3			7	2	1				**23**
METHYLPHENID SOL 5MG/5ML									1	8		3							**12**
METHYLPHENID TAB 10MG					12	12	24	69	100	91	101	99	87	49	41	15	29	9	**738**
METHYLPHENID TAB 10MG ER						3	7	14	15	10	3	1	9		1		3	1	**67**
METHYLPHENID TAB 18MG ER				1	7	12	29	49	47	26	19	22	27	25	41	8	2		**315**
METHYLPHENID TAB 20MG						7	12	15	23	32	34	21	24	12	26	22	8	1	**237**
METHYLPHENID TAB 20MG ER						2	1	7	29	18	10	23	8	8	13	5	8	2	**134**
METHYLPHENID TAB 20MG SR							1	3	1	10	4	3	6	2	6	3	3		**42**
METHYLPHENID TAB 27MG ER					3	14	32	47	81	62	65	43	44	39	22	17	14	3	**486**
METHYLPHENID TAB 36MG ER						7	40	60	93	143	143	204	132	102	119	69	54	38	**1204**
METHYLPHENID TAB 54MG ER							6	27	67	75	134	127	111	93	82	86	43	48	**899**
METHYLPHENID TAB 5MG				4	6	30	50	49	51	85	66	39	34	3	9	23		1	**450**
MODAFINIL TAB 100MG																2			**2**
MODAFINIL TAB 200MG																	5		**5**
NUVIGIL TAB 250MG												8	1			5			**14**
QUILLIVANT SUS XR					18	47	47	51	26	32	45	25	42	18	18	16	10	9	**404**
RITALIN TAB 10MG										1	6								**7**
RITALIN TAB 20MG																2			**2**
RITALIN LA CAP 10MG						10	4	5	14	6	6	3	3	3	1	2	5	2	**64**
RITALIN LA CAP 20MG						12	3	5	18	16	14	8	1	6	15	2	1	1	**102**
RITALIN LA CAP 30MG						2		9	2	7	2	20	4	4	14	8		3	**75**
RITALIN LA CAP 40MG										11	5	5	8	2	2	4	5	3	**45**
STRATTERA CAP 100MG													9	14	3	9	5	6	**46**
STRATTERA CAP 10MG					1	4	23	33	15	11	15	13	8		2	8	5		**138**
STRATTERA CAP 18MG					2	3	16	34	28	16	19	20	6	4	6	5	5		**164**
STRATTERA CAP 25MG				6	3		30	35	25	25	48	47	57	8	31	22	22	6	**365**
STRATTERA CAP 40MG							10	51	43	52	62	57	80	80	81	22	37	18	**593**
STRATTERA CAP 60MG							3	13	26	27	25	21	52	59	57	66	50	7	**406**
STRATTERA CAP 80MG								1	4	3	5	19	20	28	27	35	65	42	**249**
VYVANSE CAP 20MG					3	27	93	116	123	91	48	65	49	41	24	23	19	21	**743**
VYVANSE CAP 30MG					2	8	64	144	141	197	183	119	139	99	93	53	37	27	**1306**
VYVANSE CAP 40MG						6	9	54	74	149	145	152	138	92	89	43	44	51	**1046**
VYVANSE CAP 50MG							9	15	30	74	90	81	77	106	64	47	50	61	**704**
VYVANSE CAP 60MG								9	18	26	56	41	39	28	64	34	16	18	**349**
VYVANSE CAP 70MG								1	3	15	24	42	32	18	55	42	25	24	**281**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
ANTICONVULSANTS	**57**	**210**	**307**	**251**	**361**	**512**	**626**	**840**	**571**	**736**	**848**	**826**	**978**	**805**	**1063**	**951**	**946**	**1116**	**12004**
BANZEL SUS 40MG/ML		5	15	4	2	5	4	15	5	10	16	4							**85**
BANZEL TAB 200MG			1			3	3	8		5	4			15		5	13	1	**58**
BANZEL TAB 400MG															8				**8**
CARBAMAZEPIN CAP 100MG ER										2						5	4		**11**
CARBAMAZEPIN CAP 200MG ER									2	15	1		1	2				7	**28**
CARBAMAZEPIN CAP 300MG ER										7		1			9	3	4		**24**
CARBAMAZEPIN CHW 100MG						1	3	2				3	14	4					**27**
CARBAMAZEPIN SUS 100/5ML								8	3					5	15	8	13		**52**
CARBAMAZEPIN TAB 200MG								9	7	2	3	10	6	1	3	27	12	20	**100**
CARBAMAZEPIN TAB 200MG ER										1			1	2				4	**8**
CARBAMAZEPIN TAB 400MG ER													2						**2**
CARBATROL CAP 100MG									1										**1**
CARBATROL CAP 200MG									3			2			2	2			**9**
CARBATROL CAP 300MG									2		4	2							**8**
CLONAZEP ODT TAB 0.125MG		1				2	2	10	3								1		**19**
CLONAZEP ODT TAB 0.25MG			4		2	1	3	3				1	4	1					**19**
CLONAZEP ODT TAB 0.5MG						6	1	1			13	1	3		4				**29**
CLONAZEP ODT TAB 1MG			1	2											4	5			**12**
CLONAZEPAM TAB 0.5MG		10	21	12	11	4	10	3	13	18	25	17	24	21	30	20	10	37	**286**
CLONAZEPAM TAB 1MG			1				4	5	2	15	17	3	14	11	48	6	11	23	**160**
CLONAZEPAM TAB 2MG													3	8	12	8	11	9	**51**
DEPAKENE SYP 250/5ML										6					6				**12**
DEPAKOTE TAB 125MG DR											5	1				1			**7**
DEPAKOTE ER TAB 250MG															2			8	**10**
DEPAKOTE ER TAB 500MG											1				1	9	9		**20**
DEPAKOTE SPR CAP 125MG										27	7	10	1	21	6				**72**
DIASTAT ACDL GEL 12.5-20						1	2			1		1	1			1	6	1	**14**
DIASTAT ACDL GEL 5-10MG		2	1	1	3	3	2	2	1	1	1		1						**18**
DIASTAT PED GEL 2.5M GEL		1	1	1															**3**
DIAZEPAM GEL 10MG	2	5	12	7	9	13	21	9	4	10	11	1	5	7		1	5	5	**127**
DIAZEPAM GEL 2.5MG	5	2	1					1											**9**
DIAZEPAM GEL 20MG									1	1	12	2	3	3	1		4	6	**33**
DILANTIN CHW 50MG											8		3						**11**
DIVALPROEX CAP 125MG				10	3	37	34	40	25	11	25	34	27	9	20	26	34	6	**341**
DIVALPROEX TAB 125MG DR							1	8	13	18	22	4	5	13	14	13	1	7	**119**
DIVALPROEX TAB 250MG DR							4	1	3	21	4	11	15	12	46	14	10	18	**159**
DIVALPROEX TAB 250MG ER								18	34	20	46	31	35	57	73	49	36	47	**446**
DIVALPROEX TAB 500MG DR								1	1	4		9	12	18	11	18	8	20	**102**
DIVALPROEX TAB 500MG ER								4	11	25	20	14	52	49	47	50	69	97	**438**
EPITOL TAB 200MG									5	2	3		1		2	11	3		**27**
ETHOSUXIMIDE CAP 250MG								1	1	4	6	8						13	**33**
ETHOSUXIMIDE SOL 250/5ML					2	2		4	9	21	3	3							**44**
FELBAMATE SUS 600/5ML			2		4			3				17	4		4		1	6	**41**
FELBAMATE TAB 400MG								8		9									**17**
FELBAMATE TAB 600MG										1					1	3		9	**14**
FELBATOL SUS 600/5ML		1	6										7	10					**24**
FELBATOL TAB 400MG											5								**5**
FYCOMPA TAB 2MG						1	1							1		1			**4**
FYCOMPA TAB 4MG						5													**5**
FYCOMPA TAB 6MG						1												3	**4**
GABAPENTIN CAP 100MG								5	1	10	2	2	2	5	4	7		3	**41**
GABAPENTIN CAP 300MG				3	1				1			1		10	4	5	5	5	**35**
GABAPENTIN CAP 400MG																7	1		**8**
GABAPENTIN SOL 250/5ML		10	15	7	11	15	14	4	6	1									**83**
GABAPENTIN TAB 600MG															4	9	19	1	**33**
GABAPENTIN TAB 800MG											1					1		3	**5**
GABITRIL TAB 12MG																		1	**1**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
GABITRIL TAB 16MG																		1	**1**
KEPPRA SOL 100MG/ML					3			14	2	14	12	13	4	4	18				**84**
KEPPRA TAB 1000MG								7	2									7	**16**
KEPPRA TAB 500MG								4	4									8	**16**
KEPPRA XR TAB 750MG															4	5			**9**
KLONOPIN TAB 0.5MG												1							**1**
LAMICTAL CHW 25MG								7	3						8				**18**
LAMICTAL TAB 100MG														7	8	2		7	**24**
LAMICTAL TAB 200MG												14			9				**23**
LAMICTAL TAB 25MG									1							2			**3**
LAMICTAL ODT TAB 100MG						3		1		1	43	2					19		**69**
LAMICTAL ODT TAB 25MG										3	20	1					7		**31**
LAMICTAL ODT TAB 50MG								1		7	12	5	4			1	12		**42**
LAMICTAL XR TAB 200MG															5	4			**9**
LAMICTAL XR TAB 25MG												2							**2**
LAMICTAL XR TAB 300MG																	8	1	**9**
LAMOTRIGINE CHW 25MG					6	9	22	13	15	16	32	13	8			1			**135**
LAMOTRIGINE CHW 5MG			4	2	4	1	2	2	7		2								**24**
LAMOTRIGINE TAB 100MG							13	27	21	19	36	43	66	49	57	55	50	48	**484**
LAMOTRIGINE TAB 100MG ER														2					**2**
LAMOTRIGINE TAB 150MG							3	10	1		10	32	28	30	48	35	53	45	**295**
LAMOTRIGINE TAB 200MG							1	3	3			11	5	11	48	28	27	70	**207**
LAMOTRIGINE TAB 200MG ER												5							**5**
LAMOTRIGINE TAB 250MG ER										1						3	1	2	**7**
LAMOTRIGINE TAB 25MG					2	3	31	44	27	34	39	43	35	17	37	42	45	29	**428**
LAMOTRIGINE TAB 25MG ER												7	1						**8**
LAMOTRIGINE TAB 300MG ER																8	1		**9**
LEVETIRACETA SOL 100MG/ML	37	121	165	120	108	193	197	165	62	85	87	102	141	45	42	36	36	42	**1784**
LEVETIRACETA TAB 1000MG												6	20	1	15	3	13	15	**73**
LEVETIRACETA TAB 250MG			1	1		4	9	15	10	1	5	24	14	6	6	1	1	3	**101**
LEVETIRACETA TAB 500MG		1				3	7	34	19	8	12	19	9	17	19	35	20	44	**247**
LEVETIRACETA TAB 500MG ER											8		5	3	5	5	2	8	**36**
LEVETIRACETA TAB 750MG						5		1			4	6	13	3	5	27	21	24	**109**
LEVETIRACETA TAB 750MG ER														1		7	2		**10**
ONFI SUS 2.5MG/ML	1	3	11	7	13	10	5	28	11	6	10	6	1	12					**124**
ONFI TAB 10MG			8	8	26	33	42	37	15	17	6	23	11	8	9	11	11	24	**289**
ONFI TAB 20MG						6	1	4	14	16	6	8	10	3				1	**69**
OXCARBAZEPIN SUS 300MG/5M	2	9	8	24	53	62	60	32	37	30	22	23	46	16	13	36	18	12	**503**
OXCARBAZEPIN TAB 150MG					1	3	12	12	27	36	28	21	44	28	26	23	14	17	**292**
OXCARBAZEPIN TAB 300MG						9	15	21	37	47	30	65	98	97	59	81	83	81	**723**
OXCARBAZEPIN TAB 600MG								3	1	8	20	27	42	50	65	85	76	57	**434**
OXTELLAR XR TAB 300MG														2					**2**
PHENYTOIN CHW 50MG					1	1							5			1			**8**
PHENYTOIN SUS 125/5ML		1					1						1	1	4	2			**10**
PHENYTOIN EX CAP 100MG											1	3						1	**5**
PRIMIDONE TAB 50MG					1	1								6	1				**9**
SABRIL TAB 500MG													2						**2**
TEGRETOL TAB 200MG											3						2	1	**6**
TIAGABINE TAB 2MG												4							**4**
TIAGABINE TAB 4MG											1	6					1	8	**16**
TOPAMAX TAB 100MG											6	2							**8**
TOPAMAX TAB 200MG															9				**9**
TOPAMAX TAB 50MG											4	2			9				**15**
TOPAMAX SPR CAP 25MG										16	4								**20**
TOPIRAMATE CAP 15MG	4	11	3	13			2			7	10			3	4				**57**
TOPIRAMATE CAP 25MG	3	7	9	2		12	12	12	4	1	3		7	1				1	**74**
TOPIRAMATE CAP ER 50MG																		3	**3**
TOPIRAMATE TAB 100MG						1	3	6	16	18	11	12	20	12	40	24	31	18	**212**

Psych Product Utilization by Age - Count of Claims

	Member Age																		
Product	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
TOPIRAMATE TAB 200MG																3	10	20	**33**
TOPIRAMATE TAB 25MG	2	9	4	13	16	4	14	27	8	5	19	8	21	9	17	11	15	22	**224**
TOPIRAMATE TAB 50MG	1	6			4	3	2	6	5	17	2	18	9	23	33	21	20	35	**205**
TRILEPTAL SUS 300MG/5M						7	16	13	4	1					8	4	11	1	**65**
TRILEPTAL TAB 300MG														3				5	**8**
TROKENDI XR CAP 100MG																3	5	1	**9**
VALPROIC ACD CAP 250MG										1	3	3	7						**14**
VALPROIC ACD SOL 250/5ML					8	14	5	9	19	12	4	5	5	4	1	5	5	1	**97**
VALPROIC ACD SYP 250/5ML		5	13	8	23	16	33	35	14	16	21	13	29	7	9	3	7	12	**264**
VIMPAT SOL 10MG/ML				1	6			3	1			7	3						**21**
VIMPAT TAB 100MG								2		2	13	3	6	2	7			2	**37**
VIMPAT TAB 150MG										3			2	6	4			10	**25**
VIMPAT TAB 200MG													7	2			11	15	**35**
VIMPAT TAB 50MG									2						9	3	4	8	**26**
ZARONTIN CAP 250MG											5								**5**
ZONEGRAN CAP 100MG											2					10			**12**
ZONEGRAN CAP 25MG										6	2								**8**
ZONISAMIDE CAP 100MG				3	11	5	5	42	14	10	23	25	3	20	21	10	14	43	**249**
ZONISAMIDE CAP 25MG				2	15	4	3	27	8	3	1								**63**
ZONISAMIDE CAP 50MG					12		1			1	1			9				3	**27**
Grand Total	**154**	**306**	**420**	**402**	**667**	**1549**	**2639**	**4284**	**4456**	**5404**	**5638**	**5942**	**5959**	**5316**	**5745**	**4894**	**4792**	**4761**	**63328**

Diagnosis by Age - Count of Claims

		Member Age																	
Dx	Dx Description	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Grand Total
(blank)		151	292	406	386	636	1507	2582	4163	4259	5226	5459	5752	5818	5145	5633	4787	4676	4665	**61543**
314.01	ATTN DEFICIT W HYPERACT					2	15	25	64	120	100	120	131	85	92	74	55	40	18	**941**
314.00	ATTN DEFIC NONHYPERACT					1	3	13	15	27	9	21	23	16	19	7	9	9	12	**184**
780.39	CONVULSIONS NEC	2	7	9	15	22	14	3	11	13	2	5	11	10	3	2	3		6	**138**
314.0	ATTENTION DEFICIT DIS						1	1	3	4	3	1	5	12	8	5	3	19		**65**
312.9	CONDUCT DISTURBANCE NOS			1	1	1		3		5	17	3	2		8	2	10		8	**61**
313.81	OPPOSITION DEFIANT DISOR						1		1	5	7	6	3	1	6		2			**32**
V20.2	ROUTIN CHILD HEALTH EXAM						1			1	11	6			2	4				**25**
346.10	MGRN WO AURA WO NTRC MGR						5				3	3			1	1		1	9	**23**
314.1	HYPERKINET W DEVEL DELAY							2	2	1	6	2	3	3		2	1	1		**23**
314.9	HYPERKINETIC SYND NOS						1	2	9			2					1			**15**
300.00	ANXIETY STATE NOS									1	1		1		7	2		2		**14**
311	DEPRESSIVE DISORDER NEC								2									7	5	**14**
507.0	FOOD/VOMIT PNEUMONITIS																		12	**12**
784.0	HEADACHE										1				1		2	5	1	**10**
299.00	INFANTILE AUTISM							3		2	3	1								**9**
	Total	**153**	**299**	**416**	**402**	**662**	**1548**	**2634**	**4270**	**4438**	**5389**	**5629**	**5931**	**5945**	**5292**	**5732**	**4873**	**4760**	**4736**	**63109**

Specialty by Age - Count of Claims

	Member Age																		
Specialty	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**Grand Total**
(blank)	27	87	119	82	154	325	435	826	865	1216	1167	1223	1139	1052	1246	953	861	999	**12776**
PSYCHIATRY				1	14	72	260	480	625	613	732	1018	816	700	682	713	599	656	**7981**
FAMILY NURSE PRACTITIONER	8	10	40	45	27	178	302	342	488	680	626	669	752	692	771	750	670	707	**7757**
FAMILY PRACTICE			2		2	52	190	315	349	362	298	320	397	420	344	272	384	320	**4027**
PEDIATRICS	18	21	12	6	40	93	189	318	420	350	513	390	346	375	289	195	202	181	**3958**
ORTHOPEDIC SURGERY		8	4	12	33	82	178	182	232	209	327	385	276	191	272	219	133	178	**2921**
PEDIATRICS-ONCOLOGY				1	6	25	107	186	135	198	165	246	276	276	365	298	295	226	**2805**
ANESTHESIOLOGY	16	24	12	67	55	198	171	252	118	395	326	216	235	126	139	100	133	120	**2703**
GENERAL PRACTICE	37	55	85	88	84	97	137	183	109	162	197	162	159	200	215	125	138	164	**2397**
CARDIO-VASCULAR	18	48	49	27	83	140	114	212	141	125	125	86	178	111	266	136	147	146	**2152**
MAMMOGRAPHY					7	20	45	127	102	129	76	97	146	193	163	193	150	177	**1625**
RESPITE					1	25	44	70	201	108	82	169	174	168	98	129	88	64	**1421**
SPEECH PATHOLOGIST	2		2	8	5	19	44	88	96	97	110	100	144	67	108	65	61	55	**1071**
PAIN MANAGEMENT	2	9	31	22	79	60	131	104	73	76	89	105	62	58	69	58	24	7	**1059**
PHYSICAL THERAPY		21	9	1	28	61	52	64	30	66	94	124	78	35	84	106	100	50	**1003**
NEUROLOGY	4	14	48	27	9	12	18	74	39	107	123	54	55	86	76	38	49	52	**885**
ALLERGY					3		16	39	54	77	47	60	154	97	59	50	92	81	**829**
PSYCHIATRY-CHILD							16	17	34	53	107	83	112	56	87	56	89	80	**790**
GENERAL SURGERY		3		1		2	30	67	46	71	59	68	69	81	79	26	100	50	**752**
OPHTHALMOLOGY					3	16	25	101	76	28	83	33	99	41	101	67	39	3	**715**
HOMEMAKER SERVICES						4	40	55	52	46	57	63	66	47	35	24	73	38	**600**
INTERNAL MEDICINE				1	2	8	18	44	57	44	28	58	62	53	39	64	52	62	**592**
CHORE				1	14	27	15	37	25	42	45	43	22	33	25	22	43	15	**409**
HEMATOLOGY/ONCOLOGY, PEDS	2	4	1	5	9	9	14	10	15	35	16	17	32	38	34	57	47	59	**404**
DERMATOLOGY			1	1			8	11	16	28	26	31	48	27	36	31	89	49	**402**
CARDIO-VASCULAR SURGERY		1	3	4					5			2	1	9		30	48	122	**225**
GERIATRICS					3		1	10	6	21	34	25	15	11	5		12	8	**151**
ONCOLOGY					2	3	6	14	14	16	22	24	8		9	1	6	2	**127**
OBSTETRICS AND GYNECOLOGY	3					2	1		2	1	8	8	6	29	11	3		11	**85**
REGULAR ASSISTED LIVING	3				3		1	10	4	5		1	4		3	23	6	21	**84**
EMERGENCY MEDICINE				1		1	3	8	11	21	21	1	2	4	1	5	1	2	**82**
PEDIATRICS-HEMATOLOGY						2	9	2			4	3		23	5	16	9	3	**76**
PEDIATRICS-PULMONARY		1				3	4	6	1		8	15	4	5	9				**56**
GASTROENTEROLOGY	1					5	7	5	1			14			2	5	2	13	**55**
HEMATOLOGY								9		1	4	3	4	1	4	8	1	8	**43**
ENDOCRINOLOGY						2	1	2	1	16	7	4		2		4		1	**40**
OCCUPATIONAL THERAPY									1		1	9	1			10	16	1	**39**
URGENT CARE									1	1						16	8	7	**33**
QMHP							3	8		2	3	1		2			5		**24**
RESPIRATORY THERAPIST				1				3				10	5	3					**22**
PEDIATRICS-ALLERGY								1	4								12		**17**
NEONATOLOGY, PEDIATRICS	12				1	2									2				**17**
PEDIATRIC NEUROLOGY									2		4		3	2	5				**16**
CRITICAL CARE			2												2	4	6		**14**
PRENATAL MEDICINE																		13	**13**
PHYSICAL MEDICINE/REHAB									2		2					6		1	**11**
OBSTETRICS						3	2	1	1	2						2			**11**
INFECTIOUS DISEASE																10			**10**
ATTENDANT SERVICES												1			1	2		3	**7**
FAMILY DENTISTRY													2		4				**6**
OTOLARYNGOLOGY									1				1					3	**5**
PEDIATRIC INTENSIVE CARE	1												4						**5**
GYNECOLOGY							1	1								2	1		**5**
ORTHODONTICS							1				2							1	**4**
GENERAL DENTISTRY						1							1	1					**3**
RADIOLOGY										1		1							**2**
PATHOLOGY														1				1	**2**

Specialty by Age - Count of Claims

NEUROLOGICAL SURGERY																	1		**1**
HEAD/NECK SURGERY									1										**1**
ORAL SURGERY																		1	**1**
PEDIATRICS-CARDIOLOGY													1						**1**
Grand Total	**154**	**306**	**420**	**402**	**667**	**1549**	**2639**	**4284**	**4456**	**5404**	**5638**	**5942**	**5959**	**5316**	**5745**	**4894**	**4792**	**4761**	**63328**

Buprenorphine/Naloxone Utilization

Count of RxClaim Nbr

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
00001085303		22							1	1
	27	30							1	1
	30	21							1	1
	32	23							1	1
	22	5							1	1
	6	5							1	1
	7	13							1	1
	15	6							1	1
	27	24							1	1
	29	24							1	1
00002167095		7						1		1
	6	2						1		1
	2	14				1				1
	14	30				1				1
	15	30							1	1
	21	6						1		1
	4	30					1			1
	6	30						1		1
	23	30							1	1
	16	7				1				1
	5	3				1				1
	3	3				1				1
	3	9				1				1
	14	7				1				1
	6	14				1				1
	13	18				1				1
	17	12				1				1
00003000377		30				1				1
	27	30				1				1
00004065203		28						1		1
	29	15						1		1
	18	30						1		1
	29	30						1		1
	29	28						1		1
	28	28						1		1
	28	28						1		1
	28	26						1		1
	28	27						1		1
	34	28						1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	27	28						1			1
	28	26						1			1
	28	26						1			1
00004095778		7							1		1
	9	5							1		1
	47	8							1		1
	7	14							1		1
	30	30							1		1
	31	30							1		1
	37	11							1		1
	41	7							1		1
00004150398		8	1								1
00004154042		7							1		1
00005041028		30	1								1
	28	30	1								1
	27	30	1								1
	43	30	1								1
00005084481		7							1		1
	6	15							1		1
	8	4							1		1
	5	7							1		1
	6	7							1		1
	8	7							1		1
	7	4							1		1
	4	4							1		1
	4	7							1		1
	6	7							1		1
	8	5							1		1
	5	6							1		1
	6	4							1		1
	5	2							1		1
	3	7							1		1
	7	4							1		1
	4	4							1		1
	4	6							1		1
	6	6							1		1
	6	7							1		1
	9	7							1		1
	10	7							1		1
	13	7							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	7	7							1	1
	6	7							1	1
	13	7							1	1
	12	7							1	1
	11	7							1	1
	7	7							1	1
	11	7							1	1
	7	7							1	1
	13	7							1	1
	6	7							1	1
	7	7							1	1
	10	7							1	1
	10	7							1	1
	12	7							1	1
	12	7							1	1
00005174427		30							1	1
	29	26							1	1
	27	30							1	1
	28	30							1	1
	28	30							1	1
	28	30							1	1
	28	29							1	1
	28	29							1	1
	26	7							1	1
	6	21							1	1
	27	21							1	1
	29	14							1	1
	24	20							1	1
	19	20							1	1
00006006071		5							1	1
	14	24							1	1
00006076759		30							1	1
	32	30							1	1
	28	30							1	1
	30	30							1	1
	32	30							1	1
	29	30							1	1
	28	30							1	1
00006186171		14				1				1
	15	14		1						1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	37	14		1						1
	18	8			1					1
	9	8			1					1
	14	7					1			1
	1	7		1						1
	7	7		1						1
	22	7		1						1
00008118273		15							1	1
00023533334		30						1		1
06561900003		28							1	1
	25	7							1	1
	7	14							1	1
	13	14							1	1
	14	14							1	1
	15	12							1	1
	11	14							1	1
	13	14							1	1
	13	14							1	1
	13	14							1	1
	15	14							1	1
	14	14							1	1
	14	14							1	1
	14	14							1	1
	13	14							1	1
	13	14							1	1
	14	14							1	1
	15	14							1	1
	13	14							1	1
	15	14							1	1
	13	14							1	1
	15	14							1	1
	13	14							1	1
	14	14							1	1
	14	14							1	1
08829200001		30						1		1
	30	30						1		1
	30	30						1		1
11111100123		4							1	1
	7	30							1	1
11112216935		30					1			1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	31	28					1				1
	27	30					1				1
	27	28					1				1
	33	30					1				1
	28	25					1				1
11112256553		20					1				1
	18	10					1				1
	14	20					1				1
	19	10					1				1
	10	20					1				1
	22	10					1				1
	9	20					1				1
	22	7					1				1
	8	23					1				1
	30	28							1		1
	27	10							1		1
	14	30							1		1
	29	30							1		1
	28	30							1		1
	27	30							1		1
	27	15							1		1
	14	29							1		1
11113191077		8							1		1
	8	14							1		1
	14	8							1		1
	15	15							1		1
	13	22							1		1
	35	21							1		1
11113200030		7							1		1
11113262096		7							1		1
	7	14							1		1
	16	14							1		1
	19	30						1			1
	26	30					1				1
	29	30					1				1
11115252112		12							1		1
	12	12							1		1
	12	6							1		1
	5	12							1		1
	17	4							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	7	7							1		1
	7	9							1		1
	15	4							1		1
	7	8							1		1
	7	21							1		1
	27	18							1		1
	28	30							1		1
	62	30							1		1
	27	20							1		1
	122	30							1		1
11116187114		4							1		1
	4	3							1		1
	3	3							1		1
	3	3							1		1
	4	3							1		1
11116239459		7							1		1
	7	7							1		1
	7	7							1		1
11116256496		30							1		1
	28	30							1		1
	28	24							1		1
	33	24							1		1
	55	30							1		1
11117287851		6							1		1
	7	24							1		1
	27	23							1		1
	23	7							1		1
	6	16							1		1
	14	7							1		1
	8	5							1		1
	5	11							1		1
	27	30							1		1
	31	23							1		1
11117292422		30	1								1
11118239907		20							1		1
11118292728		7							1		1
11119262874		30							1		1
	33	26							1		1
	30	30							1		1
	32	30							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	33	30							1	1
11988788989		4							1	1
13405999990		30							1	1
	28	30							1	1
	28	30							1	1
	48	30	1							1
	15	3							1	1
	4	20							1	1
	18	8							1	1
	7	3							1	1
	3	20							1	1
	20	8							1	1
	7	22							1	1
	23	30							1	1
	27	30							1	1
	33	30							1	1
18304233336		30							1	1
20396033433		29							1	1
	24	5							1	1
	29	7							1	1
	6	30							1	1
	28	30							1	1
	28	28							1	1
	28	28							1	1
	28	28							1	1
	28	27							1	1
	28	26							1	1
	28	26							1	1
	28	25							1	1
	27	30							1	1
	28	30							1	1
21220044445		7							1	1
	7	27							1	1
	27	30							1	1
	29	30							1	1
	29	22							1	1
	21	30							1	1
22220304766		28							1	1
22222265579		28							1	1
	27	7							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	5	15	1							1
	14	15	1							1
	72	7	1							1
	8	14	1							1
	14	14	1							1
	15	28	1							1
	27	28	1							1
	28	28	1							1
	28	28	1							1
22222297943		2							1	1
	3	30							1	1
	35	30							1	1
	29	30							1	1
22222317689		23							1	1
	21	7							1	1
	8	16							1	1
	27	23							1	1
22222383271		30				1				1
	15	15				1				1
	15	30				1				1
	32	30				1				1
	31	30				1				1
	29	30				1				1
	31	30				1				1
22223273272		12							1	1
	11	11							1	1
22224228406		30						1		1
	28	30						1		1
	35	15						1		1
	18	8						1		1
	9	23						1		1
	48	18						1		1
22224328883		3							1	1
22225256198		30							1	1
22226205012		8					1			1
22226219233		7						1		1
	6	14						1		1
22227206029		30				1				1
	30	30				1				1
	27	30				1				1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	27	30				1				1
	32	30				1				1
	28	30				1				1
	28	30				1				1
	28	30				1				1
	31	30				1				1
	28	30				1				1
	28	15				1				1
	18	30				1				1
	35	30				1				1
22227306262		20			1					1
	23	10			1					1
	12	20			1					1
	36	30			1					1
	30	30			1					1
	76	15			1					1
	21	15			1					1
	62	15			1					1
22227391114		30							1	1
	28	30							1	1
	27	30							1	1
	29	30							1	1
	28	30							1	1
	28	30							1	1
	27	30							1	1
	28	30							1	1
22228205696		7							1	1
	6	15							1	1
	13	17							1	1
	17	18							1	1
	37	18							1	1
22228207658		10							1	1
	19	10							1	1
22228223812		30							1	1
	29	30							1	1
	27	30							1	1
	32	30							1	1
	29	30							1	1
	32	30							1	1
	28	30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	173	30							1	1
22228333072		25							1	1
	31	21							1	1
	28	6							1	1
	8	15							1	1
	21	15							1	1
22228339274		30							1	1
27024533334		15					1			1
	26	15					1			1
32245855655		7							1	1
33330433716		15			1					1
	28	15			1					1
	53	7			1					1
	84	15			1					1
	-41877	20							1	1
33330441582		100							1	1
	37	30							1	1
33330453417		30							1	1
	30	30							1	1
	28	30							1	1
	179	30							1	1
	53	30							1	1
33330453697		4							1	1
	8	8							1	1
	7	22							1	1
	125	7							1	1
	6	14	1							1
33331411412		30							1	1
33331439737		30							1	1
	33	30							1	1
	22	30							1	1
33331447521		14							1	1
	40	14							1	1
	14	14							1	1
	13	14							1	1
	22	14							1	1
	14	14							1	1
	14	14							1	1
33331499993		15							1	1
33333308055		30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	24	30							1	1
33333322842		6							1	1
	3	30							1	1
	30	30							1	1
	32	30						1		1
	48	30						1		1
	27	30						1		1
	30	7						1		1
	7	30					1			1
	63	15					1			1
	26	30					1			1
	27	30					1			1
	48	30					1			1
33334309387		7	1							1
33334364511		30				1				1
	58	30				1				1
	40	30				1				1
	35	30				1				1
	43	30				1				1
	35	30				1				1
	28	30				1				1
	79	30				1				1
33335382268		30				1				1
	39	30				1				1
	39	30				1				1
	36	30				1				1
	27	30				1				1
	40	30				1				1
	71	30				1				1
	61	30							1	1
33335475760		30						1		1
	27	30						1		1
	28	30						1		1
	29	30						1		1
	27	30						1		1
	27	30						1		1
	27	30						1		1
	25	30					1			1
	27	30					1			1
	27	30					1			1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	22	30						1			1
	27	30						1			1
	29	30						1			1
	27	30						1			1
33335484210		7							1		1
	9	2							1		1
	16	18							1		1
	23	30							1		1
	26	30					1				1
	29	30					1				1
33336303138		30							1		1
	34	30							1		1
	27	30							1		1
	29	30							1		1
	27	30							1		1
	54	30							1		1
	27	30							1		1
	46	30							1		1
33336419077		7							1		1
	7	7							1		1
	9	7							1		1
	7	14							1		1
33336484967		14							1		1
	17	2							1		1
	2	30							1		1
	59	30							1		1
	25	30							1		1
	28	30							1		1
33337325566		30							1		1
	28	30							1		1
	28	30							1		1
33337407718		15							1		1
	54	30							1		1
33338441692		30							1		1
33339375154		30							1		1
	27	26							1		1
	27	13							1		1
	34	20							1		1
	27	10							1		1
33339446678		29							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	25	12							1	1
	14	30							1	1
	28	24							1	1
	23	30							1	1
	29	28							1	1
	26	30							1	1
	28	23							1	1
	29	23							1	1
	27	23							1	1
	33	22							1	1
33339468962		8							1	1
	7	22							1	1
	21	8							1	1
	11	30							1	1
33339499968		25			1					1
33359211113		30				1				1
	8	10							1	1
	27	7							1	1
	7	13							1	1
	27	14							1	1
	174	14							1	1
	8	15				1				1
	16	30				1				1
35128422322		8				1				1
	8	12				1				1
	14	14				1				1
	15	14				1				1
38118411212		5							1	1
	6	4							1	1
	6	16							1	1
	15	7							1	1
	14	15							1	1
	29	7							1	1
40497344544		7					1			1
	6	7						1		1
	2	8					1		1	2
	7	7							1	1
	7	9							1	1
	9	7							1	1
	7	7							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	7	7							1	1
	6	7							1	1
	8	9							1	1
	8	5							1	1
	6	9							1	1
	9	7							1	1
	7	7							1	1
	12	7							1	1
	90	8							1	1
	8	14							1	1
	33	30							1	1
	8	7						1		1
43266800100		3							1	1
	2	6							1	1
44440580612		30			1					1
	27	30			1					1
	28	20			1					1
	17	6			1					1
	11	18			1					1
	27	20			1					1
	27	20			1					1
	27	20			1					1
	27	27			1					1
	27	24			1					1
	27	20			1					1
44441573871		30			1					1
44442544773		2							1	1
44442554853		7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
44443463268		28							1	1
	48	27						1		1
	26	5						1		1
44444433783		30							1	1
44445478477		5							1	1
	5	14							1	1
	26	10							1	1
	11	20							1	1
	19	1							1	1
	2	9							1	1
	9	9							1	1
	8	3							1	1
	3	8							1	1
	8	6							1	1
	11	13							1	1
	13	11							1	1
	10	6							1	1
	6	6							1	1
	5	3							1	1
44445585702		27							1	1
	28	27							1	1
	28	27							1	1
	29	29							1	1
	28	25							1	1
44446502180		7							1	1
	51	7							1	1
44446527606		30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	36	30							1	1
	42	30							1	1
	28	30							1	1
	63	30							1	1
44447454921		30							1	1
	59	30							1	1
44447483910		7							1	1
	6	14							1	1
	40	28							1	1
	25	26							1	1
	48	7							1	1
	7	14							1	1
	13	30							1	1
	54	27							1	1
44447594999		25							1	1
44448403269		30							1	1
	18	20							1	1
	18	15							1	1
	14	15							1	1
	14	15							1	1
	15	20							1	1
	17	30							1	1
	27	30							1	1
	29	30							1	1
44449501070		7							1	1
	35	7							1	1
	12	7					1			1
	13	7					1			1
	9	14					1			1
	7	14					1			1
	22	32					1			1
	25	16					1			1
	14	30					1			1
	27	30					1			1
	35	24					1			1
	18	10					1			1
	12	30					1			1
	28	30					1			1
	27	30					1			1
44449595022		30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
45047488989		7						1		1
48245311112		3						1		1
	3	7						1		1
	11	3						1		1
	5	8						1		1
	7	3						1		1
	3	3						1		1
	4	3						1		1
	3	3						1		1
	4	3						1		1
	3	2						1		1
	12	7						1		1
	21	7						1		1
	25	2						1		1
	4	14						1		1
	15	14						1		1
50843288981		15						1		1
	29	15						1		1
	88	20						1		1
	27	30						1		1
	28	30						1		1
	29	30						1		1
52794977879		8						1		1
	3	7						1		1
	6	7						1		1
	6	7						1		1
	6	7						1		1
	7	2						1		1
	3	7						1		1
	7	5						1		1
	7	7						1		1
	6	7						1		1
	7	7						1		1
	7	7						1		1
52825388988		30						1		1
	27	30						1		1
	33	30						1		1
	21	15						1		1
	14	15						1		1
	14	15						1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	15	15							1	1
	14	15							1	1
	14	15							1	1
	27	30							1	1
	30	30							1	1
55550620219		30							1	1
	39	4							1	1
	10	30							1	1
	28	30							1	1
	35	30							1	1
	27	14							1	1
	29	2							1	1
	4	14							1	1
	24	28							1	1
	31	8							1	1
	8	14							1	1
	40	7							1	1
	6	9							1	1
	20	7							1	1
55552613945		7							1	1
	10	7							1	1
	10	7							1	1
55552649379		27							1	1
	37	27							1	1
	61	27							1	1
	28	13							1	1
	10	10							1	1
	17	10							1	1
	17	3							1	1
	5	5							1	1
	6	10							1	1
	27	20							1	1
	27	10							1	1
	9	10							1	1
55552666901		25	1							1
	27	30	1							1
	27	30	1							1
	29	30	1							1
	28	30	1							1
	32	30	1							1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	39	30	1								1
55552680473		30							1		1
	32	30							1		1
	42	30							1		1
	43	30							1		1
	36	30							1		1
	47	30							1		1
55553677025		6							1		1
	6	5							1		1
	6	14							1		1
	17	11							1		1
	10	5							1		1
	5	5							1		1
	10	9							1		1
	13	9							1		1
	9	3							1		1
55556505545		30							1		1
55556628116		3							1		1
	6	8							1		1
	8	18							1		1
	17	3							1		1
	3	8							1		1
	7	19							1		1
	18	3							1		1
	3	6							1		1
	6	19							1		1
	20	4							1		1
	4	8							1		1
55557500684		7							1		1
	6	15							1		1
	14	15							1		1
	14	10						1			1
	9	1						1			1
	6	28							1		1
55558587949		30					1				1
	59	30					1				1
	31	30					1				1
	55	30					1				1
	75	30					1				1
	28	30					1				1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	28	30					1				1
	28	10					1				1
55558591746		7							1		1
	7	13							1		1
	21	10							1		1
	9	20							1		1
	19	10							1		1
	12	10							1		1
	9	10							1		1
	12	10							1		1
	9	10							1		1
	9	10							1		1
	10	10							1		1
	11	10							1		1
	11	10							1		1
	9	10							1		1
	9	10							1		1
	9	10							1		1
	9	10							1		1
55558594284		26							1		1
55558660839		28	1								1
55559504183		6							1		1
	7	6							1		1
	5	6							1		1
	10	6							1		1
	6	6							1		1
	5	6							1		1
	6	6							1		1
	6	6							1		1
	6	6							1		1
	6	6							1		1
	6	6							1		1
	6	6							1		1
	5	6							1		1
	5	6							1		1
	5	6							1		1
	6	6							1		1
	6	6							1		1
	5	6							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	5	6							1		1
	5	6							1		1
	6	6							1		1
	7	6							1		1
	11	6							1		1
	5	6							1		1
	6	6							1		1
	6	6							1		1
	5	6							1		1
	5	6							1		1
	6	6							1		1
	6	6							1		1
	7	6							1		1
	5	6							1		1
	5	6							1		1
	5	6							1		1
	5	6							1		1
	7	6							1		1
	5	6							1		1
	5	6							1		1
	6	6							1		1
	6	5							1		1
	6	6							1		1
	5	6							1		1
	6	6							1		1
	5	6							1		1
	6	5							1		1
	6	6							1		1
	5	6							1		1
	6	6							1		1
	5	6							1		1
	6	6							1		1
	6	6							1		1
	6	6							1		1
	5	6							1		1
	5	6							1		1
	6	5							1		1
	5	6							1		1
	5	1							2		2
	1	6							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	5	6							1	1
	5	6							1	1
	7	2							1	1
	2	3							1	1
	3	6							1	1
	5	3							1	1
	3	3							1	1
55559510898		26							1	1
	24	30							1	1
	21	10							1	1
	10	12							1	1
	18	28							1	1
	35	7							1	1
	13	28							1	1
	39	14							1	1
55559514326		5							1	1
	6	7							1	1
	7	9							1	1
	9	5							1	1
	5	4							1	1
	5	4							1	1
	4	4							1	1
	4	1							1	1
	1	11							1	1
	10	2							1	1
	4	6							1	1
	5	4							1	1
	5	3							1	1
	3	13							1	1
	14	8							1	1
	9	4							1	1
	5	15							1	1
	14	11							1	1
	11	3							1	1
	3	14							1	1
	14	13							1	1
	14	15							1	1
	14	15							1	1
	14	15							1	1
	14	15							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	14	14							1		1
	13	14							1		1
	13	2							1		1
	3	2							1		1
	2	10							1		1
	9	14							1		1
	14	4							1		1
	4	4							1		1
	4	6							1		1
	5	14							1		1
	14	6							1		1
	6	4							1		1
	4	4							1		1
	4	15							1		1
	14	7							1		1
	7	4							1		1
	4	4							1		1
	4	15							1		1
	14	7							1		1
	7	4							1		1
55559534009		30							1		1
	71	30							1		1
	30	30							1		1
	28	30							1		1
	28	30							1		1
	28	30							1		1
	28	30							1		1
	28	30							1		1
	98	2							1		1
	7	28							1		1
55559542442		28	1								1
	31	30	1								1
	28	30	1								1
	17	15	1								1
	14	6	1								1
	11	9	1								1
	8	13	1								1
	13	7	1								1
	8	9	1								1
	8	1	1								1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	1	11	1								1
	10	7	1								1
	8	9	1								1
	8	2	1								1
	2	7	1								1
	7	4	1								1
	4	7	1								1
	6	9	1								1
	8	2	1								1
	12	2	1								1
	2	17	1								1
55559647211		8							1		1
	7	7							1		1
	8	7	1								1
	6	7							1		1
	8	7							1		1
	7	7							1		1
	7	7							1		1
55559678460		7							1		1
	25	5							1		1
58132033434		2							1		1
	2	1							1		1
	2	7							1		1
58764033334		22							1		1
	20	8							1		1
	7	22							1		1
	21	8							1		1
	7	22							1		1
	20	8							1		1
	7	22							1		1
	20	8							1		1
60861933334		28							1		1
	32	30							1		1
	28	30							1		1
	28	27							1		1
	29	28							1		1
	29	28							1		1
	29	30							1		1
	27	28							1		1
	29	28							1		1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	34	26							1	1
	24	7							1	1
	6	30							1	1
	27	30							1	1
61582677778		7							1	1
	9	14							1	1
	42	14							1	1
63345488988		30							1	1
63552355655		3							1	1
66661645804		30							1	1
	50	29							1	1
	25	9							1	1
	11	2							1	1
	2	20							1	1
	21	8							1	1
	13	20							1	1
	27	28							1	1
	27	29							1	1
	34	30							1	1
	33	30							1	1
	34	30							1	1
	31	30							1	1
66661732807		7							1	1
	6	15							1	1
	14	16							1	1
	14	9							1	1
	8	5							1	1
	6	6							1	1
	5	25							1	1
	25	29							1	1
	26	28							1	1
	28	28							1	1
	30	26							1	1
66662783684		27							1	1
	27	30							1	1
	28	30							1	1
	30	30							1	1
	34	30							1	1
	40	30							1	1
	32	30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	34	30							1	1
	28	30							1	1
	32	30							1	1
	29	30						1		1
66662799317		30							1	1
	85	30							1	1
66663711989		20						1		1
	21	30						1		1
	34	30						1		1
	28	28						1		1
66663726136		30							1	1
	21	7							1	1
66663752010		23	1							1
	88	14	1							1
66666735674		15				1				1
	14	30				1				1
	27	30				1				1
	28	30				1				1
	29	30				1				1
	28	30				1				1
	27	30				1				1
	29	29				1				1
	27	30				1				1
	30	7				1				1
	6	7				1				1
	17	15				1				1
	49	30				1				1
	27	30				1				1
66667619997		5							1	1
	3	7							1	1
	10	9							1	1
	27	30							1	1
	30	30							1	1
	28	30							1	1
66667741306		7							1	1
	7	7							1	1
	9	5							1	1
	21	23							1	1
	39	30							1	1
	121	30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	28	30							1	1
66668620066		15							1	1
66668636960		5							1	1
	5	15							1	1
	17	7							1	1
	13	7							1	1
	7	5							1	1
	9	9							1	1
	21	5							1	1
66669656705		4							1	1
	4	7							1	1
	7	14							1	1
	13	5							1	1
	7	11							1	1
	17	4							1	1
71859877778		5							1	1
71947788889		30				1				1
	53	30				1				1
	28	30				1				1
	41	30				1				1
73152033435		6							1	1
	6	12							1	1
	13	16							1	1
	14	4							1	1
	7	23							1	1
	21	4							1	1
	8	5							1	1
	5	13							1	1
	14	14							1	1
76084699991		30							1	1
	34	30							1	1
	28	30							1	1
	29	30							1	1
	27	30				1				1
	27	30				1				1
	28	30				1				1
	37	30				1				1
	33	30				1				1
	31	30				1				1
	32	30				1				1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	38	24							1	1
76260222223		27	1							1
77770738378		30			1					1
	197	10			1					1
	21	30			1					1
	27	30			1					1
	28	30			1					1
77770777168		30							1	1
77770807065		30					1			1
	29	28						1		1
	28	28						1		1
77770842949		7	1							1
77771731734		30							1	1
	29	30							1	1
	29	30							1	1
	30	30							1	1
	27	30							1	1
	27	30							1	1
	55	30							1	1
	28	30							1	1
	29	30							1	1
77772805894		14							1	1
	14	25							1	1
	28	30							1	1
	28	30							1	1
	28	28							1	1
	27	13							1	1
	14	26							1	1
	27	28							1	1
	32	15							1	1
	14	30							1	1
	27	10							1	1
	12	14							1	1
77773752207		5							1	1
	8	5				1				1
	5	6				1				1
	6	6				1				1
77773754151		4							1	1
	6	7							1	1
	7	7							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
								MIS 12-3MG	MIS 2-0.5MG	MIS 4-1MG	MIS 8-2MG	
77773832325		30							1	1
	27	26							1	1
	24	4							1	1
	29	4							1	1
	4	26							1	1
	29	30							1	1
	27	30							1	1
	31	30							1	1
	18	30				1				1
	28	30				1				1
77773838374		24							1	1
	34	30							1	1
	28	30							1	1
	39	30							1	1
	31	30							1	1
	35	30							1	1
	34	30							1	1
77774831550		3							1	1
	41	1							1	1
77774864770		9							1	1
	8	7							1	1
	10	7							1	1
	6	6							1	1
	15	1							1	1
	39	10							1	1
	10	10							1	1
	9	10							1	1
77774883355		2							1	1
	1	4				1				1
	4	7				1				1
	7	9				1				1
77775858901		4							1	1
	6	15							1	1
77775868883		24							1	1
	18	30							1	1
	25	30							1	1
	7	30							1	1
77775872914		28							1	1
	28	30							1	1
	29	30							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	28	28							1		1
77775897593		9							1		1
	10	11							1		1
	10	30							1		1
	103	1							1		1
	3	30							1		1
77777734401		27		1							1
	29	27		1							1
	28	27		1							1
	28	5		1							1
	8	24		1							1
	27	30		1							1
	31	4		1							1
	2	30					1				1
	29	30					1				1
	28	30					1				1
77777770348		3							1		1
77777802793		14							1		1
77778705114		7	1								1
77778785332		7							1		1
	17	7							1		1
	62	7							1		1
	13	3							1		1
	3	14							1		1
77778857350		30			1						1
	61	30			1						1
	29	30			1						1
	29	30			1						1
77779814158		11	1								1
	13	18	1								1
	16	12	1								1
	12	18	1								1
	16	12	1								1
	13	18	1								1
	16	12	1								1
	12	18	1								1
	16	12	1								1
	11	18	1								1
	16	12	1								1
	13	18	1								1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	16	12	1							1
	15	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
	16	9	1							1
	9	3	1							1
	3	18	1							1
85874411112		15							1	1
87896133434		7							1	1
	7	10							1	1
	9	12							1	1
	18	10							1	1
	10	20							1	1
	18	10							1	1
	10	15							1	1
	14	5							1	1
	7	10							1	1
	12	15							1	1
	20	5							1	1
	5	10							1	1
	9	15							1	1
88567633433		30			1					1
	31	28			1					1
	93	7							1	1
	6	28							1	1
	109	7							1	1
	18	14							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE	SUBOXONE	SUBOXONE	SUBOXONE	Grand Total
	14	13							1	1
	16	12							1	1
	13	30							1	1
	28	30							1	1
88591644544		7							1	1
	7	7							1	1
88881894101		17							1	1
	204	30							1	1
88882870476		7	1							1
	40	7	1							1
	104	7	1							1
88883881761		30	1							1
	152	15	1							1
	51	30	1							1
	83	12	1							1
	64	15	1							1
88883972779		10			1					1
88884803856		30							1	1
	31	30							1	1
88884947820		20							1	1
88886900667		8							1	1
	9	30							1	1
88886953218		14							1	1
88886959834		7							1	1
	6	7							1	1
	7	7							1	1
	7	7							1	1
	7	7							1	1
	8	7							1	1
	6	14							1	1
	14	14							1	1
	14	15							1	1
	21	14							1	1
	16	30							1	1
	40	30							1	1
88886981488		14							1	1
	15	30							1	1
	34	30							1	1
	22	5							1	1
	16	30							1	1

Buprenorphine/Naloxone Utilization

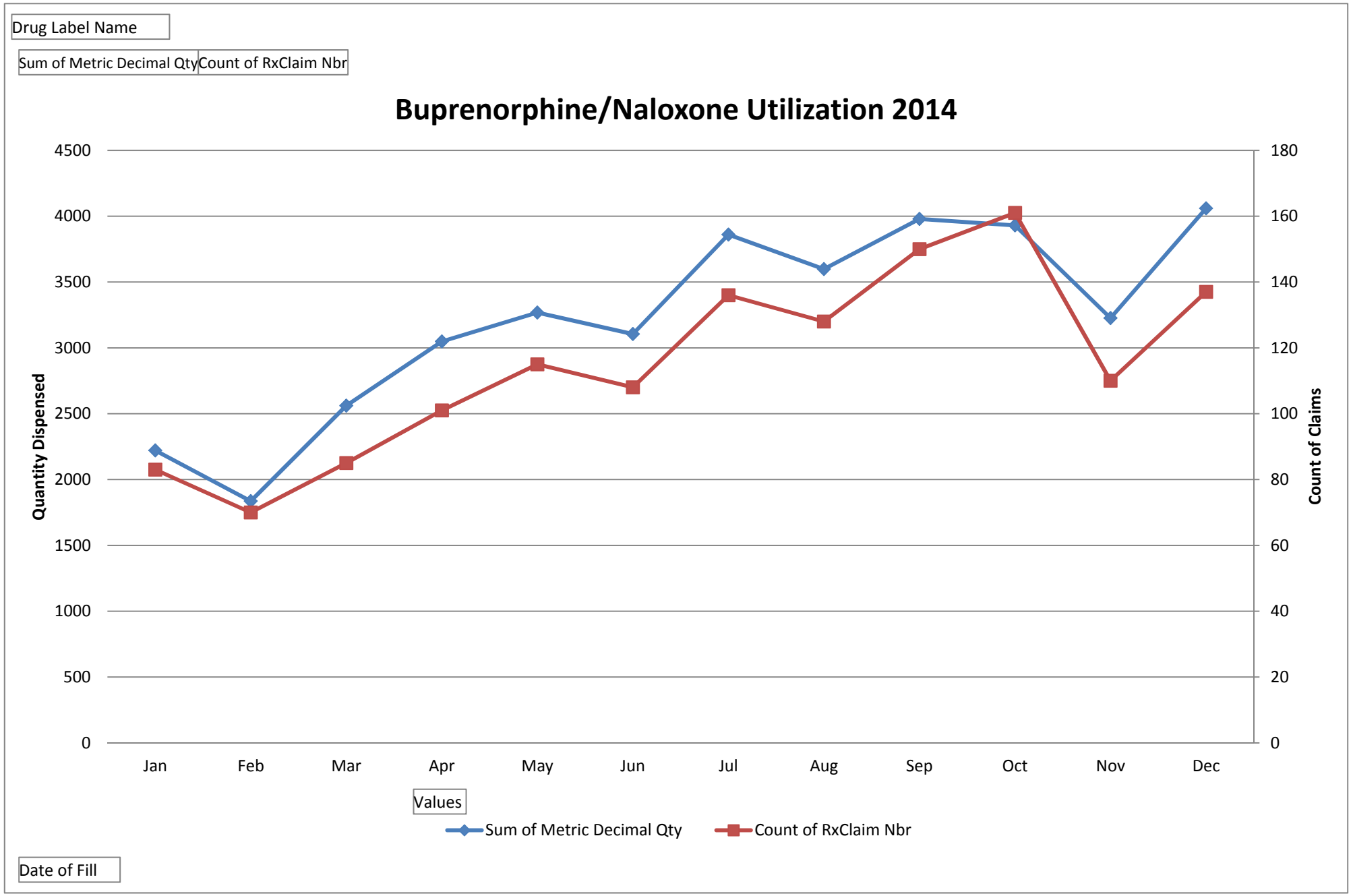
Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	28	7						1		1
	7	15						1		1
	19	7						1		1
88888821438		6						1		1
88888824345		12						1		1
88889926350		30						1		1
	31	30						1		1
	30	30						1		1
	30	30						1		1
	28	30						1		1
	35	30						1		1
	29	30						1		1
	29	30						1		1
	28	30						1		1
	28	30						1		1
	28	30						1		1
	29	30						1		1
	30	30						1		1
88889947708		30						1		1
90361266667		4						1		1
92709755556		5						1		1
	5	18						1		1
	37	7						1		1
	7	14						1		1
92943466667		7	1							1
94911477778		30			1					1
	10	30			1					1
	27	30			1					1
	14	30			1					1
97298799990		29			1					1
	29	8			1					1
	21	32			1					1
	32	6			1					1
	7	15			1					1
	17	6			1					1
	5	28			1					1
	27	22			1					1
	21	7			1					1
	7	7			1					1
	7	7			1					1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previoius Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
	7	7			1					1
	7	7			1					1
97858044544		3							1	1
	41	1							1	1
99990025168		30			1					1
99991098617		17							1	1
	19	7							1	1
	41	10							1	1
	25	10							1	1
	23	10							1	1
	27	10							1	1
	25	30							1	1
	28	30							1	1
	29	30							1	1
	29	30							1	1
99991955660		24							1	1
99992913737		5							1	1
99993009299		7							1	1
	7	15							1	1
	15	8							1	1
	7	7							1	1
	6	15							1	1
	15	8							1	1
	7	7							1	1
	6	15							1	1
	14	8							1	1
	7	7							1	1
	92	7							1	1
	47	30							1	1
99993954335		8							1	1
	22	7							1	1
99994037800		30							1	1
	28	30							1	1
	33	30							1	1
	28	30							1	1
	29	30							1	1
	28	30							1	1
	27	30							1	1
	30	30							1	1
99995051335		28							1	1

Buprenorphine/Naloxone Utilization

Member ID Encrypted	Days from Previous Fill	Days Supply	BUPREN/NALOX SUB 8-2MG	BUPRENORPHIN SUB 2MG	BUPRENORPHIN SUB 8MG	SUBOXONE MIS 12-3MG	SUBOXONE MIS 2-0.5MG	SUBOXONE MIS 4-1MG	SUBOXONE MIS 8-2MG	Grand Total
99995060939		15							1	1
	14	15							1	1
99995077472		30							1	1
	32	30							1	1
	150	30							1	1
	29	30							1	1
99995088399		7					1			1
	7	14						1		1
	14	21						1		1
99996054322		15			1					1
	15	1			1					1
	1	1			1					1
	1	1			1					1
	1	12			1					1
	11	15			1					1
99996068499		14							1	1
	72	7							1	1
	11	14							1	1
99996096164		30							1	1
	27	30							1	1
	28	30							1	1
99997013227		5	1							1
	7	15	1							1
Grand Total			**96**	**12**	**63**	**87**	**61**	**60**	**1005**	**1384**


Drug Label Name
Sum of Metric Decimal Qty
Count of RxClaim Nbr
Buprenorphine/Naloxone Utilization 2014
Quantity Dispensed
Count of Claims
4500
4000
3500
3000
2500
2000
1500
1000
500
0
180
160
140
120
100
80
60
40
20
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Values
Sum of Metric Decimal Qty
Count of RxClaim Nbr
Date of Fill

Lock-in Program Savings

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims October 2012	Total Amount October 2012	Total Savings October 2012
Oct-12	3,351	$211,272.67	2,881	$181,385.61	$ 29,887.06

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims November 2012	Total Amount November 2012	Total Savings November 2012
Nov-12	3,621	$225,612.11	2,862	$183,399.24	$ 42,212.87

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims December 2012	Total Amount December 2012	Total Savings December 2012
Dec-12	4,003	$243,775.34	3,066	$194,727.71	$ 49,047.63

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims January 2013	Total Amount January 2013	Total Savings January 2013
Jan-13	4,272	$263,340.18	3,276	$193,756.58	$ 69,583.60

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims February 2013	Total Amount February 2013	Total Savings February 2013
Feb-13	4,389	$258,212.28	3,144	$199,478.15	$ 58,734.13

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims March 2013	Total Amount March 2013	Total Savings March 2013
Mar-13	4,864	$299,998.75	3,525	$224,706.62	$ 75,498.06

Lock-in Program Savings

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims April 2013	Total Amount April 2013	Total Savings April 2013
Apr-13	107	$5,180.98	77	$5,651.90	$ (470.92)

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims May 2013	Total Amount May 2013	Total Savings May 2013
May-13	4,742	$286,483.91	3,594	$241,012.16	$ 45,471.75

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims June 2013	Total Amount June 2013	Total Savings June 2013
Jun-13	5,307	$337,065.30	3,453	$223,297.39	$ 113,767.91

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims July 2013	Total Amount July 2013	Total Savings July 2013
Jul-13	5,307	$337,065.30	3,747	$260,362.28	$ 76,703.02

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims August 2013	Total Amount August 2013	Total Savings August 2013
Aug-13	5,307	$337,065.30	3,549	$256,920.36	$ 80,144.94

	Total Claims Month Before Lock-In	Total Amount Month Before Lock-In	Total Claims September 2013	Total Amount September 2013	Total Savings September 2013
Sep-13	5,307	$337,065.30	3,747	$260,362.28	$ 76,703.02

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
36	ACE INHIBITORS***	LISINOPRIL TAB 2.5MG	30	30	4	$ 21.84
	ACE INHIBITORS* Total**				**4**	**$ 21.84**
	ANTIDOTES - CHELATING AGENTS***	EXJADE TAB 500MG	90	30	7	$ 65,439.15
	ANTIDOTES - CHELATING AGENTS* Total**				**7**	**$ 65,439.15**
	ANTIDOTES***	DEFEROXAMINE INJ 2GM	4	1	29	$ 3,665.60
	ANTIDOTES* Total**				**29**	**$ 3,665.60**
	ANTIEMETICS - MISCELLANEOUS***	DRONABINOL CAP 5MG	60	30	5	$ 2,561.45
	ANTIEMETICS - MISCELLANEOUS* Total**				**5**	**$ 2,561.45**
	ANTIFUNGALS - TOPICAL***	NYSTATIN CRE 100000	1	1	1	$ 0.10
	ANTIFUNGALS - TOPICAL* Total**				**1**	**$ 0.10**
	ANTIHISTAMINES - ETHANOLAMINES***	DIPHENHYDRAM CAP 25MG	1	1	2	$ 0.06
		DIPHENHYDRAM CAP 50MG	1	1	1	$ 0.01
		DIPHENHYDRAM INJ 50MG/ML	1	1	43	$ 42.12
			2	1	2	$ 3.96
			3	1	1	$ 2.97
	ANTIHISTAMINES - ETHANOLAMINES* Total**				**49**	**$ 49.12**
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE INJ 25MG/ML	1	1	3	$ 4.05
		PROMETHAZINE TAB 25MG	1	1	3	$ 0.36
			20	3	1	$ 7.10
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**7**	**$ 11.51**
	BENZODIAZEPINES***	LORAZEPAM INJ 2MG/ML	1	1	33	$ 25.41
			2	1	2	$ 3.06
		LORAZEPAM TAB 2MG	60	30	1	$ 9.47
	BENZODIAZEPINES* Total**				**36**	**$ 37.94**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	3	1	2	$ 0.32
			12	1	1	$ 0.64
		PROVENTIL AER HFA	6.7	25	1	$ 63.26
	BETA ADRENERGICS* Total**				**4**	**$ 64.22**
	BETA BLOCKERS CARDIO-SELECTIVE***	METOPROL TAR TAB 25MG	60	30	4	$ 30.20
		METOPROL TAR TAB 50MG	1	1	1	$ 0.03
			2	1	1	$ 0.07
	BETA BLOCKERS CARDIO-SELECTIVE* Total**				**6**	**$ 30.30**
	CEPHALOSPORINS - 1ST GENERATION***	CEPHALEXIN CAP 500MG	28	7	1	$ 10.65
			40	10	1	$ 14.68
	CEPHALOSPORINS - 1ST GENERATION* Total**				**2**	**$ 25.33**
	CEPHALOSPORINS - 3RD GENERATION***	CEFTRIAXONE INJ 1GM	2	1	1	$ 4.21
			4	1	2	$ 16.86
		CEFTRIAXONE INJ 250MG	1	1	1	$ 2.30
			1.4	1	1	$ 3.21
			4	1	5	$ 45.90
		CEFTRIAXONE/ INJ DEX 1GM	50	1	1	$ 14.47
	CEPHALOSPORINS - 3RD GENERATION* Total**				**11**	**$ 86.95**
	COMPLEMENT INHIBITORS***	SOLIRIS INJ 10MG/ML	30	1	2	$ 12,233.88
			90	1	27	$ 491,980.68
	COMPLEMENT INHIBITORS* Total**				**29**	**$ 504,214.56**
	CORTICOSTEROIDS - TOPICAL***	TRIAMCINOLON CRE 0.025%	80	15	1	$ 7.76
	CORTICOSTEROIDS - TOPICAL* Total**				**1**	**$ 7.76**
	DIAGNOSTIC DRUGS***	LEXISCAN INJ 0.4MG	5	1	1	$ 223.41
	DIAGNOSTIC DRUGS* Total**				**1**	**$ 223.41**
	DIAGNOSTIC TESTS***	FREESTYLE TES LITE	100	30	2	$ 288.84
	DIAGNOSTIC TESTS* Total**				**2**	**$ 288.84**
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)***	ARANESP INJ 200MCG	0.4	1	6	$ 8,266.92
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)* Total**				**6**	**$ 8,266.92**
	FLUOROQUINOLONES***	CIPROFLOXACN TAB 500MG	14	7	1	$ 7.99
	FLUOROQUINOLONES* Total**				**1**	**$ 7.99**
	FOLIC ACID/FOLATES***	FOLIC ACID TAB 1MG	1	1	2	$ 0.04
	FOLIC ACID/FOLATES* Total**				**2**	**$ 0.04**
	GLUCOCORTICOSTEROIDS***	DEXAMETH PHO INJ 10MG/ML	1	1	29	$ 24.65
		PREDNISONE TAB 50MG	3	2	1	$ 5.76
	GLUCOCORTICOSTEROIDS* Total**				**30**	**$ 30.41**
	H-2 ANTAGONISTS***	FAMOTIDINE INJ 20MG/2ML	2	1	1	$ 0.81
	H-2 ANTAGONISTS* Total**				**1**	**$ 0.81**
	HEPARINS AND HEPARINOID-LIKE AGENTS***	HEPARIN LOCK INJ 100/ML	10	1	1	$ 0.99
	HEPARINS AND HEPARINOID-LIKE AGENTS* Total**				**1**	**$ 0.99**
	HMG COA REDUCTASE INHIBITORS***	ATORVASTATIN TAB 10MG	2	1	2	$ 1.26

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
36	HMG COA REDUCTASE INHIBITORS***	ATORVASTATIN TAB 40MG	30	30	4	$ 62.20
	HMG COA REDUCTASE INHIBITORS* Total**				**6**	**$ 63.46**
	LOW MOLECULAR WEIGHT HEPARINS***	ENOXAPARIN INJ 80/0.8ML	0.8	1	2	$ 89.76
			1.6	1	1	$ 89.76
		LOVENOX INJ 100MG/ML	30	30	2	$ 5,076.08
	LOW MOLECULAR WEIGHT HEPARINS* Total**				**5**	**$ 5,255.60**
	NITRATES***	ISOSORB MONO TAB 30MG ER	1	1	2	$ 0.62
	NITRATES* Total**				**2**	**$ 0.62**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS***	ZOLPIDEM TAB 10MG	30	30	1	$ 5.78
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**1**	**$ 5.78**
	NON-NARC ANTITUSSIVE-ANTIHISTAMINE***	PROMETHAZINE SYP DM	240	12	1	$ 11.55
	NON-NARC ANTITUSSIVE-ANTIHISTAMINE* Total**				**1**	**$ 11.55**
	OPIOID AGONISTS***	DEMEROL INJ 100MG/ML	1	1	2	$ 6.00
			4	1	7	$ 21.00
		DEMEROL INJ 25MG/ML	1	1	26	$ 78.00
		DEMEROL INJ 50MG/ML	1	1	1	$ 3.00
			2	1	1	$ 3.00
		HYDROMORPHON INJ 1MG/ML	1	1	2	$ 4.24
			2	1	3	$ 12.72
			3	1	1	$ 6.36
			6	1	1	$ 12.73
		HYDROMORPHON TAB 2MG	60	7	4	$ 54.68
				8	2	$ 27.34
		METHADONE TAB 10MG	0.5	1	1	$ 0.06
			60	30	3	$ 35.49
		METHADONE TAB 5MG	58	29	1	$ 8.88
			60	30	3	$ 27.06
		OXYCODONE TAB 30MG	120	20	8	$ 711.58
	OPIOID AGONISTS* Total**				**66**	**$ 1,012.14**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	120	4	5	$ 35.00
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**5**	**$ 35.00**
	PROTON PUMP INHIBITORS***	PANTOPRAZOLE TAB 40MG	1	1	2	$ 0.32
	PROTON PUMP INHIBITORS* Total**				**2**	**$ 0.32**
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	PAROXETINE TAB 20MG	0.5	1	2	$ 0.20
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)* Total**				**2**	**$ 0.20**
	SODIUM***	SOD CHLORIDE INJ 0.9%	50	1	1	$ 1.80
			1000	1	3	$ 5.42
	SODIUM* Total**				**4**	**$ 7.22**
	STEROID INHALANTS***	BUDESONIDE SUS 0.5MG/2	2	1	1	$ 9.04
			4	1	1	$ 18.08
	STEROID INHALANTS* Total**				**2**	**$ 27.12**
	THIENOPYRIDINE DERIVATIVES***	CLOPIDOGREL TAB 75MG	30	30	4	$ 43.12
	THIENOPYRIDINE DERIVATIVES* Total**				**4**	**$ 43.12**
36 Total					**335**	**$ 591,497.37**
19	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	1	$ 294.16
	ADRENERGIC COMBINATIONS* Total**				**1**	**$ 294.16**
	ALPHA-BETA BLOCKERS***	CARVEDILOL TAB 3.125MG	60	30	1	$ 10.05
	ALPHA-BETA BLOCKERS* Total**				**1**	**$ 10.05**
	ANGIOTENSIN II RECEPTOR ANTAGONISTS***	LOSARTAN POT TAB 25MG	30	30	5	$ 33.85
	ANGIOTENSIN II RECEPTOR ANTAGONISTS* Total**				**5**	**$ 33.85**
	ANTACIDS - BICARBONATE***	SODIUM BICAR TAB 10GR	30	30	1	$ 0.54
			60	30	6	$ 6.48
	ANTACIDS - BICARBONATE* Total**				**7**	**$ 7.02**
	ANTICONVULSANTS - MISC.***	GABAPENTIN CAP 100MG	90	30	6	$ 51.60
	ANTICONVULSANTS - MISC.* Total**				**6**	**$ 51.60**
	ANTIHISTAMINES - ETHANOLAMINES***	DIPHENHYDRAM INJ 50MG/ML	2	1	1	$ 1.98
	ANTIHISTAMINES - ETHANOLAMINES* Total**				**1**	**$ 1.98**
	ANTIHISTAMINES - NON-SEDATING***	LORATADINE TAB 10MG	30	30	2	$ 13.66
	ANTIHISTAMINES - NON-SEDATING* Total**				**2**	**$ 13.66**
	ANTINEOPLASTIC - TYROSINE KINASE INHIBITORS***	SPRYCEL TAB 100MG	30	30	5	$ 47,322.94
	ANTINEOPLASTIC - TYROSINE KINASE INHIBITORS* Total**				**5**	**$ 47,322.94**
	ANTITUSSIVE - NONNARCOTIC***	BENZONATATE CAP 200MG	21	7	1	$ 8.58
	ANTITUSSIVE - NONNARCOTIC* Total**				**1**	**$ 8.58**
	BELLADONNA ALKALOIDS***	ATROPINE SUL INJ 0.1MG/ML	10	1	1	$ 5.36
	BELLADONNA ALKALOIDS* Total**				**1**	**$ 5.36**

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
19	BENZODIAZEPINE HYPNOTICS***	MIDAZOLAM INJ 2MG/2ML	10	1	1	$ 3.32
	BENZODIAZEPINE HYPNOTICS* Total**				**1**	**$ 3.32**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	375	30	4	$ 99.00
		ALBUTEROL NEB 0.63MG/3	150	7	1	$ 72.59
		PROAIR HFA AER	8.5	16	2	$ 105.78
				17	1	$ 52.89
				25	1	$ 52.89
	BETA ADRENERGICS* Total**				**9**	**$ 383.15**
	BICARBONATES***	SOD BICARB INJ 8.4%	100	1	1	$ 16.08
	BICARBONATES* Total**				**1**	**$ 16.08**
	BRONCHODILATORS - ANTICHOLINERGICS***	SPIRIVA CAP HANDIHLR	30	30	4	$ 1,182.52
	BRONCHODILATORS - ANTICHOLINERGICS* Total**				**4**	**$ 1,182.52**
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 2.5MG	30	30	3	$ 16.86
	CALCIUM CHANNEL BLOCKERS* Total**				**3**	**$ 16.86**
	CALCIUM***	CALCIUM CL INJ 10%	10	1	1	$ 4.85
	CALCIUM* Total**				**1**	**$ 4.85**
	CENTRAL MUSCLE RELAXANTS***	CYCLOBENZAPR TAB 10MG	50	25	1	$ 7.49
			60	20	1	$ 8.04
				30	1	$ 8.04
	CENTRAL MUSCLE RELAXANTS* Total**				**3**	**$ 23.57**
	CEPHALOSPORINS - 1ST GENERATION***	CEPHALEXIN CAP 500MG	40	10	2	$ 29.36
	CEPHALOSPORINS - 1ST GENERATION* Total**				**2**	**$ 29.36**
	COUMARIN ANTICOAGULANTS***	WARFARIN TAB 1MG	30	30	2	$ 19.06
		WARFARIN TAB 4MG	30	30	5	$ 53.00
	COUMARIN ANTICOAGULANTS* Total**				**7**	**$ 72.06**
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	50	25	1	$ 65.48
			100	30	2	$ 258.82
	DIAGNOSTIC TESTS* Total**				**3**	**$ 324.30**
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)***	PROCRIT INJ 10000/ML	1	1	13	$ 2,820.35
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)* Total**				**13**	**$ 2,820.35**
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 750MG	3	3	1	$ 6.36
			4	7	1	$ 6.89
	FLUOROQUINOLONES* Total**				**2**	**$ 13.25**
	GLUCOCORTICOSTEROIDS***	DEXAMETH PHO INJ 10MG/ML	2	1	1	$ 2.65
		METHYLPRED PAK 4MG	21	6	1	$ 13.80
		METHYLPRED TAB 4MG	7	7	2	$ 15.54
		PREDNISONE TAB 10MG	23	12	1	$ 6.17
	GLUCOCORTICOSTEROIDS* Total**				**5**	**$ 38.16**
	GLUCOSE MONITORING TEST SUPPLIES***	ONETOUCH MIS LANCETS	100	30	2	$ 19.92
	GLUCOSE MONITORING TEST SUPPLIES* Total**				**2**	**$ 19.92**
	H-2 ANTAGONISTS***	RANITIDINE TAB 300MG	30	30	2	$ 17.02
	H-2 ANTAGONISTS* Total**				**2**	**$ 17.02**
	HUMAN INSULIN***	HUMALOG KWIK INJ 100/ML	15	30	1	$ 386.13
	HUMAN INSULIN* Total**				**1**	**$ 386.13**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	90	30	4	$ 130.60
	HYDROCODONE COMBINATIONS* Total**				**4**	**$ 130.60**
	HYPERPARATHYROID TREATMENT - VITAMIN D ANALOGS***	CALCITRIOL CAP 0.25MCG	12	28	2	$ 30.38
			30	30	1	$ 32.22
	HYPERPARATHYROID TREATMENT - VITAMIN D ANALOGS* Total**				**3**	**$ 62.60**
	LOOP DIURETICS***	FUROSEMIDE TAB 20MG	30	30	1	$ 5.46
	LOOP DIURETICS* Total**				**1**	**$ 5.46**
	MIXED ADRENERGICS***	EPINEPHRINE INJ 0.1MG/ML	50	1	1	$ 51.82
	MIXED ADRENERGICS* Total**				**1**	**$ 51.82**
	NASAL STEROIDS***	FLUTICASONE SPR 50MCG	16	30	2	$ 54.40
	NASAL STEROIDS* Total**				**2**	**$ 54.40**
	NEEDLES & SYRINGES***	BD PEN NEEDL MIS 31GX3/16	100	30	4	$ 139.04
	NEEDLES & SYRINGES* Total**				**4**	**$ 139.04**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	120	6	1	$ 7.00
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**1**	**$ 7.00**
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 5-325MG	15	3	1	$ 7.34
		OXYCOD/APAP TAB 7.5-325	50	25	1	$ 53.22
	OPIOID COMBINATIONS* Total**				**2**	**$ 60.56**
	PENICILLIN COMBINATIONS***	AMOX/K CLAV TAB 250MG	10	5	1	$ 41.59
		AMOX/K CLAV TAB 500MG	14	7	1	$ 15.50
	PENICILLIN COMBINATIONS* Total**				**2**	**$ 57.09**

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
19	SCABICIDES & PEDICULICIDES***	PERMETHRIN CRE 5%	60	7	1	$ 89.99
	SCABICIDES & PEDICULICIDES*** Total				1	$ 89.99
19 Total					110	$ 53,758.66
22	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON SOL 4MG/5ML	30	3	1	$ 58.87
		ONDANSETRON TAB 4MG ODT	0.25	1	2	$ 0.32
			3	1	1	$ 7.66
	5-HT3 RECEPTOR ANTAGONISTS*** Total				4	$ 66.85
	AMINOGLYCOSIDES***	TOBRAMYCIN NEB 300/5ML	280	28	2	$ 11,778.24
	AMINOGLYCOSIDES*** Total				2	$ 11,778.24
	ANTIBIOTICS - TOPICAL***	MUPIROCIN OIN 2%	66	30	1	$ 33.87
	ANTIBIOTICS - TOPICAL*** Total				1	$ 33.87
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	360	20	1	$ 23.95
		LEVALBUTEROL NEB 0.63MG	216	20	1	$ 398.83
			288	30	3	$ 1,590.54
		XOPENEX NEB 0.63MG	360	13	2	$ 1,529.72
		XOPENEX NEB 1.25/3ML	3	1	1	$ 6.33
	BETA ADRENERGICS*** Total				8	$ 3,549.37
	CEPHALOSPORINS - 3RD GENERATION***	CEFDINIR SUS 250/5ML	60	10	1	$ 50.67
	CEPHALOSPORINS - 3RD GENERATION*** Total				1	$ 50.67
	GLUCOCORTICOSTEROIDS***	DEXAMETH PHO INJ 10MG/ML	10	1	1	$ 13.26
		PREDNISOLONE SOL 15MG/5ML	12	3	1	$ 5.86
			25	5	1	$ 6.45
	GLUCOCORTICOSTEROIDS*** Total				3	$ 25.57
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST GRA 4MG	30	30	4	$ 573.04
	LEUKOTRIENE RECEPTOR ANTAGONISTS*** Total				4	$ 573.04
	STEROID INHALANTS***	FLOVENT HFA AER 44MCG	10.6	30	5	$ 716.60
	STEROID INHALANTS*** Total				5	$ 716.60
22 Total					28	$ 16,794.21
34	ADRENERGIC COMBINATIONS***	SYMBICORT AER 160-4.5	10.2	30	6	$ 1,585.32
	ADRENERGIC COMBINATIONS*** Total				6	$ 1,585.32
	ALPHA-BETA BLOCKERS***	CARVEDILOL TAB 25MG	60	30	6	$ 50.58
	ALPHA-BETA BLOCKERS*** Total				6	$ 50.58
	ANTIARRHYTHMICS TYPE III***	AMIODARONE TAB 200MG	30	30	6	$ 76.50
	ANTIARRHYTHMICS TYPE III*** Total				6	$ 76.50
	ANTICONVULSANTS - MISC.***	LYRICA CAP 100MG	90	30	6	$ 2,445.00
		TOPIRAMATE TAB 100MG	60	30	6	$ 81.72
	ANTICONVULSANTS - MISC.*** Total				12	$ 2,526.72
	ANTIFUNGALS - TOPICAL***	NYSTATIN POW 100000	30	30	3	$ 110.91
	ANTIFUNGALS - TOPICAL*** Total				3	$ 110.91
	APPLICATORS,COTTON BALLS,ETC***	BD SWAB REG PAD SNGL USE	100	30	6	$ 37.98
	APPLICATORS,COTTON BALLS,ETC*** Total				6	$ 37.98
	BENZODIAZEPINES***	ALPRAZOLAM TAB 2MG	90	30	7	$ 102.97
	BENZODIAZEPINES*** Total				7	$ 102.97
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	375	22	6	$ 148.50
		PROAIR HFA AER	8.5	16	2	$ 105.78
				25	4	$ 211.56
	BETA ADRENERGICS*** Total				12	$ 465.84
	CALCIUM CHANNEL BLOCKERS***	DILTIAZEM CAP 180MG CD	30	30	2	$ 55.04
		DILTIAZEM CAP 180MG ER	30	30	4	$ 110.08
	CALCIUM CHANNEL BLOCKERS*** Total				6	$ 165.12
	CARDIAC GLYCOSIDES***	DIGOX TAB 0.25MG	30	30	6	$ 66.96
	CARDIAC GLYCOSIDES*** Total				6	$ 66.96
	DIAGNOSTIC TESTS***	FREESTYLE TES LITE	100	33	6	$ 896.64
	DIAGNOSTIC TESTS*** Total				6	$ 896.64
	DIRECT FACTOR XA INHIBITORS***	XARELTO TAB 20MG	30	30	4	$ 1,216.27
	DIRECT FACTOR XA INHIBITORS*** Total				4	$ 1,216.27
	FLUOROQUINOLONES***	CIPROFLOXACN TAB 500MG	20	10	1	$ 9.37
	FLUOROQUINOLONES*** Total				1	$ 9.37
	GLUCOSE MONITORING TEST SUPPLIES***	FREESTYLE MIS LANCETS	100	33	2	$ 20.04
	GLUCOSE MONITORING TEST SUPPLIES*** Total				2	$ 20.04
	GOUT AGENTS***	ALLOPURINOL TAB 300MG	30	30	6	$ 49.44
	GOUT AGENTS*** Total				6	$ 49.44
	H-2 ANTAGONISTS***	FAMOTIDINE TAB 40MG	30	30	4	$ 31.84
	H-2 ANTAGONISTS*** Total				4	$ 31.84
	HUMAN INSULIN***	HUMALOG KWIK INJ 100/ML	15	33	6	$ 2,316.78

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
34	HUMAN INSULIN***	LANTUS INJ SOLOSTAR	9	30	6	$ 1,251.78
	HUMAN INSULIN* Total**				**12**	**$ 3,568.56**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	30	30	7	$ 135.94
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**7**	**$ 135.94**
	LOOP DIURETICS***	TORSEMIDE TAB 20MG	30	30	6	$ 67.80
	LOOP DIURETICS* Total**				**6**	**$ 67.80**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS***	ZOLPIDEM TAB 10MG	30	30	4	$ 23.12
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**4**	**$ 23.12**
	OPIOID AGONISTS***	MORPHINE SUL TAB 30MG ER	90	30	4	$ 339.24
		MORPHINE SUL TAB 60MG ER	60	30	1	$ 102.10
		OXYCODONE TAB 30MG	120	30	7	$ 658.80
	OPIOID AGONISTS* Total**				**12**	**$ 1,100.14**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	120	25	2	$ 14.00
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**2**	**$ 14.00**
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	60	30	8	$ 217.92
	POTASSIUM* Total**				**8**	**$ 217.92**
	PULMONARY HYPERTENSION - PHOSPHODIESTERASE INHIBITORS***	SILDENAFIL TAB 20MG	90	30	6	$ 561.76
	PULMONARY HYPERTENSION - PHOSPHODIESTERASE INHIBITORS* Total**				**6**	**$ 561.76**
	THIAZIDES AND THIAZIDE-LIKE DIURETICS***	METOLAZONE TAB 2.5MG	30	30	6	$ 171.84
	THIAZIDES AND THIAZIDE-LIKE DIURETICS* Total**				**6**	**$ 171.84**
	TRIAZOLES***	FLUCONAZOLE TAB 200MG	3	3	4	$ 35.92
	TRIAZOLES* Total**				**4**	**$ 35.92**
34 Total					**160**	**$ 13,309.50**
13	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	4	$ 1,176.64
	ADRENERGIC COMBINATIONS* Total**				**4**	**$ 1,176.64**
	ANTICONVULSANTS - BENZODIAZEPINES***	CLONAZEPAM TAB 0.5MG	30	30	6	$ 31.20
		CLONAZEPAM TAB 1MG	15	15	1	$ 5.12
			30	30	1	$ 5.49
	ANTICONVULSANTS - BENZODIAZEPINES* Total**				**8**	**$ 41.81**
	ANTICONVULSANTS - MISC.***	CARBAMAZEPIN TAB 200MG	120	30	4	$ 59.80
			150	30	1	$ 13.25
		LAMOTRIGINE TAB 100MG	30	30	1	$ 10.00
		LAMOTRIGINE TAB 25MG	45	30	1	$ 10.86
			60	15	1	$ 12.90
		TOPIRAMATE TAB 200MG	60	30	1	$ 15.64
	ANTICONVULSANTS - MISC.* Total**				**9**	**$ 122.45**
	ANTIDEPRESSANTS - MISC.***	BUPROPION TAB 150MG SR	60	30	1	$ 42.51
			90	30	1	$ 61.39
		BUPROPN HCL TAB 300MG XL	30	30	1	$ 39.72
	ANTIDEPRESSANTS - MISC.* Total**				**3**	**$ 143.62**
	ANTIFUNGALS - TOPICAL***	NYSTOP POW 100000	15	7	1	$ 24.55
	ANTIFUNGALS - TOPICAL* Total**				**1**	**$ 24.55**
	ANTIPSYCHOTICS - MISC.***	LATUDA TAB 120MG	30	30	1	$ 1,070.86
	ANTIPSYCHOTICS - MISC.* Total**				**1**	**$ 1,070.86**
	BENZISOXAZOLES***	INVEGA SUST INJ 156MG/ML	1	28	6	$ 7,615.58
		INVEGA SUST INJ 234/1.5	1.5	28	1	$ 1,920.08
	BENZISOXAZOLES* Total**				**7**	**$ 9,535.66**
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 500MG	3	3	1	$ 5.94
	FLUOROQUINOLONES* Total**				**1**	**$ 5.94**
	LOOP DIURETICS***	FUROSEMIDE TAB 40MG	30	30	4	$ 21.70
	LOOP DIURETICS* Total**				**4**	**$ 21.70**
	MAGNESIUM***	MAGNESIUM SU INJ 40MG/ML	50	1	1	$ 7.61
	MAGNESIUM* Total**				**1**	**$ 7.61**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS***	ZOLPIDEM TAB 10MG	5	5	1	$ 4.93
			15	15	1	$ 5.27
			30	30	1	$ 5.78
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**3**	**$ 15.98**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	INDOMETHACIN CAP 25MG	90	30	6	$ 125.34
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**6**	**$ 125.34**
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	60	30	5	$ 136.20
	POTASSIUM* Total**				**5**	**$ 136.20**
	SELECTIVE MELATONIN RECEPTOR AGONISTS***	ROZEREM TAB 8MG	30	30	1	$ 239.81
	SELECTIVE MELATONIN RECEPTOR AGONISTS* Total**				**1**	**$ 239.81**
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	CITALOPRAM TAB 40MG	30	30	4	$ 28.40
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)* Total**				**4**	**$ 28.40**

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
13	STEROID INHALANTS***	FLOVENT HFA AER 44MCG	10.6	30	1	$ 143.32
	STEROID INHALANTS* Total**				**1**	**$ 143.32**
	TETRACYCLINES***	DOXYCYCL HYC TAB 100MG	30	30	1	$ 8.62
	TETRACYCLINES* Total**				**1**	**$ 8.62**
	THYROID HORMONES***	LEVOTHYROXIN TAB 125MCG	30	30	1	$ 14.59
		LEVOTHYROXIN TAB 150MCG	30	30	3	$ 44.97
		LEVOTHYROXIN TAB 300MCG	30	30	5	$ 108.77
	THYROID HORMONES* Total**				**9**	**$ 168.33**
13 Total					**69**	**$ 13,016.84**
42	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG	12	4	43	$ 355.18
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**43**	**$ 355.18**
	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 500/50	60	30	7	$ 2,697.80
	ADRENERGIC COMBINATIONS* Total**				**7**	**$ 2,697.80**
	ANTICONVULSANTS - BENZODIAZEPINES***	CLONAZEPAM TAB 0.5MG	90	30	7	$ 42.63
	ANTICONVULSANTS - BENZODIAZEPINES* Total**				**7**	**$ 42.63**
	ANTICONVULSANTS - MISC.***	GABAPENTIN CAP 100MG	90	30	6	$ 51.60
		LAMOTRIGINE TAB 200MG	30	30	6	$ 69.78
	ANTICONVULSANTS - MISC.* Total**				**12**	**$ 121.38**
	ANTI-INFECTIVE AGENTS - MISC.***	METRONIDAZOL TAB 500MG	21	7	1	$ 7.50
	ANTI-INFECTIVE AGENTS - MISC.* Total**				**1**	**$ 7.50**
	ANTIPARKINSON DOPAMINERGICS***	AMANTADINE CAP 100MG	30	30	7	$ 265.60
	ANTIPARKINSON DOPAMINERGICS* Total**				**7**	**$ 265.60**
	ANTITUSSIVE - OPIOID***	HYDROCOD/HOM SYP 5-1.5/5	240	12	1	$ 40.26
	ANTITUSSIVE - OPIOID* Total**				**1**	**$ 40.26**
	BENZODIAZEPINE HYPNOTICS***	TEMAZEPAM CAP 30MG	30	30	4	$ 33.04
	BENZODIAZEPINE HYPNOTICS* Total**				**4**	**$ 33.04**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	360	10	2	$ 32.00
				30	7	$ 112.00
	BETA ADRENERGICS* Total**				**9**	**$ 144.00**
	BETA BLOCKERS CARDIO-SELECTIVE***	METOPROL TAR TAB 50MG	60	30	7	$ 28.00
	BETA BLOCKERS CARDIO-SELECTIVE* Total**				**7**	**$ 28.00**
	BOWEL EVACUANT COMBINATIONS***	GAVILYTE-G SOL	4000	1	1	$ 22.36
	BOWEL EVACUANT COMBINATIONS* Total**				**1**	**$ 22.36**
	BRONCHODILATORS - ANTICHOLINERGICS***	SPIRIVA CAP HANDIHLR	30	30	7	$ 2,090.91
	BRONCHODILATORS - ANTICHOLINERGICS* Total**				**7**	**$ 2,090.91**
	CEPHALOSPORINS - 3RD GENERATION***	CEFPODOXIME TAB 200MG	14	7	2	$ 178.60
	CEPHALOSPORINS - 3RD GENERATION* Total**				**2**	**$ 178.60**
	DIBENZOTHIAZEPINES***	QUETIAPINE TAB 100MG	60	30	3	$ 89.49
		QUETIAPINE TAB 200MG	30	30	3	$ 76.41
		QUETIAPINE TAB 50MG	30	30	3	$ 52.50
	DIBENZOTHIAZEPINES* Total**				**9**	**$ 218.40**
	FLUOROQUINOLONES***	CIPROFLOXACN TAB 500MG	14	7	1	$ 4.00
	FLUOROQUINOLONES* Total**				**1**	**$ 4.00**
	GASTROINTESTINAL CHLORIDE CHANNEL ACTIVATORS***	AMITIZA CAP 24MCG	30	30	5	$ 787.70
	GASTROINTESTINAL CHLORIDE CHANNEL ACTIVATORS* Total**				**5**	**$ 787.70**
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 10MG	30	15	2	$ 13.22
	GLUCOCORTICOSTEROIDS* Total**				**2**	**$ 13.22**
	H-2 ANTAGONISTS***	RANITIDINE CAP 150MG	60	30	6	$ 215.96
		RANITIDINE CAP 300MG	30	30	1	$ 30.70
		RANITIDINE TAB 300MG	60	30	3	$ 24.00
	H-2 ANTAGONISTS* Total**				**10**	**$ 270.66**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	120	30	7	$ 293.58
	HYDROCODONE COMBINATIONS* Total**				**7**	**$ 293.58**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	30	30	9	$ 174.78
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**9**	**$ 174.78**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS***	ZOLPIDEM TAB 10MG	30	30	5	$ 28.90
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**5**	**$ 28.90**
	OPIOID AGONISTS***	MORPHINE SUL TAB 30MG ER	90	30	1	$ 84.81
		MORPHINE SUL TAB 60MG ER	60	30	1	$ 102.10
	OPIOID AGONISTS* Total**				**2**	**$ 186.91**
	PENICILLIN COMBINATIONS***	AMOX/K CLAV TAB 500MG	14	7	2	$ 31.00
	PENICILLIN COMBINATIONS* Total**				**2**	**$ 31.00**
	POTASSIUM***	POT CHLORIDE TAB 10MEQ ER	30	30	7	$ 106.74
	POTASSIUM* Total**				**7**	**$ 106.74**
	PROTON PUMP INHIBITORS***	NEXIUM CAP 40MG	30	30	4	$ 984.92

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
42	PROTON PUMP INHIBITORS***	NEXIUM CAP 40MG	60	30	1	$ 487.71
	PROTON PUMP INHIBITORS*** Total				5	$ 1,472.63
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	CITALOPRAM TAB 20MG	30	30	5	$ 20.00
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)*** Total				5	$ 20.00
	THIAZIDES AND THIAZIDE-LIKE DIURETICS***	CHLORTHALID TAB 25MG	30	30	7	$ 165.13
	THIAZIDES AND THIAZIDE-LIKE DIURETICS*** Total				7	$ 165.13
	TRIAZOLES***	FLUCONAZOLE TAB 150MG	3	6	1	$ 10.00
	TRIAZOLES*** Total				1	$ 10.00
	VAGINAL ESTROGENS***	ESTRACE VAG CRE 0.1MG/GM	42.5	21	2	$ 342.02
				30	3	$ 524.52
	VAGINAL ESTROGENS*** Total				5	$ 866.54
42 Total					190	$ 10,677.45
35	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG ODT	12	3	1	$ 16.37
	5-HT3 RECEPTOR ANTAGONISTS*** Total				1	$ 16.37
	ADRENERGIC COMBINATIONS***	SYMBICORT AER 160-4.5	10.2	30	1	$ 264.22
	ADRENERGIC COMBINATIONS*** Total				1	$ 264.22
	ANTIDOTES - CHELATING AGENTS***	EXJADE TAB 250MG	90	30	2	$ 9,048.85
	ANTIDOTES - CHELATING AGENTS*** Total				2	$ 9,048.85
	ANTISPASMODICS***	DICYCLOMINE TAB 20MG	120	30	1	$ 9.62
	ANTISPASMODICS*** Total				1	$ 9.62
	BETA ADRENERGICS***	PROAIR HFA AER	8.5	25	1	$ 52.89
	BETA ADRENERGICS*** Total				1	$ 52.89
	CENTRAL MUSCLE RELAXANTS***	CYCLOBENZAPR TAB 10MG	90	30	1	$ 9.67
	CENTRAL MUSCLE RELAXANTS*** Total				1	$ 9.67
	CEPHALOSPORINS - 1ST GENERATION***	CEPHALEXIN CAP 500MG	7	1	1	$ 6.23
	CEPHALOSPORINS - 1ST GENERATION*** Total				1	$ 6.23
	FLUOROQUINOLONES***	CIPROFLOXACN TAB 500MG	10	5	1	$ 7.07
			20	10	1	$ 9.37
		LEVOFLOXACIN TAB 500MG	10	10	1	$ 8.69
	FLUOROQUINOLONES*** Total				3	$ 25.13
	FOLIC ACID/FOLATES***	FOLIC ACID TAB 1MG	30	30	1	$ 5.38
	FOLIC ACID/FOLATES*** Total				1	$ 5.38
	H-2 ANTAGONISTS***	FAMOTIDINE TAB 40MG	30	30	1	$ 7.96
	H-2 ANTAGONISTS*** Total				1	$ 7.96
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 5-325MG	40	10	1	$ 16.39
			42	7	2	$ 33.94
	HYDROCODONE COMBINATIONS*** Total				3	$ 50.33
	OPIOID AGONISTS***	HYDROMORPHON INJ 2MG/ML	2	1	1	$ 2.94
		HYDROMORPHON TAB 4MG	30	5	1	$ 8.47
		MORPHINE SUL TAB 15MG ER	30	15	1	$ 18.38
			60	30	1	$ 32.00
		MORPHINE SUL TAB 30MG	30	5	1	$ 11.18
	OPIOID AGONISTS*** Total				5	$ 72.97
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 10-325MG	20	3	1	$ 20.86
	OPIOID COMBINATIONS*** Total				1	$ 20.86
35 Total					22	$ 9,590.48
10	5-HT3 RECEPTOR ANTAGONISTS***	ALOXI INJ 0.25MG/5	5	1	9	$ 3,632.22
		ONDANSETRON INJ 4MG/2ML	1	1	1	$ 0.31
	5-HT3 RECEPTOR ANTAGONISTS*** Total				10	$ 3,632.53
	ALKYLATING AGENTS***	CARBOPLATIN INJ 600/60ML	21.6	1	9	$ 313.92
	ALKYLATING AGENTS*** Total				9	$ 313.92
	ANTIEMETICS - MISCELLANEOUS***	DRONABINOL CAP 10MG	60	30	1	$ 439.41
	ANTIEMETICS - MISCELLANEOUS*** Total				1	$ 439.41
	ANTIHISTAMINES - ETHANOLAMINES***	DIPHENHYDRAM INJ 50MG/ML	1	1	6	$ 5.94
	ANTIHISTAMINES - ETHANOLAMINES*** Total				6	$ 5.94
	GLUCOCORTICOSTEROIDS***	DEXAMETH PHO INJ 10MG/ML	1	1	9	$ 7.65
	GLUCOCORTICOSTEROIDS*** Total				9	$ 7.65
	GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSF)***	NEULASTA INJ 6MG/0.6M	0.6	1	1	$ 4,555.68
	GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSF)*** Total				1	$ 4,555.68
	H-2 ANTAGONISTS***	ZANTAC INJ 25MG/ML	2	1	9	$ 23.58
	H-2 ANTAGONISTS*** Total				9	$ 23.58
	MITOTIC INHIBITORS***	PACLITAXEL INJ 300/50ML	20	1	9	$ 466.38
	MITOTIC INHIBITORS*** Total				9	$ 466.38
	OPIOID AGONISTS***	MORPHINE SUL INJ 10MG/ML	1	1	3	$ 4.98
		MORPHINE SUL INJ 5MG/ML	1	1	2	$ 2.02

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
10	**OPIOID AGONISTS*** Total**				**5**	**$ 7.00**
	OPIOID COMBINATIONS*	OXYCOD/APAP TAB 5-325MG	**1**	1	1	$ 0.17
	OPIOID COMBINATIONS* Total**				**1**	**$ 0.17**
10 Total					**60**	**$ 9,452.26**
38	**5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG ODT	**12**	3	1	$ 16.37
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**1**	**$ 16.37**
	ADRENERGIC COMBINATIONS*	IPRATROPIUM/ SOL ALBUTER	**180**	6	2	$ 70.72
				15	1	$ 35.36
			360	30	5	$ 268.60
	ADRENERGIC COMBINATIONS* Total**				**8**	**$ 374.68**
	ANTIBIOTICS - TOPICAL*	MUPIROCIN OIN 2%	**22**	10	2	$ 28.92
	ANTIBIOTICS - TOPICAL* Total**				**2**	**$ 28.92**
	ANTIHISTAMINES - NON-SEDATING*	CETIRIZINE TAB 10MG	**30**	30	5	$ 35.60
	ANTIHISTAMINES - NON-SEDATING* Total**				**5**	**$ 35.60**
	ANTISEPTICS - MOUTH/THROAT*	CHLORHEX GLU SOL 0.12%	**473**	20	1	$ 8.26
	ANTISEPTICS - MOUTH/THROAT* Total**				**1**	**$ 8.26**
	AZITHROMYCIN*	AZITHROMYCIN TAB 250MG	**4**	4	1	$ 8.34
			6	5	1	$ 8.67
		AZITHROMYCIN TAB 500MG	**3**	3	1	$ 10.38
	AZITHROMYCIN* Total**				**3**	**$ 27.39**
	BENZODIAZEPINES*	LORAZEPAM TAB 0.5MG	**3**	1	1	$ 4.91
			30	7	3	$ 18.93
				10	2	$ 12.62
			33	10	1	$ 6.46
			90	30	5	$ 47.00
	BENZODIAZEPINES* Total**				**12**	**$ 89.92**
	BETA ADRENERGICS*	ALBUTEROL NEB 0.083%	**300**	25	2	$ 41.50
		PROAIR HFA AER	**8.5**	30	1	$ 52.89
		PROVENTIL AER HFA	**13.4**	30	5	$ 608.75
		SEREVENT DIS AER 50MCG	**60**	30	4	$ 886.48
	BETA ADRENERGICS* Total**				**12**	**$ 1,589.62**
	BISPHOSPHONATES*	ALENDRONATE TAB 70MG	**4**	26	5	$ 45.50
	BISPHOSPHONATES* Total**				**5**	**$ 45.50**
	CALCIUM CHANNEL BLOCKERS*	VERAPAMIL CAP 240MG ER	**30**	30	1	$ 28.07
		VERAPAMIL CAP 360MG SR	**30**	30	2	$ 101.92
	CALCIUM CHANNEL BLOCKERS* Total**				**3**	**$ 129.99**
	CENTRAL MUSCLE RELAXANTS*	CARISOPRODOL TAB 350MG	**15**	5	4	$ 22.60
			60	30	7	$ 58.31
	CENTRAL MUSCLE RELAXANTS* Total**				**11**	**$ 80.91**
	ESTROGENS*	PREMARIN TAB 0.3MG	**36**	12	1	$ 126.79
			90	30	1	$ 309.20
		PREMARIN TAB 0.9MG	**30**	30	3	$ 318.30
	ESTROGENS* Total**				**5**	**$ 754.29**
	FLUOROQUINOLONES*	LEVOFLOXACIN TAB 500MG	**7**	7	1	$ 7.51
			10	10	2	$ 17.38
	FLUOROQUINOLONES* Total**				**3**	**$ 24.89**
	GLUCOCORTICOSTEROIDS*	METHYLPRED PAK 4MG	**21**	6	3	$ 41.40
		PREDNISONE TAB 10MG	**16**	32	1	$ 5.74
			27	27	1	$ 6.42
			29	29	1	$ 6.54
			30	30	4	$ 26.44
			40	10	1	$ 7.22
		PREDNISONE TAB 20MG	**5.5**	8	1	$ 5.20
		PREDNISONE TAB 5MG	**2**	1	1	$ 4.80
	GLUCOCORTICOSTEROIDS* Total**				**13**	**$ 103.76**
	H-2 ANTAGONISTS*	RANITIDINE TAB 150MG	**60**	30	5	$ 39.00
	H-2 ANTAGONISTS* Total**				**5**	**$ 39.00**
	HYDROCODONE COMBINATIONS*	HYDROCO/APAP TAB 10-325MG	**5**	1	1	$ 6.31
			9	1	1	$ 7.55
			30	4	2	$ 28.12
				5	2	$ 28.12
			33	5	1	$ 14.99
			36	4	1	$ 15.91
			150	25	1	$ 51.24
			180	30	1	$ 60.53

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
38	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	240	30	5	$ 314.01
	HYDROCODONE COMBINATIONS* Total**				**15**	**$ 526.78**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	1	1	1	$ 5.25
			10	10	1	$ 9.65
			12	12	1	$ 10.63
			30	30	5	$ 97.10
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**8**	**$ 122.63**
	NONERGOLINE DOPAMINE RECEPTOR AGONISTS***	ROPINIROLE TAB 0.5MG	30	30	5	$ 38.25
	NONERGOLINE DOPAMINE RECEPTOR AGONISTS* Total**				**5**	**$ 38.25**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	MELOXICAM TAB 7.5MG	30	30	4	$ 23.92
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**4**	**$ 23.92**
	OPIOID AGONISTS***	FENTANYL DIS 12MCG/HR	10	30	4	$ 562.48
	OPIOID AGONISTS* Total**				**4**	**$ 562.48**
	PROTON PUMP INHIBITORS***	NEXIUM CAP 20MG	30	30	1	$ 246.23
		OMEPRAZOLE CAP 40MG	30	30	1	$ 13.08
	PROTON PUMP INHIBITORS* Total**				**2**	**$ 259.31**
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	FLUOXETINE CAP 40MG	10	10	1	$ 8.69
			30	30	5	$ 82.70
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)* Total**				**6**	**$ 91.39**
	STEROID INHALANTS***	QVAR AER 80MCG	8.7	2	2	$ 365.64
				14	1	$ 182.82
				30	1	$ 182.82
	STEROID INHALANTS* Total**				**4**	**$ 731.28**
	VIRAL VACCINES***	FLUVIRIN PF INJ 2014-15	0.5	1	1	$ 15.11
	VIRAL VACCINES* Total**				**1**	**$ 15.11**
	XANTHINES***	THEO-24 CAP 400MG ER	30	30	5	$ 551.72
	XANTHINES* Total**				**5**	**$ 551.72**
38 Total					**143**	**$ 6,271.97**
24	ADRENERGIC COMBINATIONS***	IPRATROPIUM/ SOL ALBUTER	360	20	1	$ 53.72
	ADRENERGIC COMBINATIONS* Total**				**1**	**$ 53.72**
	ANTIHISTAMINES - NON-SEDATING***	LORATADINE TAB 10MG	30	30	1	$ 4.00
	ANTIHISTAMINES - NON-SEDATING* Total**				**1**	**$ 4.00**
	ANTI-INFECTIVES - THROAT***	NYSTATIN SUS 100000	250	12	4	$ 156.56
	ANTI-INFECTIVES - THROAT* Total**				**4**	**$ 156.56**
	ANTIPSYCHOTICS - MISC.***	ZIPRASIDONE CAP 20MG	60	30	1	$ 177.83
		ZIPRASIDONE CAP 60MG	60	30	4	$ 747.96
		ZIPRASIDONE CAP 80MG	30	30	2	$ 177.96
	ANTIPSYCHOTICS - MISC.* Total**				**7**	**$ 1,103.75**
	BENZODIAZEPINES***	ALPRAZOLAM TAB 0.25MG	4	1	1	$ 0.13
		ALPRAZOLAM TAB 1MG	60	30	1	$ 7.60
		ALPRAZOLAM TAB 2MG	60	30	4	$ 46.12
			90	30	2	$ 29.82
	BENZODIAZEPINES* Total**				**8**	**$ 83.67**
	BETA ADRENERGICS***	PROVENTIL AER HFA	6.7	25	1	$ 63.26
	BETA ADRENERGICS* Total**				**1**	**$ 63.26**
	CENTRAL MUSCLE RELAXANTS***	METHOCARBAM TAB 500MG	56	7	1	$ 14.39
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 14.39**
	CORTICOSTEROIDS - TOPICAL***	BETAMETH DIP CRE 0.05%	15	10	1	$ 8.21
	CORTICOSTEROIDS - TOPICAL* Total**				**1**	**$ 8.21**
	COUMARIN ANTICOAGULANTS***	WARFARIN TAB 5MG	30	30	3	$ 24.36
	COUMARIN ANTICOAGULANTS* Total**				**3**	**$ 24.36**
	DIBENZOTHIAZEPINES***	QUETIAPINE TAB 100MG	60	30	1	$ 29.83
	DIBENZOTHIAZEPINES* Total**				**1**	**$ 29.83**
	EXPECTORANTS***	MUCINEX TAB 1200MG	14	7	1	$ 13.98
	EXPECTORANTS* Total**				**1**	**$ 13.98**
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 750MG	3	3	1	$ 6.36
			7	7	1	$ 8.49
			10	10	1	$ 10.09
	FLUOROQUINOLONES* Total**				**3**	**$ 24.94**
	GASTROINTESTINAL STIMULANTS***	METOCLOPRAM INJ 5MG/ML	2	1	1	$ 1.13
	GASTROINTESTINAL STIMULANTS* Total**				**1**	**$ 1.13**
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 20MG	60	30	4	$ 38.32
	GLUCOCORTICOSTEROIDS* Total**				**4**	**$ 38.32**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 7.5-325	20	3	1	$ 8.88
				4	1	$ 8.88

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
24	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 7.5-325	20	5	1	$ 8.88
	HYDROCODONE COMBINATIONS*** Total				3	$ 26.64
	IMIDAZOLE-RELATED ANTIFUNGALS - TOPICAL***	KETOCONAZOLE CRE 2%	60	15	1	$ 41.79
	IMIDAZOLE-RELATED ANTIFUNGALS - TOPICAL*** Total				1	$ 41.79
	LINCOSAMIDES***	CLINDAMYCIN CAP 150MG	28	7	2	$ 20.71
		CLINDAMYCIN CAP 300MG	30	10	1	$ 17.43
	LINCOSAMIDES*** Total				3	$ 38.14
	LOW MOLECULAR WEIGHT HEPARINS***	LOVENOX INJ 80/0.8ML	8	5	1	$ 680.32
	LOW MOLECULAR WEIGHT HEPARINS*** Total				1	$ 680.32
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	KETOROLAC TAB 10MG	20	6	1	$ 14.76
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*** Total				1	$ 14.76
	OPIOID AGONISTS***	FENTANYL DIS 50MCG/HR	10	30	6	$ 721.85
		HYDROMORPHON INJ 2MG/ML	3	1	1	$ 4.41
		OXYCODONE TAB 30MG	210	30	6	$ 962.63
	OPIOID AGONISTS*** Total				13	$ 1,688.89
	PROTON PUMP INHIBITORS***	NEXIUM CAP 40MG	30	30	6	$ 1,477.38
	PROTON PUMP INHIBITORS*** Total				6	$ 1,477.38
	SEROTONIN MODULATORS***	TRAZODONE TAB 150MG	60	30	5	$ 40.00
	SEROTONIN MODULATORS*** Total				5	$ 40.00
	TETRACYCLINES***	DOXYCYCL HYC TAB 100MG	20	10	1	$ 7.33
	TETRACYCLINES*** Total				1	$ 7.33
	TRIAZOLES***	FLUCONAZOLE TAB 200MG	7	7	1	$ 14.61
	TRIAZOLES*** Total				1	$ 14.61
	TRICYCLIC AGENTS***	AMITRIPTYLIN TAB 25MG	30	30	2	$ 8.00
	TRICYCLIC AGENTS*** Total				2	$ 8.00
24 Total					74	$ 5,657.98
4	ANTIHISTAMINES - ETHANOLAMINES***	DIPHENHYDRAM CAP 25MG	240	30	1	$ 11.79
		DIPHENHYDRAM INJ 50MG/ML	1	1	1	$ 0.99
	ANTIHISTAMINES - ETHANOLAMINES*** Total				2	$ 12.78
	ANTIPARKINSON ANTICHOLINERGICS***	BENZTROPINE TAB 1MG	60	30	1	$ 9.85
	ANTIPARKINSON ANTICHOLINERGICS*** Total				1	$ 9.85
	QUINOLINONE DERIVATIVES***	ABILIFY TAB 15MG	60	30	1	$ 1,588.41
		ABILIFY MAIN INJ 300MG	1	1	1	$ 1,181.56
				28	2	$ 2,363.12
	QUINOLINONE DERIVATIVES*** Total				4	$ 5,133.09
	VIRAL VACCINES***	FLUVIRIN INJ 2014-15	0.5	1	1	$ 21.70
	VIRAL VACCINES*** Total				1	$ 21.70
4 Total					8	$ 5,177.42
23	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	2	1	3	$ 3.36
			3	1	1	$ 0.70
		ONDANSETRON TAB 4MG	12	3	5	$ 41.30
				4	2	$ 16.52
				21	1	$ 8.26
		ONDANSETRON TAB 8MG ODT	30	7	1	$ 30.61
		ZOFRAN TAB 4MG ODT	1	1	1	$ 21.31
	5-HT3 RECEPTOR ANTAGONISTS*** Total				14	$ 122.06
	ACE INHIBITORS***	LISINOPRIL TAB 20MG	1	1	1	$ 0.06
			30	30	1	$ 6.69
		LISINOPRIL TAB 30MG	30	30	5	$ 40.10
	ACE INHIBITORS*** Total				7	$ 46.85
	ALPHA-BETA BLOCKERS***	LABETALOL INJ 5MG/ML	4	1	1	$ 3.55
		LABETALOL TAB 200MG	30	30	5	$ 75.05
	ALPHA-BETA BLOCKERS*** Total				6	$ 78.60
	ANESTHETICS TOPICAL ORAL***	LIDOCAINE SOL 2% VISC	40	1	1	$ 1.04
	ANESTHETICS TOPICAL ORAL*** Total				1	$ 1.04
	ANTIDEPRESSANTS - MISC.***	BUPROPION TAB 150MG SR	60	30	1	$ 42.51
	ANTIDEPRESSANTS - MISC.*** Total				1	$ 42.51
	ANTIHISTAMINES - ETHANOLAMINES***	DIPHENHYDRAM CAP 50MG	30	30	4	$ 20.80
		DIPHENHYDRAM INJ 50MG/ML	1	1	1	$ 0.84
	ANTIHISTAMINES - ETHANOLAMINES*** Total				5	$ 21.64
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE INJ 25MG/ML	1	1	1	$ 0.88
			50	1	1	$ 67.32
		PROMETHEGAN SUP 25MG	12	3	1	$ 17.19
	ANTIHISTAMINES - PHENOTHIAZINES*** Total				3	$ 85.39
	ANTISPASMODICS***	DICYCLOMINE TAB 20MG	14	7	1	$ 5.33

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
23	**ANTISPASMODICS*** Total**				**1**	**$ 5.33**
	BENZISOXAZOLES*	RISPERIDONE TAB 1MG	**2**	1	1	$ 0.35
		RISPERIDONE TAB 2MG	**30**	30	1	$ 15.85
		RISPERIDONE TAB 3MG	**30**	30	1	$ 19.71
	BENZISOXAZOLES* Total**				**3**	**$ 35.91**
	BENZODIAZEPINES*	ALPRAZOLAM TAB 2MG	**90**	30	7	$ 106.05
	BENZODIAZEPINES* Total**				**7**	**$ 106.05**
	BETA ADRENERGICS*	PROAIR HFA AER	**17**	30	1	$ 101.03
	BETA ADRENERGICS* Total**				**1**	**$ 101.03**
	CALCIUM CHANNEL BLOCKERS*	AMLODIPINE TAB 10MG	**30**	30	1	$ 6.10
		AMLODIPINE TAB 5MG	**2**	1	1	$ 0.16
	CALCIUM CHANNEL BLOCKERS* Total**				**2**	**$ 6.26**
	CEPHALOSPORINS - 3RD GENERATION*	CEFDINIR CAP 300MG	**14**	7	1	$ 37.35
	CEPHALOSPORINS - 3RD GENERATION* Total**				**1**	**$ 37.35**
	DIABETIC OTHER*	GLUCAGON KIT 1MG	**1**	1	1	$ 188.21
	DIABETIC OTHER* Total**				**1**	**$ 188.21**
	DIAGNOSTIC TESTS*	ONETOUCH TES ULTRA BL	**100**	30	1	$ 129.41
	DIAGNOSTIC TESTS* Total**				**1**	**$ 129.41**
	GASTROINTESTINAL STIMULANTS*	METOCLOPRAM INJ 5MG/ML	**2**	1	3	$ 3.18
		METOCLOPRAM TAB 10MG	**25**	8	1	$ 6.59
			60	30	1	$ 9.14
	GASTROINTESTINAL STIMULANTS* Total**				**5**	**$ 18.91**
	GLUCOSE MONITORING TEST SUPPLIES*	ONETOUCH KIT ULT MINI	**1**	30	1	$ 17.74
		ONETOUCH MIS 30G	**100**	30	5	$ 49.80
	GLUCOSE MONITORING TEST SUPPLIES* Total**				**6**	**$ 67.54**
	H-2 ANTAGONISTS*	FAMOTIDINE INJ 10MG/ML	**2**	1	1	$ 1.21
		FAMOTIDINE TAB 20MG	**1**	1	1	$ 0.09
	H-2 ANTAGONISTS* Total**				**2**	**$ 1.30**
	HUMAN INSULIN*	LANTUS INJ 100/ML	**20**	30	4	$ 1,831.20
		LEVEMIR INJ FLEXTOUC	**15**	30	1	$ 361.31
		NOVOLOG INJ 100/ML	**10**	28	1	$ 212.06
				30	4	$ 773.24
		NOVOLOG INJ FLEXPEN	**15**	30	1	$ 369.00
	HUMAN INSULIN* Total**				**11**	**$ 3,546.81**
	HYDROCODONE COMBINATIONS*	HYDROCO/APAP TAB 10-325MG	**30**	7	1	$ 14.06
		HYDROCO/APAP TAB 5-325MG	**15**	2	1	$ 9.13
	HYDROCODONE COMBINATIONS* Total**				**2**	**$ 23.19**
	LOW MOLECULAR WEIGHT HEPARINS*	LOVENOX INJ 40/0.4ML	**0.4**	1	1	$ 33.74
	LOW MOLECULAR WEIGHT HEPARINS* Total**				**1**	**$ 33.74**
	MISC. ANTI-ULCER*	SUCRALFATE TAB 1GM	**60**	30	1	$ 19.52
			90	30	1	$ 26.90
	MISC. ANTI-ULCER* Total**				**2**	**$ 46.42**
	NEEDLES & SYRINGES*	BD PEN NEEDL MIS 31GX3/16	**100**	30	1	$ 34.76
		INSULIN SYRG MIS 1ML/30G	**30**	30	1	$ 6.49
			100	30	1	$ 16.99
	NEEDLES & SYRINGES* Total**				**3**	**$ 58.24**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS*	ZOLPIDEM TAB 5MG	**1**	1	1	$ 0.03
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**1**	**$ 0.03**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	IBUPROFEN TAB 800MG	**20**	6	1	$ 6.04
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**1**	**$ 6.04**
	OPIOID AGONISTS*	HYDROMORPHON INJ 1MG/ML	**1**	1	1	$ 2.12
		HYDROMORPHON INJ 2MG/ML	**2**	1	1	$ 2.94
		MORPHINE SUL INJ 2MG/ML	**1**	1	1	$ 1.87
		MORPHINE SUL INJ 4MG/ML	**1**	1	2	$ 3.74
	OPIOID AGONISTS* Total**				**5**	**$ 10.67**
	OPIOID COMBINATIONS*	OXYCOD/APAP TAB 10-325MG	**15**	3	1	$ 16.84
			20	3	1	$ 20.86
			28	7	1	$ 27.31
			30	7	1	$ 28.92
			40	10	1	$ 36.97
			60	10	1	$ 53.07
		OXYCOD/APAP TAB 7.5-325	**15**	4	1	$ 19.30
			24	7	1	$ 28.02
		PERCOCET TAB 10-325MG	**1**	1	1	$ 9.00
	OPIOID COMBINATIONS* Total**				**9**	**$ 240.29**

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
23	PHENOTHIAZINES***	PROCHLORPER INJ 5MG/ML	2	1	1	$ 4.69
	PHENOTHIAZINES* Total**				**1**	**$ 4.69**
	POTASSIUM***	KLOR-CON 10 TAB 10MEQ ER	1	1	2	$ 1.02
	POTASSIUM* Total**				**2**	**$ 1.02**
	PROTON PUMP INHIBITORS***	PROTONIX INJ 40MG	1	1	1	$ 5.10
			2	1	1	$ 10.20
	PROTON PUMP INHIBITORS* Total**				**2**	**$ 15.30**
	SEROTONIN MODULATORS***	TRAZODONE TAB 100MG	30	30	4	$ 27.00
	SEROTONIN MODULATORS* Total**				**4**	**$ 27.00**
	SODIUM***	SOD CHLORIDE INJ 0.9%	1000	1	1	$ 1.85
			2000	1	1	$ 3.71
	SODIUM* Total**				**2**	**$ 5.56**
	TRAMADOL COMBINATIONS***	TRAMADL/APAP TAB 37.5-325	120	30	1	$ 53.57
	TRAMADOL COMBINATIONS* Total**				**1**	**$ 53.57**
23 Total					**114**	**$ 5,167.96**
8	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	2	$ 588.32
		SYMBICORT AER 160-4.5	10.2	30	2	$ 528.44
	ADRENERGIC COMBINATIONS* Total**				**4**	**$ 1,116.76**
	ANTITUSSIVE-EXPECTORANT***	CHERATUSSIN SYP AC	400	10	1	$ 39.01
	ANTITUSSIVE-EXPECTORANT* Total**				**1**	**$ 39.01**
	ANTIVIRALS - TOPICAL***	ACYCLOVIR OIN 5%	30	8	2	$ 1,256.92
	ANTIVIRALS - TOPICAL* Total**				**2**	**$ 1,256.92**
	AZITHROMYCIN***	AZITHROMYCIN TAB 250MG	6	5	1	$ 10.14
	AZITHROMYCIN* Total**				**1**	**$ 10.14**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	300	17	3	$ 39.99
			525	30	5	$ 116.65
		PROAIR HFA AER	8.5	17	2	$ 105.78
	BETA ADRENERGICS* Total**				**10**	**$ 262.42**
	BRONCHODILATORS - ANTICHOLINERGICS***	SPIRIVA CAP HANDIHLR	30	30	4	$ 1,199.72
		TUDORZA PRES AER 400/ACT	1	30	1	$ 245.47
	BRONCHODILATORS - ANTICHOLINERGICS* Total**				**5**	**$ 1,445.19**
	CENTRAL MUSCLE RELAXANTS***	BACLOFEN TAB 20MG	60	30	1	$ 10.12
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 10.12**
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 500MG	5	5	1	$ 6.72
		LEVOFLOXACIN TAB 750MG	5	5	1	$ 7.42
	FLUOROQUINOLONES* Total**				**2**	**$ 14.14**
	GLUCOCORTICOSTEROIDS***	METHYLPRED PAK 4MG	21	6	3	$ 41.40
	GLUCOCORTICOSTEROIDS* Total**				**3**	**$ 41.40**
	HERPES AGENTS - PURINE ANALOGUES***	ACYCLOVIR TAB 400MG	30	30	4	$ 37.84
	HERPES AGENTS - PURINE ANALOGUES* Total**				**4**	**$ 37.84**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 5-325MG	20	5	1	$ 10.58
	HYDROCODONE COMBINATIONS* Total**				**1**	**$ 10.58**
	IMIDAZOLE-RELATED ANTIFUNGALS***	TERCONAZOLE CRE 0.4%	45	8	2	$ 61.62
	IMIDAZOLE-RELATED ANTIFUNGALS* Total**				**2**	**$ 61.62**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	30	30	1	$ 19.42
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**1**	**$ 19.42**
	THYROID HORMONES***	LEVOTHYROXIN TAB 50MCG	30	30	2	$ 8.00
	THYROID HORMONES* Total**				**2**	**$ 8.00**
	TRIAZOLES***	FLUCONAZOLE TAB 150MG	1	7	2	$ 8.00
	TRIAZOLES* Total**				**2**	**$ 8.00**
	VAGINAL ANTI-INFECTIVES***	CLINDAMYCIN CRE 2% VAG	40	7	1	$ 65.55
	VAGINAL ANTI-INFECTIVES* Total**				**1**	**$ 65.55**
8 Total					**42**	**$ 4,407.11**
21	ANALGESICS OTHER***	MAPAP LIQ 160/5ML	180	10	1	$ 5.85
	ANALGESICS OTHER* Total**				**1**	**$ 5.85**
	ANTIADRENERGICS - CENTRALLY ACTING***	CLONIDINE TAB 0.1MG	30	30	1	$ 6.49
	ANTIADRENERGICS - CENTRALLY ACTING* Total**				**1**	**$ 6.49**
	ANTIBIOTICS - TOPICAL***	MUPIROCIN OIN 2%	22	10	1	$ 13.94
	ANTIBIOTICS - TOPICAL* Total**				**1**	**$ 13.94**
	ANTIFUNGALS - TOPICAL COMBINATIONS***	CLOTRIM/BETA CRE DIPROP	45	5	1	$ 41.80
				10	1	$ 41.80
		NYSTAT/TRIAM CRE	60	7	1	$ 10.61
	ANTIFUNGALS - TOPICAL COMBINATIONS* Total**				**3**	**$ 94.21**
	ANTIFUNGALS - TOPICAL***	NYSTATIN POW 100000	30	5	5	$ 173.05
	ANTIFUNGALS - TOPICAL* Total**				**5**	**$ 173.05**

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
21	ANTI-INFECTIVE MISC. - COMBINATIONS***	SMZ-TMP SUS 200-40/5	70	5	1	$ 8.62
			75	7	1	$ 8.89
	ANTI-INFECTIVE MISC. - COMBINATIONS*** Total				2	$ 17.51
	BARBITURATE HYPNOTICS***	PHENOBARB ELX 20MG/5ML	473	18	1	$ 82.79
				19	9	$ 745.11
			2100	14	1	$ 351.19
	BARBITURATE HYPNOTICS*** Total				11	$ 1,179.09
	BENZODIAZEPINES***	DIAZEPAM SOL 1MG/ML	16	8	1	$ 6.40
	BENZODIAZEPINES*** Total				1	$ 6.40
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	75	5	29	$ 254.04
		PROAIR HFA AER	8.5	17	2	$ 105.78
		VENTOLIN HFA AER	18	16	1	$ 48.28
				25	1	$ 48.28
	BETA ADRENERGICS*** Total				33	$ 456.38
	CARNITINE REPLENISHER - AGENTS***	LEVOCARNITIN SOL 1GM/10ML	15	4	1	$ 7.42
			36	9	1	$ 11.14
			60	15	1	$ 15.39
			118	30	7	$ 179.69
	CARNITINE REPLENISHER - AGENTS*** Total				10	$ 213.64
	CENTRAL MUSCLE RELAXANTS***	BACLOFEN TAB 10MG	135	30	1	$ 12.28
		BACLOFEN TAB 20MG	90	30	5	$ 66.15
			135	30	2	$ 34.50
	CENTRAL MUSCLE RELAXANTS*** Total				8	$ 112.93
	CORTICOSTEROIDS - TOPICAL***	HYDROCORT CRE 2.5%	28	5	1	$ 8.64
			30	10	1	$ 9.71
				14	1	$ 8.13
		TRIAMCINOLON OIN 0.1%	15	7	1	$ 5.51
	CORTICOSTEROIDS - TOPICAL*** Total				4	$ 31.99
	GLUCOCORTICOSTEROIDS***	PREDNISOLONE SOL 15MG/5ML	5	3	1	$ 5.22
			50	30	1	$ 8.15
	GLUCOCORTICOSTEROIDS*** Total				2	$ 13.37
	H-2 ANTAGONISTS***	RANITIDINE SYP 15MG/ML	6	9	1	$ 5.47
			80	30	8	$ 106.04
	H-2 ANTAGONISTS*** Total				9	$ 111.51
	LAXATIVES - MISCELLANEOUS***	POLYETH GLYC POW 3350 NF	255	15	6	$ 99.54
			527	15	1	$ 29.21
		SANI-SUPP SUP PEDIATRI	25	25	1	$ 4.98
	LAXATIVES - MISCELLANEOUS*** Total				8	$ 133.73
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	IBUPROFEN SUS 100/5ML	120	6	2	$ 19.32
			473	9	1	$ 24.06
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*** Total				3	$ 43.38
	OPHTHALMIC ANTIBIOTICS***	ERYTHROMYCIN OIN 5MG/GM	3.5	5	1	$ 20.03
		ERYTHROMYCIN OIN OP	3.5	7	1	$ 20.26
		GENTAK OIN 0.3% OP	3.5	7	1	$ 19.81
		GENTAMICIN SOL 0.3% OP	5	3	1	$ 7.61
	OPHTHALMIC ANTIBIOTICS*** Total				4	$ 67.71
	OPIOID AGONISTS***	METHADONE SOL 5MG/5ML	2	10	1	$ 4.89
	OPIOID AGONISTS*** Total				1	$ 4.89
	STEROID INHALANTS***	BUDESONIDE SUS 0.5MG/2	60	9	1	$ 275.98
				15	1	$ 275.98
		FLOVENT HFA AER 44MCG	10.6	30	7	$ 1,003.24
	STEROID INHALANTS*** Total				9	$ 1,555.20
	VITAMIN D***	VITAMIN D DRO 400UNIT	50	25	2	$ 20.64
		VITAMIN D3 DRO 400UNIT	50	25	8	$ 65.20
	VITAMIN D*** Total				10	$ 85.84
21 Total					126	$ 4,327.11
1	ACE INHIBITORS***	LISINOPRIL TAB 10MG	30	30	1	$ 6.08
		LISINOPRIL TAB 20MG	1	1	1	$ 0.06
			60	30	1	$ 8.63
		LISINOPRIL TAB 40MG	30	30	3	$ 24.75
	ACE INHIBITORS*** Total				6	$ 39.52
	ALPHA-BETA BLOCKERS***	CARVEDILOL TAB 12.5MG	60	30	3	$ 31.19
		CARVEDILOL TAB 25MG	60	30	1	$ 10.27
		CARVEDILOL TAB 6.25MG	60	30	1	$ 10.27
	ALPHA-BETA BLOCKERS*** Total				5	$ 51.73

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
1	ANTIADRENERGICS - CENTRALLY ACTING***	CLONIDINE TAB 0.2MG	60	30	3	$ 28.68
		CLONIDINE TAB 0.3MG	60	30	2	$ 22.28
			90	30	1	$ 14.33
	ANTIADRENERGICS - CENTRALLY ACTING*** Total				6	$ 65.29
	ANTIADRENERGICS - PERIPHERALLY ACTING***	DOXAZOSIN TAB 4MG	30	30	1	$ 23.39
	ANTIADRENERGICS - PERIPHERALLY ACTING*** Total				1	$ 23.39
	AZITHROMYCIN***	AZITHROMYCIN TAB 250MG	6	5	1	$ 8.67
	AZITHROMYCIN*** Total				1	$ 8.67
	B-COMPLEX W/ C & FOLIC ACID***	DIALYVITE TAB	30	30	3	$ 26.91
		FULL SPECT TAB B/ VIT C	30	30	1	$ 5.86
		RENAL CAP SOFTGEL	30	30	1	$ 18.13
		VOL-CARE RX TAB	60	30	1	$ 16.53
	B-COMPLEX W/ C & FOLIC ACID*** Total				6	$ 67.43
	BETA ADRENERGICS***	PROVENTIL AER HFA	6.7	16	1	$ 63.26
	BETA ADRENERGICS*** Total				1	$ 63.26
	BETA BLOCKERS CARDIO-SELECTIVE***	METOPROL TAR TAB 25MG	2	1	1	$ 0.10
			3	1	1	$ 0.14
		METOPROL TAR TAB 50MG	1	1	1	$ 0.03
			60	30	5	$ 32.66
	BETA BLOCKERS CARDIO-SELECTIVE*** Total				8	$ 32.93
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 10MG	30	30	6	$ 36.60
	CALCIUM CHANNEL BLOCKERS*** Total				6	$ 36.60
	CENTRAL MUSCLE RELAXANTS***	BACLOFEN TAB 10MG	1	1	1	$ 0.05
	CENTRAL MUSCLE RELAXANTS*** Total				1	$ 0.05
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)***	PROCRIT INJ 20000/ML	0.2	1	1	$ 86.78
	ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)*** Total				1	$ 86.78
	GOUT AGENTS***	ALLOPURINOL TAB 300MG	30	30	6	$ 49.44
	GOUT AGENTS*** Total				6	$ 49.44
	H-2 ANTAGONISTS***	FAMOTIDINE TAB 20MG	60	30	4	$ 38.03
	H-2 ANTAGONISTS*** Total				4	$ 38.03
	HEPARINS AND HEPARINOID-LIKE AGENTS***	HEPARIN SOD INJ 1000/ML	3	1	1	$ 11.84
		HEPARIN SOD INJ 5000/ML	1	1	2	$ 8.48
			2	1	2	$ 16.98
	HEPARINS AND HEPARINOID-LIKE AGENTS*** Total				5	$ 37.30
	HMG COA REDUCTASE INHIBITORS***	ATORVASTATIN TAB 20MG	30	30	1	$ 17.62
		ATORVASTATIN TAB 40MG	1	1	1	$ 0.36
			30	30	3	$ 46.65
		LIPITOR TAB 10MG	1	1	1	$ 5.95
		SIMVASTATIN TAB 40MG	30	30	1	$ 7.94
	HMG COA REDUCTASE INHIBITORS*** Total				7	$ 78.52
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	120	30	1	$ 41.94
	HYDROCODONE COMBINATIONS*** Total				1	$ 41.94
	NITRATES***	ISOSORB MONO TAB 60MG ER	1	1	2	$ 0.58
			30	30	4	$ 53.48
		NITRO-BID OIN 2%	1	1	1	$ 2.05
	NITRATES*** Total				7	$ 56.11
	OPIOID AGONISTS***	MORPHINE SUL INJ 5MG/ML	0.4	1	1	$ 0.41
			1.4	1	1	$ 1.42
		MORPHINE SUL TAB 30MG ER	60	30	1	$ 58.13
		OXYCODONE TAB 30MG	60	20	1	$ 50.63
			90	30	4	$ 281.76
	OPIOID AGONISTS*** Total				8	$ 392.35
	PHOSPHATE BINDER AGENTS***	CALC ACETATE CAP 667MG	9	1	1	$ 5.69
			90	30	2	$ 123.22
			270	30	1	$ 175.32
			300	33	2	$ 388.54
		ELIPHOS TAB 667MG	3	1	1	$ 1.51
		RENAGEL TAB 800MG	180	30	2	$ 1,871.19
	PHOSPHATE BINDER AGENTS*** Total				9	$ 2,565.47
	POTASSIUM REMOVING RESINS***	SPS SUS 15GM/60	60	1	1	$ 9.18
	POTASSIUM REMOVING RESINS*** Total				1	$ 9.18
	SALICYLATES***	ASPIRIN CHW 81MG	1	1	1	$ 0.02
		ASPIRIN TAB 325MG EC	30	30	2	$ 10.04
	SALICYLATES*** Total				3	$ 10.06
	THIENOPYRIDINE DERIVATIVES***	CLOPIDOGREL TAB 75MG	1	1	1	$ 0.20

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
1	THIENOPYRIDINE DERIVATIVES***	CLOPIDOGREL TAB 75MG	30	30	6	$ 64.68
	THIENOPYRIDINE DERIVATIVES*** Total				7	$ 64.88
	VASODILATORS***	HYDRALAZINE INJ 20MG/ML	1	1	2	$ 24.48
		HYDRALAZINE TAB 25MG	2	1	1	$ 0.34
		HYDRALAZINE TAB 50MG	2	1	1	$ 0.43
	VASODILATORS*** Total				4	$ 25.25
1 Total					104	$ 3,844.18
39	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG	12	2	1	$ 8.69
	5-HT3 RECEPTOR ANTAGONISTS*** Total				1	$ 8.69
	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	5	$ 1,470.80
		IPRATROPIUM/ SOL ALBUTER	90	8	2	$ 55.46
			540	30	1	$ 78.20
	ADRENERGIC COMBINATIONS*** Total				8	$ 1,604.46
	AMINOPENICILLINS***	AMOXICILLIN CAP 500MG	21	7	1	$ 7.70
			30	10	1	$ 7.31
	AMINOPENICILLINS*** Total				2	$ 15.01
	ANGIOTENSIN II RECEPTOR ANTAGONISTS***	LOSARTAN POT TAB 25MG	30	30	1	$ 7.20
	ANGIOTENSIN II RECEPTOR ANTAGONISTS*** Total				1	$ 7.20
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE TAB 12.5MG	28	7	2	$ 17.52
		PROMETHAZINE TAB 25MG	60	10	2	$ 23.56
				20	1	$ 11.78
			90	30	2	$ 30.58
	ANTIHISTAMINES - PHENOTHIAZINES*** Total				7	$ 83.44
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	75	4	2	$ 17.52
			375	30	2	$ 49.50
		PROAIR HFA AER	8.5	25	1	$ 52.89
	BETA ADRENERGICS*** Total				5	$ 119.91
	BIGUANIDES***	METFORMIN TAB 500MG	60	30	4	$ 32.75
	BIGUANIDES*** Total				4	$ 32.75
	BRONCHODILATORS - ANTICHOLINERGICS***	IPRATROPIUM SOL 0.02%INH	250	30	1	$ 22.92
	BRONCHODILATORS - ANTICHOLINERGICS*** Total				1	$ 22.92
	COUMARIN ANTICOAGULANTS***	JANTOVEN TAB 2MG	7	7	1	$ 4.70
		WARFARIN TAB 2.5MG	30	30	2	$ 21.58
		WARFARIN TAB 2MG	20	20	1	$ 7.94
			30	30	1	$ 9.54
	COUMARIN ANTICOAGULANTS*** Total				5	$ 43.76
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	100	30	1	$ 129.41
	DIAGNOSTIC TESTS*** Total				1	$ 129.41
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 750MG	7	7	1	$ 8.49
	FLUOROQUINOLONES*** Total				1	$ 8.49
	GLUCOCORTICOSTEROIDS***	METHYLPRED PAK 4MG	21	6	4	$ 55.20
		PREDNISONE TAB 10MG	30	30	1	$ 6.61
	GLUCOCORTICOSTEROIDS*** Total				5	$ 61.81
	GLUCOSE MONITORING TEST SUPPLIES***	ONETOUCH MIS LANCETS	100	30	1	$ 9.96
	GLUCOSE MONITORING TEST SUPPLIES*** Total				1	$ 9.96
	H-2 ANTAGONISTS***	RANITIDINE CAP 300MG	30	30	4	$ 179.52
	H-2 ANTAGONISTS*** Total				4	$ 179.52
	HMG COA REDUCTASE INHIBITORS***	SIMVASTATIN TAB 40MG	30	30	3	$ 24.25
	HMG COA REDUCTASE INHIBITORS*** Total				3	$ 24.25
	HUMAN INSULIN***	HUMULIN R INJ U-100	10	10	1	$ 116.65
	HUMAN INSULIN*** Total				1	$ 116.65
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	30	8	3	$ 42.18
			120	30	1	$ 41.94
		HYDROCO/APAP TAB 5-325MG	40	5	1	$ 16.41
	HYDROCODONE COMBINATIONS*** Total				5	$ 100.53
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	30	30	6	$ 116.52
	LEUKOTRIENE RECEPTOR ANTAGONISTS*** Total				6	$ 116.52
	MISC. ANTI-ULCER***	SUCRALFATE TAB 1GM	30	30	4	$ 48.56
			120	30	2	$ 68.99
	MISC. ANTI-ULCER*** Total				6	$ 117.55
	NASAL STEROIDS***	FLUTICASONE SPR 50MCG	16	16	1	$ 27.20
	NASAL STEROIDS*** Total				1	$ 27.20
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS***	ZOLPIDEM TAB 5MG	30	30	5	$ 28.45
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS*** Total				5	$ 28.45
	OPIOID AGONISTS***	HYDROMORPHON TAB 2MG	60	15	1	$ 13.67

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
39	OPIOID AGONISTS***	HYDROMORPHON TAB 2MG	60	20	1	$ 17.86
	OPIOID AGONISTS* Total**				**2**	**$ 31.53**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	118	6	1	$ 6.97
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**1**	**$ 6.97**
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 5-325MG	120	30	1	$ 25.38
	OPIOID COMBINATIONS* Total**				**1**	**$ 25.38**
	PENICILLIN COMBINATIONS***	AMOX/K CLAV SUS 400/5ML	150	7	1	$ 34.00
		AMOX/K CLAV TAB 875MG	20	10	1	$ 22.01
	PENICILLIN COMBINATIONS* Total**				**2**	**$ 56.01**
	POTASSIUM***	POT CHLORIDE LIQ 20%	7.5	1	1	$ 1.40
	POTASSIUM* Total**				**1**	**$ 1.40**
	URINARY ANTISPASMODIC - ANTIMUSCARINIC (ANTICHOLINERGIC)***	OXYBUTYNIN TAB 10MG ER	60	20	1	$ 99.19
			90	30	1	$ 146.18
		OXYBUTYNIN TAB 15MG ER	60	30	1	$ 124.42
		OXYBUTYNIN TAB 5MG ER	30	15	1	$ 38.72
				30	1	$ 38.72
	URINARY ANTISPASMODIC - ANTIMUSCARINIC (ANTICHOLINERGIC)* Total**				**5**	**$ 447.23**
	VIRAL VACCINES***	FLUVIRIN INJ 2014-15	0.5	1	1	$ 21.70
	VIRAL VACCINES* Total**				**1**	**$ 21.70**
39 Total					**86**	**$ 3,448.70**
5	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	2	1	4	$ 2.02
		ONDANSETRON TAB 4MG	12	5	1	$ 8.26
				21	1	$ 6.20
		ONDANSETRON TAB 8MG	6	2	1	$ 6.50
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**7**	**$ 22.98**
	ACE INHIBITORS***	LISINOPRIL TAB 20MG	30	30	2	$ 9.21
	ACE INHIBITORS* Total**				**2**	**$ 9.21**
	ANTICONVULSANTS - MISC.***	LYRICA CAP 100MG	30	30	1	$ 139.00
		LYRICA CAP 50MG	60	30	1	$ 63.74
	ANTICONVULSANTS - MISC.* Total**				**2**	**$ 202.74**
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE INJ 25MG/ML	2	1	1	$ 2.69
		PROMETHAZINE TAB 25MG	60	12	1	$ 11.78
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**2**	**$ 14.47**
	ANTISPASMODICS***	BENTYL INJ 10MG/ML	2	1	1	$ 40.79
		DICYCLOMINE TAB 20MG	1	1	1	$ 0.04
	ANTISPASMODICS* Total**				**2**	**$ 40.83**
	BENZODIAZEPINES***	ALPRAZOLAM TAB 0.25MG	30	8	1	$ 5.74
		ALPRAZOLAM TAB 0.5MG	30	10	1	$ 5.07
	BENZODIAZEPINES* Total**				**2**	**$ 10.81**
	CARBOHYDRATES***	DEXTROSE INJ 50%	50	1	1	$ 2.09
	CARBOHYDRATES* Total**				**1**	**$ 2.09**
	CENTRAL MUSCLE RELAXANTS***	CARISOPRODOL TAB 350MG	90	22	1	$ 6.93
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 6.93**
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	100	25	1	$ 129.41
				30	1	$ 129.41
	DIAGNOSTIC TESTS* Total**				**2**	**$ 258.82**
	GLUCOSE MONITORING TEST SUPPLIES***	ONETOUCH KIT ULT MINI	1	1	1	$ 17.74
		ONETOUCH MIS LANCETS	100	25	1	$ 9.96
				30	1	$ 9.96
	GLUCOSE MONITORING TEST SUPPLIES* Total**				**3**	**$ 37.66**
	HUMAN INSULIN***	HUMALOG INJ 100/ML	10	30	1	$ 220.35
		HUMALOG KWIK INJ 100/ML	15	30	2	$ 391.03
		LANTUS INJ 100/ML	10	30	1	$ 258.24
		LANTUS INJ SOLOSTAR	15	30	2	$ 415.03
		LEVEMIR INJ	10	66	1	$ 241.39
		NOVOLIN R INJ U-100	10	1	1	$ 20.00
			20	1	1	$ 203.29
	HUMAN INSULIN* Total**				**9**	**$ 1,749.33**
	IRON***	FERROUS SULF TAB 325MG	30	30	1	$ 5.00
	IRON* Total**				**1**	**$ 5.00**
	LOOP DIURETICS***	FUROSEMIDE TAB 20MG	30	30	1	$ 4.86
		FUROSEMIDE TAB 40MG	30	30	1	$ 5.37
	LOOP DIURETICS* Total**				**2**	**$ 10.23**
	MISC. ANTI-ULCER***	SUCRALFATE TAB 1GM	40	10	1	$ 14.60
			90	30	1	$ 11.33

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
5	**MISC. ANTI-ULCER*** Total**				**2**	**$ 25.93**
	NEEDLES & SYRINGES* **	BD PEN NEEDL MIS 32GX4MM	**100**	30	1	$ 39.09
	NEEDLES & SYRINGES* Total**				**1**	**$ 39.09**
	OPIOID AGONISTS* **	HYDROMORPHON INJ 1MG/ML	**1**	1	1	$ 1.09
			2	1	1	$ 2.18
			4	1	1	$ 8.49
		HYDROMORPHON INJ 2MG/ML	**2**	1	1	$ 2.94
		HYDROMORPHON TAB 2MG	**20**	3	1	$ 7.73
			80	14	1	$ 16.64
		HYDROMORPHON TAB 4MG	**30**	7	1	$ 6.26
			40	10	1	$ 9.70
			200	10	1	$ 29.46
		MORPHINE SUL INJ 5MG/ML	**1**	1	1	$ 1.01
			2	1	1	$ 2.02
		MORPHINE SUL TAB 15MG ER	**20**	10	1	$ 13.84
		MORPHINE SUL TAB 30MG ER	**30**	10	1	$ 31.44
				15	1	$ 31.44
			60	30	1	$ 21.78
		OXYCODONE TAB 5MG	**20**	5	1	$ 8.43
	OPIOID AGONISTS* Total**				**16**	**$ 194.45**
	PROTON PUMP INHIBITORS* **	ESOMEPRAZOLE INJ 40MG	**2**	1	1	$ 71.20
		PANTOPRAZOLE TAB 40MG	**30**	30	1	$ 9.66
		PROTONIX INJ 40MG	**1**	1	2	$ 10.20
	PROTON PUMP INHIBITORS* Total**				**4**	**$ 91.06**
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* **	DULOXETINE CAP 30MG	**30**	30	1	$ 88.73
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* Total**				**1**	**$ 88.73**
	SODIUM* **	SOD CHLORIDE INJ 0.9%	**1000**	1	3	$ 5.55
			2000	1	2	$ 6.86
	SODIUM* Total**				**5**	**$ 12.41**
	THIENBENZODIAZEPINES* **	ZYPREXA INJ 10MG	**1**	1	1	$ 39.84
	THIENBENZODIAZEPINES* Total**				**1**	**$ 39.84**
	VITAMIN D* **	VITAMIN D CAP 50000UNT	**1**	7	1	$ 5.37
			4	28	1	$ 7.21
	VITAMIN D* Total**				**2**	**$ 12.58**
5 Total					**68**	**$ 2,875.19**
30	**5-HT3 RECEPTOR ANTAGONISTS*** **	ONDANSETRON INJ 4MG/2ML	**1**	1	1	$ 0.22
			2	1	4	$ 2.96
		ONDANSETRON TAB 4MG	**16**	2	1	$ -
		ONDANSETRON TAB 4MG ODT	**0.033**	1	1	$ 0.03
			9	3	1	$ -
			10	6	1	$ -
			20	5	1	$ 24.11
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**10**	**$ 27.32**
	ADRENERGIC COMBINATIONS* **	ADVAIR DISKU AER 250/50	**60**	30	4	$ 1,176.64
	ADRENERGIC COMBINATIONS* Total**				**4**	**$ 1,176.64**
	ANALGESICS OTHER* **	MAPAP TAB 325MG	**4**	1	1	$ 0.04
	ANALGESICS OTHER* Total**				**1**	**$ 0.04**
	ANTIBIOTICS - TOPICAL* **	MUPIROCIN OIN 2%	**22**	7	1	$ 14.46
	ANTIBIOTICS - TOPICAL* Total**				**1**	**$ 14.46**
	ANTICONVULSANTS - MISC.* **	LAMICTAL ODT TAB 25MG	**90**	30	1	$ 666.00
	ANTICONVULSANTS - MISC.* Total**				**1**	**$ 666.00**
	ANTIHISTAMINES - PHENOTHIAZINES* **	PROMETHAZINE INJ 25MG/ML	**1**	1	2	$ 2.70
		PROMETHAZINE SYP 6.25/5ML	**500**	6	1	$ 16.73
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**3**	**$ 19.43**
	ANTI-INFECTIVE MISC. - COMBINATIONS* **	SMZ/TMP DS TAB 800-160	**1**	1	1	$ 0.10
			14	7	1	$ 6.14
			20	10	1	$ 4.00
	ANTI-INFECTIVE MISC. - COMBINATIONS* Total**				**3**	**$ 10.24**
	BENZODIAZEPINES* **	LORAZEPAM TAB 2MG	**90**	30	6	$ 71.78
	BENZODIAZEPINES* Total**				**6**	**$ 71.78**
	BETA ADRENERGICS* **	ALBUTEROL NEB 0.083%	**75**	7	1	$ 8.76
		PROAIR HFA AER	**8.5**	30	3	$ 158.67
	BETA ADRENERGICS* Total**				**4**	**$ 167.43**
	H-2 ANTAGONISTS* **	FAMOTIDINE TAB 20MG	**1**	1	1	$ 0.09
	H-2 ANTAGONISTS* Total**				**1**	**$ 0.09**

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
30	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 5-325MG	12	2	1	$ 6.78
			16	2	1	$ 9.42
	HYDROCODONE COMBINATIONS*** Total				2	$ 16.20
	LINCOSAMIDES***	CLINDAMYCIN CAP 300MG	40	10	1	$ 21.65
	LINCOSAMIDES*** Total				1	$ 21.65
	OPIOID AGONISTS***	OXYCODONE TAB 10MG	60	30	1	$ 24.33
	OPIOID AGONISTS*** Total				1	$ 24.33
	SCABICIDES & PEDICULICIDES***	PERMETHRIN CRE 5%	60	1	1	$ 77.20
	SCABICIDES & PEDICULICIDES*** Total				1	$ 77.20
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)***	VENLAFAXINE TAB 75MG	60	30	1	$ 38.64
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)*** Total				1	$ 38.64
	SODIUM***	SOD CHLORIDE INJ 0.9%	1000	1	2	$ 6.54
	SODIUM*** Total				2	$ 6.54
	TETRACYCLINES***	DOXYCYCL HYC CAP 100MG	20	10	1	$ 7.74
	TETRACYCLINES*** Total				1	$ 7.74
	URINARY ANTI-INFECTIVES***	NITROFURANTN CAP 100MG	1	1	2	$ 4.77
			14	7	2	$ 78.54
	URINARY ANTI-INFECTIVES*** Total				4	$ 83.31
	VIRAL VACCINES***	AFLURIA INJ PF 14-15	0.5	1	1	$ 19.33
	VIRAL VACCINES*** Total				1	$ 19.33
30 Total					48	$ 2,448.37
37	ADRENERGIC COMBINATIONS***	SYMBICORT AER 160-4.5	10.2	30	5	$ 1,321.10
	ADRENERGIC COMBINATIONS*** Total				5	$ 1,321.10
	ANTIHISTAMINES - NON-SEDATING***	CETIRIZINE TAB 10MG	30	30	2	$ 11.57
	ANTIHISTAMINES - NON-SEDATING*** Total				2	$ 11.57
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	180	10	2	$ 28.70
			300	17	3	$ 62.25
		PROAIR HFA AER	8.5	16	2	$ 105.78
			17	30	3	$ 303.09
				33	1	$ 101.03
	BETA ADRENERGICS*** Total				11	$ 600.85
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 20MG	12	28	1	$ 5.72
			24	6	2	$ 13.38
			32	8	1	$ 7.33
	GLUCOCORTICOSTEROIDS*** Total				4	$ 26.43
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST CHW 5MG	30	30	3	$ 82.03
		MONTELUKAST TAB 10MG	30	30	2	$ 38.84
	LEUKOTRIENE RECEPTOR ANTAGONISTS*** Total				5	$ 120.87
	NASAL STEROIDS***	FLUTICASONE SPR 50MCG	16	30	5	$ 137.05
	NASAL STEROIDS*** Total				5	$ 137.05
37 Total					32	$ 2,217.87
15	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	1	1	1	$ 0.23
			2	1	1	$ 0.61
	5-HT3 RECEPTOR ANTAGONISTS*** Total				2	$ 0.84
	ACE INHIBITORS***	LISINOPRIL TAB 5MG	30	30	1	$ 5.74
	ACE INHIBITORS*** Total				1	$ 5.74
	ANTICONVULSANTS - MISC.***	LYRICA CAP 50MG	60	30	1	$ 273.25
	ANTICONVULSANTS - MISC.*** Total				1	$ 273.25
	ANTIFUNGALS - TOPICAL COMBINATIONS***	CLOTRIM/BETA CRE DIPROP	45	22	1	$ 41.80
	ANTIFUNGALS - TOPICAL COMBINATIONS*** Total				1	$ 41.80
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE TAB 12.5MG	20	3	1	$ 7.62
	ANTIHISTAMINES - PHENOTHIAZINES*** Total				1	$ 7.62
	ANTI-INFECTIVE MISC. - COMBINATIONS***	SMZ/TMP DS TAB 800-160	14	7	1	$ 6.14
	ANTI-INFECTIVE MISC. - COMBINATIONS*** Total				1	$ 6.14
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 5MG	30	30	1	$ 8.63
	CALCIUM CHANNEL BLOCKERS*** Total				1	$ 8.63
	CARBOHYDRATES***	DEXTROSE INJ 50%	50	1	1	$ 9.70
	CARBOHYDRATES*** Total				1	$ 9.70
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	50	25	2	$ 130.96
			100	30	1	$ 129.41
	DIAGNOSTIC TESTS*** Total				3	$ 260.37
	ELECTROLYTES & DEXTROSE***	D5W/LR INJ	2000	1	1	$ 3.57
	ELECTROLYTES & DEXTROSE*** Total				1	$ 3.57
	ENZYMES - TOPICAL***	SANTYL OIN 250/GM	30	30	1	$ 194.25
	ENZYMES - TOPICAL*** Total				1	$ 194.25

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
15	H-2 ANTAGONISTS***	FAMOTIDINE TAB 20MG	14	7	1	$ 5.99
	H-2 ANTAGONISTS* Total**				**1**	**$ 5.99**
	HUMAN INSULIN***	LEVEMIR INJ	10	40	1	$ 241.39
			20	30	1	$ 481.23
			120	1	1	$ 48.00
		NOVOLIN R INJ U-100	10	1	1	$ 20.00
		NOVOLOG INJ 100/ML	10	30	1	$ 193.31
		NOVOLOG MIX INJ 70/30	10	40	1	$ 208.63
	HUMAN INSULIN* Total**				**6**	**$ 1,192.56**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	15	3	1	$ 9.41
		HYDROCO/APAP TAB 5-325MG	50	9	1	$ 19.32
	HYDROCODONE COMBINATIONS* Total**				**2**	**$ 28.73**
	MAGNESIUM***	MAG OXIDE TAB 400MG	2	1	1	$ 0.23
	MAGNESIUM* Total**				**1**	**$ 0.23**
	MISC. ANTI-ULCER***	SUCRALFATE TAB 1GM	56	14	1	$ 18.54
	MISC. ANTI-ULCER* Total**				**1**	**$ 18.54**
	MULTIVITAMINS***	MULTI-VITAMN TAB	30	30	1	$ 0.77
	MULTIVITAMINS* Total**				**1**	**$ 0.77**
	NEEDLES & SYRINGES***	INSULIN SYRG MIS 0.3/31G	100	30	1	$ 26.14
	NEEDLES & SYRINGES* Total**				**1**	**$ 26.14**
	OPIOID AGONISTS***	MORPHINE SUL INJ 5MG/ML	1	1	1	$ 1.01
	OPIOID AGONISTS* Total**				**1**	**$ 1.01**
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 5-325MG	1	1	1	$ 0.17
	OPIOID COMBINATIONS* Total**				**1**	**$ 0.17**
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	2	1	1	$ 0.75
	POTASSIUM* Total**				**1**	**$ 0.75**
	PROGESTIN CONTRACEPTIVES - INJECTABLE***	MEDROXYPR AC INJ 150MG/ML	1	30	1	$ 55.12
	PROGESTIN CONTRACEPTIVES - INJECTABLE* Total**				**1**	**$ 55.12**
	PROTON PUMP INHIBITORS***	PROTONIX INJ 40MG	1	1	2	$ 10.20
	PROTON PUMP INHIBITORS* Total**				**2**	**$ 10.20**
	TRICYCLIC AGENTS***	NORTRIPTYLIN CAP 50MG	30	30	1	$ 7.21
	TRICYCLIC AGENTS* Total**				**1**	**$ 7.21**
	VITAMIN B-1***	THIAMINE HCL TAB 100MG	30	30	1	$ 1.04
	VITAMIN B-1* Total**				**1**	**$ 1.04**
15 Total					**35**	**$ 2,160.37**
31	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG	12	4	1	$ 8.26
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**1**	**$ 8.26**
	ACE INHIBITORS***	LISINOPRIL TAB 20MG	60	30	1	$ 8.63
	ACE INHIBITORS* Total**				**1**	**$ 8.63**
	ANGIOTENSIN II RECEPTOR ANTAGONISTS***	LOSARTAN POT TAB 100MG	30	30	1	$ 10.56
		LOSARTAN POT TAB 50MG	30	30	2	$ 14.38
	ANGIOTENSIN II RECEPTOR ANTAGONISTS* Total**				**3**	**$ 24.94**
	ANTIANXIETY AGENTS - MISC.***	HYDROXYZ HCL TAB 10MG	60	30	1	$ 13.09
	ANTIANXIETY AGENTS - MISC.* Total**				**1**	**$ 13.09**
	ANTIBIOTICS - TOPICAL***	MUPIROCIN OIN 2%	66	30	2	$ 64.60
	ANTIBIOTICS - TOPICAL* Total**				**2**	**$ 64.60**
	ANTIDIARRHEAL AGENTS - MISC.***	FLORANEX TAB	36	9	1	$ 8.69
	ANTIDIARRHEAL AGENTS - MISC.* Total**				**1**	**$ 8.69**
	ANTI-INFECTIVE MISC. - COMBINATIONS***	SMZ/TMP DS TAB 800-160	20	10	1	$ 4.00
	ANTI-INFECTIVE MISC. - COMBINATIONS* Total**				**1**	**$ 4.00**
	BENZODIAZEPINES***	ALPRAZOLAM TAB 0.25MG	60	30	3	$ 20.16
	BENZODIAZEPINES* Total**				**3**	**$ 20.16**
	BETA ADRENERGICS***	PROAIR HFA AER	8.5	16	1	$ 52.89
	BETA ADRENERGICS* Total**				**1**	**$ 52.89**
	BETA BLOCKERS CARDIO-SELECTIVE***	METOPROL TAR TAB 50MG	60	30	2	$ 8.00
	BETA BLOCKERS CARDIO-SELECTIVE* Total**				**2**	**$ 8.00**
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 10MG	30	30	1	$ 6.10
	CALCIUM CHANNEL BLOCKERS* Total**				**1**	**$ 6.10**
	DIAGNOSTIC TESTS***	FREESTYLE TES LITE	50	25	1	$ 75.49
	DIAGNOSTIC TESTS* Total**				**1**	**$ 75.49**
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 20MG	6	2	1	$ 5.24
	GLUCOCORTICOSTEROIDS* Total**				**1**	**$ 5.24**
	HUMAN INSULIN***	LANTUS INJ SOLOSTAR	15	60	1	$ 384.98
		NOVOLOG INJ 100/ML	10	28	1	$ 193.31
				30	2	$ 386.62

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
31	**HUMAN INSULIN*** Total**				**4**	**$ 964.91**
	HYDROCODONE COMBINATIONS* **	HYDROCO/APAP TAB 7.5-325	**107**	26	1	$ 26.81
			120	30	5	$ 147.40
	HYDROCODONE COMBINATIONS* Total**				**6**	**$ 174.21**
	LEUKOTRIENE RECEPTOR ANTAGONISTS* **	MONTELUKAST TAB 10MG	**30**	30	1	$ 19.42
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**1**	**$ 19.42**
	LOOP DIURETICS* **	FUROSEMIDE TAB 40MG	**30**	30	1	$ 5.37
	LOOP DIURETICS* Total**				**1**	**$ 5.37**
	NEEDLES & SYRINGES* **	INSULIN SYRG MIS 0.3/31G	**100**	30	1	$ 16.99
	NEEDLES & SYRINGES* Total**				**1**	**$ 16.99**
	NITRATES* **	NITROSTAT SUB 0.4MG	**25**	30	1	$ 16.61
	NITRATES* Total**				**1**	**$ 16.61**
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* **	ZOLPIDEM TAB 10MG	**30**	30	7	$ 40.46
	NON-BENZODIAZEPINE - GABA-RECEPTOR MODULATORS* Total**				**7**	**$ 40.46**
	PENICILLIN COMBINATIONS* **	AMOX/K CLAV TAB 250MG	**12**	6	1	$ 52.49
		AMOX/K CLAV TAB 875MG	**14**	7	1	$ 19.85
	PENICILLIN COMBINATIONS* Total**				**2**	**$ 72.34**
	PHENOTHIAZINES* **	PROCHLORPER TAB 10MG	**30**	10	1	$ 7.51
	PHENOTHIAZINES* Total**				**1**	**$ 7.51**
	PHOSPHATE BINDER AGENTS* **	SEVELAMER TAB 800MG	**30**	10	1	$ 96.95
	PHOSPHATE BINDER AGENTS* Total**				**1**	**$ 96.95**
	POTASSIUM* **	POT CHLORIDE POW 20MEQ	**30**	30	1	$ 55.79
	POTASSIUM* Total**				**1**	**$ 55.79**
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* **	DULOXETINE CAP 30MG	**30**	30	1	$ 196.97
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* Total**				**1**	**$ 196.97**
	THYROID HORMONES* **	LEVOTHYROXIN TAB 175MCG	**90**	90	1	$ 41.89
	THYROID HORMONES* Total**				**1**	**$ 41.89**
31 Total					**47**	**$ 2,009.51**
20	**ANTICONVULSANTS - MISC.*** **	GABAPENTIN CAP 100MG	**180**	30	1	$ 12.44
		GABAPENTIN TAB 600MG	**60**	30	3	$ 72.96
		LEVETIRACETA TAB 500MG	**60**	30	3	$ 62.22
	ANTICONVULSANTS - MISC.* Total**				**7**	**$ 147.62**
	ANTIHISTAMINES - PHENOTHIAZINES* **	PROMETHAZINE SUP 25MG	**1**	1	1	$ 1.04
		PROMETHAZINE TAB 25MG	**30**	30	3	$ 24.81
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**4**	**$ 25.85**
	BENZODIAZEPINES* **	ALPRAZOLAM TAB 0.25MG	**15**	5	1	$ 5.25
	BENZODIAZEPINES* Total**				**1**	**$ 5.25**
	BETA ADRENERGICS* **	ALBUTEROL NEB 0.083%	**375**	30	2	$ 49.50
	BETA ADRENERGICS* Total**				**2**	**$ 49.50**
	BIGUANIDES* **	METFORMIN TAB 850MG	**90**	30	3	$ 40.62
	BIGUANIDES* Total**				**3**	**$ 40.62**
	CALCIUM CHANNEL BLOCKERS* **	DILTIAZEM CAP 120MG ER	**30**	30	3	$ 53.43
	CALCIUM CHANNEL BLOCKERS* Total**				**3**	**$ 53.43**
	CENTRAL MUSCLE RELAXANTS* **	BACLOFEN TAB 10MG	**90**	30	3	$ 28.47
	CENTRAL MUSCLE RELAXANTS* Total**				**3**	**$ 28.47**
	GLUCOCORTICOSTEROIDS* **	DEXAMETHASON TAB 2MG	**60**	20	1	$ 31.64
		DEXAMETHASON TAB 4MG	**21**	14	1	$ 7.21
	GLUCOCORTICOSTEROIDS* Total**				**2**	**$ 38.85**
	HMG COA REDUCTASE INHIBITORS* **	SIMVASTATIN TAB 20MG	**30**	30	3	$ 21.81
	HMG COA REDUCTASE INHIBITORS* Total**				**3**	**$ 21.81**
	HUMAN INSULIN* **	LEVEMIR INJ	**10**	30	1	$ 241.39
	HUMAN INSULIN* Total**				**1**	**$ 241.39**
	LEUKOTRIENE RECEPTOR ANTAGONISTS* **	MONTELUKAST TAB 10MG	**30**	30	3	$ 58.26
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**3**	**$ 58.26**
	LINCOSAMIDES* **	CLINDAMYCIN CAP 300MG	**20**	5	1	$ 13.20
			40	10	1	$ 21.65
	LINCOSAMIDES* Total**				**2**	**$ 34.85**
	LOOP DIURETICS* **	FUROSEMIDE TAB 20MG	**30**	30	1	$ 5.46
			60	30	1	$ 6.18
		FUROSEMIDE TAB 40MG	**14**	14	1	$ 5.04
	LOOP DIURETICS* Total**				**3**	**$ 16.68**
	OPIOID AGONISTS* **	DILAUDID INJ 1MG/ML	**1**	1	1	$ 1.40
		OXYCODONE TAB 10MG	**45**	11	1	$ 25.47
				12	1	$ 25.47
	OPIOID AGONISTS* Total**				**3**	**$ 52.34**

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
20	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 10-325MG	56	14	1	$ 49.85
		OXYCOD/APAP TAB 5-325MG	42	7	1	$ 11.98
	OPIOID COMBINATIONS*** Total				2	$ 61.83
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	14	14	1	$ 10.01
	POTASSIUM*** Total				1	$ 10.01
	PROTON PUMP INHIBITORS***	PANTOPRAZOLE TAB 40MG	30	30	1	$ 9.01
	PROTON PUMP INHIBITORS*** Total				1	$ 9.01
	SALICYLATES***	SALSALATE TAB 750MG	120	30	3	$ 822.12
	SALICYLATES*** Total				3	$ 822.12
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	PAROXETINE TAB 10MG	30	30	2	$ 21.52
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)*** Total				2	$ 21.52
20 Total					49	$ 1,739.41
26	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	1	1	1	$ 0.31
	5-HT3 RECEPTOR ANTAGONISTS*** Total				1	$ 0.31
	ANTIARRHYTHMICS - MISC.***	ADENOSINE INJ 6MG/2ML	2	1	1	$ 6.12
	ANTIARRHYTHMICS - MISC.*** Total				1	$ 6.12
	ANTIARRHYTHMICS TYPE I-A***	PROCAINAMIDE INJ 500MG/ML	2	1	1	$ 46.40
	ANTIARRHYTHMICS TYPE I-A*** Total				1	$ 46.40
	ANTI-INFECTIVE AGENTS - MISC.***	METRONIDAZOL TAB 500MG	21	7	1	$ 9.35
	ANTI-INFECTIVE AGENTS - MISC.*** Total				1	$ 9.35
	BICARBONATES***	SOD BICARB INJ 8.4%	200	1	1	$ 21.42
	BICARBONATES*** Total				1	$ 21.42
	CALCIUM***	CALCIUM CL INJ 10%	10	1	1	$ 4.08
	CALCIUM*** Total				1	$ 4.08
	CEPHALOSPORINS - 3RD GENERATION***	CEFTRIAXONE/ INJ DEX 1GM	50	1	1	$ 14.47
	CEPHALOSPORINS - 3RD GENERATION*** Total				1	$ 14.47
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	50	25	1	$ 65.48
	DIAGNOSTIC TESTS*** Total				1	$ 65.48
	HUMAN INSULIN***	NOVOLOG INJ FLEXPEN	15	30	1	$ 369.00
		NOVOLOG MIX INJ FLEXPEN	30	30	1	$ 772.88
	HUMAN INSULIN*** Total				2	$ 1,141.88
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	45	15	1	$ 18.70
	HYDROCODONE COMBINATIONS*** Total				1	$ 18.70
	LOOP DIURETICS***	FUROSEMIDE SOL 40MG/4ML	4	1	1	$ 0.35
	LOOP DIURETICS*** Total				1	$ 0.35
	MIXED ADRENERGICS***	EPINEPHRINE INJ 0.1MG/ML	70	1	1	$ 72.54
	MIXED ADRENERGICS*** Total				1	$ 72.54
	NITRATES***	NITRO-BID OIN 2%	1	1	1	$ 2.05
	NITRATES*** Total				1	$ 2.05
	OPIOID AGONISTS***	MORPHINE SUL INJ 5MG/ML	1	1	1	$ 1.01
	OPIOID AGONISTS*** Total				1	$ 1.01
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	CITALOPRAM TAB 20MG	30	30	1	$ 7.49
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)*** Total				1	$ 7.49
26 Total					16	$ 1,411.65
33	BENZODIAZEPINES***	LORAZEPAM TAB 0.5MG	10	5	1	$ 4.00
			30	15	1	$ 6.10
	BENZODIAZEPINES*** Total				2	$ 10.10
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	12	1	1	$ 0.64
		PROAIR HFA AER	8.5	17	9	$ 476.01
				18	2	$ 105.78
	BETA ADRENERGICS*** Total				12	$ 582.43
	DIRECT FACTOR XA INHIBITORS***	XARELTO TAB 20MG	30	30	2	$ 593.68
	DIRECT FACTOR XA INHIBITORS*** Total				2	$ 593.68
	FLUOROQUINOLONES***	LEVOFLOX/D5W INJ 750/150	150	1	1	$ 11.22
	FLUOROQUINOLONES*** Total				1	$ 11.22
	GLUCOCORTICOSTEROIDS***	SOLU-MEDROL INJ 125MG	1	1	1	$ 5.46
	GLUCOCORTICOSTEROIDS*** Total				1	$ 5.46
	H-2 ANTAGONISTS***	RANITIDINE TAB 150MG	60	30	1	$ 4.00
	H-2 ANTAGONISTS*** Total				1	$ 4.00
	NASAL STEROIDS***	NASONEX SPR 50MCG/AC	17	30	1	$ 182.24
	NASAL STEROIDS*** Total				1	$ 182.24
	PENICILLIN COMBINATIONS***	AMOX/K CLAV TAB 500MG	10	5	1	$ 12.43
	PENICILLIN COMBINATIONS*** Total				1	$ 12.43
33 Total					21	$ 1,401.56
11	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON TAB 4MG ODT	10	3	1	$ 14.44

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
11	**5-HT3 RECEPTOR ANTAGONISTS*** Total**				**1**	**$ 14.44**
	ADRENERGIC COMBINATIONS***	IPRATROPIUM/ SOL ALBUTER	**360**	20	1	$ 96.63
	ADRENERGIC COMBINATIONS* Total**				**1**	**$ 96.63**
	ANTICONVULSANTS - MISC.***	LEVETIRACETA TAB 250MG	**28**	14	1	$ 10.41
		LYRICA CAP 75MG	**60**	30	1	$ 273.25
	ANTICONVULSANTS - MISC.* Total**				**2**	**$ 283.66**
	ANTI-INFECTIVE AGENTS - MISC.***	METRONIDAZOL TAB 500MG	**30**	10	1	$ 11.31
			39	13	1	$ 13.28
	ANTI-INFECTIVE AGENTS - MISC.* Total**				**2**	**$ 24.59**
	BETA ADRENERGICS***	PROAIR HFA AER	**8.5**	16	2	$ 105.78
				17	1	$ 52.89
	BETA ADRENERGICS* Total**				**3**	**$ 158.67**
	CENTRAL MUSCLE RELAXANTS***	CYCLOBENZAPR TAB 10MG	**9**	3	1	$ 4.00
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 4.00**
	DIBENZOTHIAZEPINES***	QUETIAPINE TAB 200MG	**30**	30	1	$ 25.47
			60	20	2	$ 92.36
	DIBENZOTHIAZEPINES* Total**				**3**	**$ 117.83**
	FOLIC ACID/FOLATES***	FOLIC ACID TAB 1MG	**30**	30	2	$ 8.00
	FOLIC ACID/FOLATES* Total**				**2**	**$ 8.00**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 5-325MG	**12**	2	1	$ 8.25
	HYDROCODONE COMBINATIONS* Total**				**1**	**$ 8.25**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	KETOROLAC INJ 60MG/2ML	**2**	1	1	$ 0.89
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**1**	**$ 0.89**
	OPIOID AGONISTS***	HYDROMORPHON INJ 1MG/ML	**1**	1	1	$ 2.12
		OXYCODONE TAB 5MG	**20**	7	1	$ 8.43
		TRAMADOL HCL TAB 50MG	**180**	30	1	$ 15.46
	OPIOID AGONISTS* Total**				**3**	**$ 26.01**
	OPIOID ANTAGONISTS***	NALTREXONE TAB 50MG	**30**	30	1	$ 109.99
	OPIOID ANTAGONISTS* Total**				**1**	**$ 109.99**
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 5-325MG	**15**	2	1	$ 7.34
			16	4	1	$ 7.51
			18	3	1	$ 7.85
			30	5	1	$ 9.91
	OPIOID COMBINATIONS* Total**				**4**	**$ 32.61**
	SMOKING DETERRENTS***	NICOTINE DIS 14MG/24H	**28**	28	1	$ 55.54
		NICOTINE DIS 7MG/24HR	**14**	14	1	$ 30.15
	SMOKING DETERRENTS* Total**				**2**	**$ 85.69**
	STEROID INHALANTS***	QVAR AER 40MCG	**8.7**	30	1	$ 137.76
	STEROID INHALANTS* Total**				**1**	**$ 137.76**
	VITAMIN B-1***	CVS VIT B1 TAB 100MG	**30**	30	1	$ 1.44
	VITAMIN B-1* Total**				**1**	**$ 1.44**
	VITAMIN D***	VITAMIN D CAP 50000UNT	**4**	28	1	$ 6.49
	VITAMIN D* Total**				**1**	**$ 6.49**
11 Total					**30**	**$ 1,116.95**
27	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	**60**	30	1	$ 294.16
		IPRATROPIUM/ SOL ALBUTER	**180**	15	1	$ 29.24
	ADRENERGIC COMBINATIONS* Total**				**2**	**$ 323.40**
	ANTIPSYCHOTICS - MISC.***	LATUDA TAB 80MG	**30**	30	1	$ 718.96
	ANTIPSYCHOTICS - MISC.* Total**				**1**	**$ 718.96**
	SALICYLATES***	ASPIRIN TAB 81MG EC	**30**	30	1	$ 5.26
	SALICYLATES* Total**				**1**	**$ 5.26**
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)***	DULOXETINE CAP 30MG	**60**	30	1	$ 1.20
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* Total**				**1**	**$ 1.20**
	SURFACTANT LAXATIVES***	STOOL SOFTNR CAP 100MG	**60**	30	1	$ 5.93
	SURFACTANT LAXATIVES* Total**				**1**	**$ 5.93**
	VITAMIN D***	VITAMIN D TAB 1000UNIT	**30**	30	4	$ 24.08
	VITAMIN D* Total**				**4**	**$ 24.08**
27 Total					**10**	**$ 1,078.83**
29	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	**2**	1	8	$ 4.53
			4	1	1	$ 0.94
		ONDANSETRON TAB 4MG ODT	**42**	10	1	$ 45.40
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**10**	**$ 50.87**
	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	**60**	30	1	$ 294.16
		BREO ELLIPTA INH 100-25	**1**	1	1	$ 3.75
		IPRATROPIUM/ SOL ALBUTER	**3**	1	1	$ 0.41

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
29	**ADRENERGIC COMBINATIONS*** Total**				**3**	**$ 298.32**
	ANTIHISTAMINES - ETHANOLAMINES*	DIPHENHYDRAM INJ 50MG/ML	**1**	1	13	$ 12.57
			2	1	2	$ 3.96
	ANTIHISTAMINES - ETHANOLAMINES* Total**				**15**	**$ 16.53**
	ANTIHISTAMINES - PHENOTHIAZINES*	PROMETHAZINE INJ 25MG/ML	**1**	1	2	$ 2.70
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**2**	**$ 2.70**
	ANTINEOPLASTICS MISC.*	HYDROXYUREA CAP 500MG	**60**	30	1	$ 35.20
			90	30	1	$ 50.42
	ANTINEOPLASTICS MISC.* Total**				**2**	**$ 85.62**
	BETA ADRENERGICS*	PROAIR HFA AER	**8.5**	16	1	$ 52.89
	BETA ADRENERGICS* Total**				**1**	**$ 52.89**
	CEPHALOSPORINS - 3RD GENERATION*	CEFTRIAXONE/ INJ DEX 1GM	**50**	1	2	$ 28.94
	CEPHALOSPORINS - 3RD GENERATION* Total**				**2**	**$ 28.94**
	CODEINE COMBINATIONS*	APAP/CODEINE TAB 300-30MG	**28**	7	1	$ 8.90
	CODEINE COMBINATIONS* Total**				**1**	**$ 8.90**
	FLUOROQUINOLONES*	LEVOFLOXACIN TAB 750MG	**3**	3	1	$ 6.36
	FLUOROQUINOLONES* Total**				**1**	**$ 6.36**
	FOLIC ACID/FOLATES*	FOLIC ACID TAB 1MG	**30**	30	1	$ 5.38
	FOLIC ACID/FOLATES* Total**				**1**	**$ 5.38**
	HYDROCODONE COMBINATIONS*	HYDROCO/APAP TAB 10-325MG	**28**	7	1	$ 13.44
		HYDROCO/APAP TAB 5-325MG	**42**	7	1	$ 16.99
	HYDROCODONE COMBINATIONS* Total**				**2**	**$ 30.43**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	KETOROLAC INJ 15MG/ML	**4**	1	1	$ 4.00
		KETOROLAC INJ 30MG/ML	**1**	1	1	$ 0.86
			2	1	1	$ 1.71
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**3**	**$ 6.57**
	OPIOID AGONISTS*	HYDROMORPHON INJ 1MG/ML	**1**	1	2	$ 4.24
			2	1	1	$ 4.24
			3	1	2	$ 12.72
		HYDROMORPHON INJ 2MG/ML	**1**	1	4	$ 6.69
			2	1	2	$ 5.88
			3	1	2	$ 8.82
			5	1	3	$ 22.02
		HYDROMORPHON TAB 2MG	**60**	10	1	$ 13.67
		HYDROMORPHON TAB 4MG	**20**	5	1	$ 7.23
			30	5	2	$ 16.94
			40	7	1	$ 9.70
			120	30	1	$ 19.58
		MORPHINE SUL INJ 25MG/ML	**4**	1	1	$ 10.00
			12	1	1	$ 30.00
		MORPHINE SUL INJ 5MG/ML	**1**	1	1	$ 1.01
		MORPHINE SUL TAB 30MG	**12**	2	1	$ 7.33
		MORPHINE SUL TAB 30MG ER	**24**	12	1	$ 26.11
		OXYCODONE TAB 10MG	**14**	7	1	$ 9.33
		OXYCODONE TAB 30MG	**30**	15	2	$ 48.10
			60	30	1	$ 43.34
		OXYCONTIN TAB 10MG CR	**1**	1	1	$ 2.33
	OPIOID AGONISTS* Total**				**32**	**$ 309.28**
	OPIOID COMBINATIONS*	OXYCOD/APAP TAB 10-325MG	**28**	7	1	$ 27.31
			42	7	1	$ 38.58
		OXYCOD/APAP TAB 5-325MG	**28**	7	1	$ 9.57
	OPIOID COMBINATIONS* Total**				**3**	**$ 75.46**
	POTASSIUM*	KLOR-CON M10 TAB 10MEQ ER	**3**	1	1	$ 0.76
	POTASSIUM* Total**				**1**	**$ 0.76**
	SODIUM*	SOD CHLORIDE INJ 0.9%	**250**	1	1	$ 2.51
			1000	1	4	$ 7.40
			2000	1	1	$ 4.00
			3000	1	1	$ 5.56
	SODIUM* Total**				**7**	**$ 19.47**
29 Total					**86**	**$ 998.48**
3	**ADRENERGIC COMBINATIONS***	IPRATROPIUM/ SOL ALBUTER	**3**	1	1	$ 0.77
			6	1	2	$ 3.06
			9	1	2	$ 4.60
			12	1	3	$ 9.18
			15	1	1	$ 3.83

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
3	ADRENERGIC COMBINATIONS***	SYMBICORT AER 80-4.5	6.9	1	1	$ 153.27
	ADRENERGIC COMBINATIONS* Total**				**10**	**$ 174.71**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	12	1	1	$ 0.64
			24	1	1	$ 1.28
			75	7	1	$ 8.76
		PROAIR HFA AER	8.5	16	2	$ 105.78
				21	1	$ 52.89
		PROVENTIL AER HFA	6.7	25	1	$ 4.83
	BETA ADRENERGICS* Total**				**7**	**$ 174.18**
	BIGUANIDES***	METFORMIN TAB 500MG	2	1	1	$ 0.11
			60	30	2	$ 13.40
	BIGUANIDES* Total**				**3**	**$ 13.51**
	FLUOROQUINOLONES***	AVELOX INJ	250	1	3	$ 129.36
		MOXIFLOXACIN TAB 400MG	5	5	1	$ 4.81
	FLUOROQUINOLONES* Total**				**4**	**$ 134.17**
	GLUCOCORTICOSTEROIDS***	METHYLPRED PAK 4MG	21	6	1	$ 13.80
		PREDNISONE TAB 20MG	3	1	3	$ 0.72
			8	4	1	$ 5.17
		PREDNISONE TAB 50MG	5	5	1	$ 6.42
		SOLU-MEDROL INJ 125MG	2	1	1	$ 10.90
			4	1	1	$ 21.82
	GLUCOCORTICOSTEROIDS* Total**				**8**	**$ 58.83**
	HEPARINS AND HEPARINOID-LIKE AGENTS***	HEPARIN SOD INJ 5000/ML	1	1	1	$ 4.24
			3	1	2	$ 25.46
	HEPARINS AND HEPARINOID-LIKE AGENTS* Total**				**3**	**$ 29.70**
	HMG COA REDUCTASE INHIBITORS***	ATORVASTATIN TAB 20MG	4	1	1	$ 1.71
		ATORVASTATIN TAB 40MG	1	1	2	$ 0.72
			30	30	1	$ 9.02
	HMG COA REDUCTASE INHIBITORS* Total**				**4**	**$ 11.45**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	1	1	1	$ 0.49
			30	30	2	$ 26.66
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**3**	**$ 27.15**
	LOW MOLECULAR WEIGHT HEPARINS***	LOVENOX INJ 30/0.3ML	0.3	1	1	$ 25.31
		LOVENOX INJ 40/0.4ML	0.4	1	2	$ 67.48
	LOW MOLECULAR WEIGHT HEPARINS* Total**				**3**	**$ 92.79**
	MAGNESIUM***	MAGNESIUM SU INJ 40MG/ML	50	1	1	$ 7.11
	MAGNESIUM* Total**				**1**	**$ 7.11**
	NITRATES***	ISOSORB MONO TAB 60MG ER	1	1	1	$ 0.29
		NITROSTAT SUB 0.4MG	1	1	1	$ 0.47
	NITRATES* Total**				**2**	**$ 0.76**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	IBUPROFEN TAB 600MG	1	1	1	$ 0.04
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**1**	**$ 0.04**
	OPIOID AGONISTS***	TRAMADOL HCL TAB 50MG	3	1	1	$ 0.24
			20	5	1	$ 4.93
	OPIOID AGONISTS* Total**				**2**	**$ 5.17**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	100	5	1	$ 6.63
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**1**	**$ 6.63**
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 5-325MG	15	5	1	$ 7.34
		OXYCOD/APAP TAB 7.5-325	30	5	1	$ 33.84
	OPIOID COMBINATIONS* Total**				**2**	**$ 41.18**
	PROTON PUMP INHIBITORS***	NEXIUM CAP 40MG	1	1	2	$ 16.10
	PROTON PUMP INHIBITORS* Total**				**2**	**$ 16.10**
	SALICYLATES***	ASPIRIN CHW 81MG	1	1	1	$ 0.02
			4	1	1	$ 0.09
	SALICYLATES* Total**				**2**	**$ 0.11**
	SODIUM***	SOD CHLORIDE INJ 0.9%	1000	1	1	$ 1.72
	SODIUM* Total**				**1**	**$ 1.72**
	SURFACTANT LAXATIVES***	DOK CAP 100MG	1	1	1	$ 0.02
	SURFACTANT LAXATIVES* Total**				**1**	**$ 0.02**
3 Total					**60**	**$ 795.33**
40	ACE INHIBITORS***	LISINOPRIL TAB 10MG	30	30	1	$ 1.20
	ACE INHIBITORS* Total**				**1**	**$ 1.20**
	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	1	$ 290.16
		IPRATROPIUM/ SOL ALBUTER	540	30	1	$ 1.20
	ADRENERGIC COMBINATIONS* Total**				**2**	**$ 291.36**

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
40	ANTI-INFECTIVE MISC. - COMBINATIONS***	SMZ/TMP DS TAB 800-160	10	5	1	$ 1.20
	ANTI-INFECTIVE MISC. - COMBINATIONS* Total**				**1**	**$ 1.20**
	ANTITUSSIVE-EXPECTORANT***	GUAIATUSSIN SYP AC	180	3	1	$ 18.62
	ANTITUSSIVE-EXPECTORANT* Total**				**1**	**$ 18.62**
	AZITHROMYCIN***	AZITHROMYCIN TAB 250MG	6	5	2	$ 2.40
	AZITHROMYCIN* Total**				**2**	**$ 2.40**
	BETA ADRENERGICS***	PROAIR HFA AER	8.5	16	2	$ 7.20
				18	3	$ 10.80
	BETA ADRENERGICS* Total**				**5**	**$ 18.00**
	BIGUANIDES***	METFORMIN TAB 500MG	60	30	4	$ 4.80
	BIGUANIDES* Total**				**4**	**$ 4.80**
	CLARITHROMYCIN***	CLARITHROMYC TAB 500MG	14	7	1	$ 1.20
	CLARITHROMYCIN* Total**				**1**	**$ 1.20**
	DIAGNOSTIC TESTS***	FREESTYLE TES LITE	100	90	2	$ 288.88
	DIAGNOSTIC TESTS* Total**				**2**	**$ 288.88**
	DIBENZOTHIAZEPINES***	QUETIAPINE TAB 100MG	30	30	1	$ 1.20
		QUETIAPINE TAB 50MG	60	30	3	$ 3.60
	DIBENZOTHIAZEPINES* Total**				**4**	**$ 4.80**
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 750MG	7	7	1	$ 1.20
	FLUOROQUINOLONES* Total**				**1**	**$ 1.20**
	GLUCOCORTICOSTEROIDS***	METHYLPRED PAK 4MG	21	6	5	$ 6.00
		PREDNISONE TAB 10MG	30	5	1	$ -
				12	1	$ -
	GLUCOCORTICOSTEROIDS* Total**				**7**	**$ 6.00**
	GLUCOSE MONITORING TEST SUPPLIES***	FREESTYLE MIS LANCETS	100	90	2	$ 25.54
	GLUCOSE MONITORING TEST SUPPLIES* Total**				**2**	**$ 25.54**
	H-2 ANTAGONISTS***	FAMOTIDINE TAB 20MG	60	30	3	$ 3.60
		FAMOTIDINE TAB 40MG	30	30	1	$ 1.20
	H-2 ANTAGONISTS* Total**				**4**	**$ 4.80**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	20	5	1	$ 1.20
			30	7	1	$ 1.20
			40	6	2	$ 2.40
			90	15	1	$ 1.20
			120	20	2	$ 2.40
	HYDROCODONE COMBINATIONS* Total**				**7**	**$ 8.40**
	NON-NARC ANTITUSSIVE-ANTIHISTAMINE***	PROMETHAZINE SYP DM	200	10	1	$ 10.42
				12	1	$ 10.42
	NON-NARC ANTITUSSIVE-ANTIHISTAMINE* Total**				**2**	**$ 20.84**
	OPHTHALMIC NONSTEROIDAL ANTI-INFLAMMATORY AGENTS***	NEVANAC SUS 0.1%	3	15	2	$ 7.20
	OPHTHALMIC NONSTEROIDAL ANTI-INFLAMMATORY AGENTS* Total**				**2**	**$ 7.20**
	OPHTHALMIC STEROIDS***	PREDNISOLONE SUS 1% OP	10	50	2	$ 2.40
	OPHTHALMIC STEROIDS* Total**				**2**	**$ 2.40**
	PROTON PUMP INHIBITORS***	PANTOPRAZOLE TAB 40MG	14	14	1	$ 1.20
	PROTON PUMP INHIBITORS* Total**				**1**	**$ 1.20**
	SALICYLATES***	ASPIRIN TAB 325MG EC	90	90	1	$ 5.53
	SALICYLATES* Total**				**1**	**$ 5.53**
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	SERTRALINE TAB 50MG	30	30	4	$ 4.80
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)* Total**				**4**	**$ 4.80**
40 Total					**56**	**$ 720.37**
17	ACE INHIBITORS***	LISINOPRIL TAB 10MG	30	30	1	$ 6.08
		LISINOPRIL TAB 20MG	60	30	1	$ 8.63
	ACE INHIBITORS* Total**				**2**	**$ 14.71**
	ADRENERGIC COMBINATIONS***	ADVAIR DISKU AER 250/50	60	30	1	$ 294.16
	ADRENERGIC COMBINATIONS* Total**				**1**	**$ 294.16**
	AZITHROMYCIN***	AZITHROMYCIN TAB 250MG	6	5	1	$ 10.14
	AZITHROMYCIN* Total**				**1**	**$ 10.14**
	BETA ADRENERGICS***	PROAIR HFA AER	8.5	30	1	$ 52.89
		PROVENTIL AER HFA	6.7	25	1	$ 63.26
	BETA ADRENERGICS* Total**				**2**	**$ 116.15**
	BIGUANIDES***	METFORMIN TAB 500MG	30	30	1	$ 6.42
	BIGUANIDES* Total**				**1**	**$ 6.42**
	GLUCOCORTICOSTEROIDS***	METHYLPRED PAK 4MG	21	6	1	$ 13.80
		PREDNISONE TAB 20MG	6	3	1	$ 5.24
	GLUCOCORTICOSTEROIDS* Total**				**2**	**$ 19.04**
	HMG COA REDUCTASE INHIBITORS***	SIMVASTATIN TAB 20MG	30	30	1	$ 7.27

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
17	**HMG COA REDUCTASE INHIBITORS*** Total**				**1**	**$ 7.27**
	LEUKOTRIENE RECEPTOR ANTAGONISTS*	MONTELUKAST TAB 10MG	**30**	30	1	$ 19.42
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**1**	**$ 19.42**
	NASAL STEROIDS*	FLUTICASONE SPR 50MCG	**16**	30	1	$ 27.41
	NASAL STEROIDS* Total**				**1**	**$ 27.41**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	IBUPROFEN TAB 800MG	**20**	10	1	$ 6.04
			90	22	1	$ 9.00
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**2**	**$ 15.04**
	OPIOID AGONISTS*	TRAMADOL HCL TAB 50MG	**12**	4	1	$ 5.47
	OPIOID AGONISTS* Total**				**1**	**$ 5.47**
	SALICYLATES*	ASPIRIN TAB 325MG	**1**	1	1	$ 0.01
	SALICYLATES* Total**				**1**	**$ 0.01**
	VASODILATORS*	HYDRALAZINE TAB 25MG	**30**	10	1	$ 9.92
	VASODILATORS* Total**				**1**	**$ 9.92**
17 Total					**17**	**$ 545.16**
2	**ADRENERGIC COMBINATIONS***	DUONEB SOL	**3**	1	2	$ 4.60
	ADRENERGIC COMBINATIONS* Total**				**2**	**$ 4.60**
	ANTIANXIETY AGENTS - MISC.*	HYDROXYZ PAM CAP 25MG	**2**	1	2	$ 0.30
	ANTIANXIETY AGENTS - MISC.* Total**				**2**	**$ 0.30**
	ANTICONVULSANTS - BENZODIAZEPINES*	CLONAZEPAM TAB 1MG	**1**	1	2	$ 0.04
			2	1	1	$ 0.05
	ANTICONVULSANTS - BENZODIAZEPINES* Total**				**3**	**$ 0.09**
	ANTICONVULSANTS - MISC.*	LAMICTAL TAB 100MG	**2**	1	1	$ 15.99
			4	1	4	$ 127.96
		VIMPAT TAB 50MG	**1**	1	1	$ 6.29
			2	1	4	$ 50.36
	ANTICONVULSANTS - MISC.* Total**				**10**	**$ 200.60**
	ANTIHISTAMINES - ETHANOLAMINES*	DIPHENHYDRAM INJ 50MG/ML	**3**	1	1	$ 2.97
			4	1	2	$ 7.92
			5	1	2	$ 9.90
	ANTIHISTAMINES - ETHANOLAMINES* Total**				**5**	**$ 20.79**
	ANTIHISTAMINES - PHENOTHIAZINES*	PROMETHAZINE INJ 25MG/ML	**2**	1	3	$ 8.07
			3	1	2	$ 8.08
	ANTIHISTAMINES - PHENOTHIAZINES* Total**				**5**	**$ 16.15**
	BENZODIAZEPINES*	DIAZEPAM INJ 5MG/ML	**2**	1	1	$ 11.28
			4	1	2	$ 45.12
	BENZODIAZEPINES* Total**				**3**	**$ 56.40**
	COBALAMINS*	CYANOCOBALAM INJ 1000MCG	**1**	1	2	$ 4.40
	COBALAMINS* Total**				**2**	**$ 4.40**
	DIRECT FACTOR XA INHIBITORS*	XARELTO TAB 20MG	**1**	1	4	$ 38.96
	DIRECT FACTOR XA INHIBITORS* Total**				**4**	**$ 38.96**
	EXPECTORANTS*	GUAIFENESIN TAB 600MG ER	**1**	1	2	$ 0.68
			2	1	2	$ 1.34
	EXPECTORANTS* Total**				**4**	**$ 2.02**
	GLUCOCORTICOSTEROIDS*	SOLU-MEDROL INJ 500MG	**1**	1	2	$ 41.04
	GLUCOCORTICOSTEROIDS* Total**				**2**	**$ 41.04**
	HEPARINS AND HEPARINOID-LIKE AGENTS*	HEPARIN SOD INJ 5000/ML	**1**	1	1	$ 4.24
	HEPARINS AND HEPARINOID-LIKE AGENTS* Total**				**1**	**$ 4.24**
	MINERALOCORTICOIDS*	FLUDROCORT TAB 0.1MG	**1**	1	4	$ 2.40
	MINERALOCORTICOIDS* Total**				**4**	**$ 2.40**
	MULTIVITAMINS*	THERA BETA- TAB CAROTENE	**1**	1	5	$ 0.20
	MULTIVITAMINS* Total**				**5**	**$ 0.20**
	OPIOID AGONISTS*	HYDROMORPHON INJ 1MG/ML	**1**	1	2	$ 4.24
		HYDROMORPHON INJ 2MG/ML	**4**	1	1	$ 5.88
			5	1	1	$ 7.34
			6	1	3	$ 26.43
	OPIOID AGONISTS* Total**				**7**	**$ 43.89**
	POTASSIUM*	POT CHLORIDE CAP 10MEQ ER	**6**	1	1	$ 3.81
	POTASSIUM* Total**				**1**	**$ 3.81**
	SELECTIVE SEROTONIN AGONISTS 5-HT(1)*	IMITREX TAB 50MG	**2**	1	3	$ 9.21
	SELECTIVE SEROTONIN AGONISTS 5-HT(1)* Total**				**3**	**$ 9.21**
	VITAMIN D*	VITAMIN D3 TAB 1000UNIT	**2**	1	5	$ 0.15
	VITAMIN D* Total**				**5**	**$ 0.15**
2 Total					**68**	**$ 449.25**
14	**ADRENERGIC COMBINATIONS***	SYMBICORT AER 80-4.5	**10.2**	30	1	$ 231.75

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
14	**ADRENERGIC COMBINATIONS*** Total**				**1**	**$ 231.75**
	ANTICONVULSANTS - MISC.***	LEVETIRACETA SOL 100MG/ML	**450**	30	3	$ 151.80
	ANTICONVULSANTS - MISC.* Total**				**3**	**$ 151.80**
	GLUCOCORTICOSTEROIDS***	PREDNISOLONE SOL 15MG/5ML	**40**	5	1	$ 7.47
	GLUCOCORTICOSTEROIDS* Total**				**1**	**$ 7.47**
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST CHW 4MG	**30**	30	1	$ 18.63
	LEUKOTRIENE RECEPTOR ANTAGONISTS* Total**				**1**	**$ 18.63**
	PENICILLIN COMBINATIONS***	AMOX/K CLAV SUS 400/5ML	**75**	7	1	$ 19.38
	PENICILLIN COMBINATIONS* Total**				**1**	**$ 19.38**
14 Total					**7**	**$ 429.03**
12	ANTIHISTAMINES - NON-SEDATING***	CETIRIZINE TAB 10MG	**30**	30	6	$ 42.72
	ANTIHISTAMINES - NON-SEDATING* Total**				**6**	**$ 42.72**
	ANTIPERISTALTIC AGENTS***	DIPHEN/ATROP TAB 2.5MG	**90**	30	3	$ 72.00
	ANTIPERISTALTIC AGENTS* Total**				**3**	**$ 72.00**
	BENZODIAZEPINE HYPNOTICS***	TEMAZEPAM CAP 30MG	**30**	30	7	$ 57.26
	BENZODIAZEPINE HYPNOTICS* Total**				**7**	**$ 57.26**
	BETA ADRENERGICS***	ALBUTEROL NEB 0.083%	**360**	20	5	$ 119.75
	BETA ADRENERGICS* Total**				**5**	**$ 119.75**
	BRONCHODILATORS - ANTICHOLINERGICS***	IPRATROPIUM SOL 0.02%INH	**300**	30	2	$ 34.56
	BRONCHODILATORS - ANTICHOLINERGICS* Total**				**2**	**$ 34.56**
	CALCIUM COMBINATIONS***	CALCIUM + D3 TAB 600MG	**30**	30	4	$ 21.00
	CALCIUM COMBINATIONS* Total**				**4**	**$ 21.00**
12 Total					**27**	**$ 347.29**
7	AMINOPENICILLINS***	AMOXICILLIN TAB 500MG	**24**	8	1	$ 13.73
	AMINOPENICILLINS* Total**				**1**	**$ 13.73**
	ANTIHISTAMINES - ETHANOLAMINES***	Q-DRYL CAP 25MG	**60**	20	1	$ 6.69
	ANTIHISTAMINES - ETHANOLAMINES* Total**				**1**	**$ 6.69**
	CENTRAL MUSCLE RELAXANTS***	BACLOFEN TAB 10MG	**30**	30	1	$ 6.34
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 6.34**
	GASTROINTESTINAL STIMULANTS***	METOCLOPRAM TAB 10MG	**90**	30	1	$ 11.33
	GASTROINTESTINAL STIMULANTS* Total**				**1**	**$ 11.33**
	HYDROCODONE COMBINATIONS***	HYDROCO/APAP TAB 10-325MG	**60**	30	5	$ 116.75
	HYDROCODONE COMBINATIONS* Total**				**5**	**$ 116.75**
	LAXATIVES - MISCELLANEOUS***	POLYETH GLYC POW 3350 NF	**527**	30	1	$ 29.21
	LAXATIVES - MISCELLANEOUS* Total**				**1**	**$ 29.21**
	OPIOID AGONISTS***	METHADONE TAB 10MG	**60**	30	2	$ 23.66
			120	30	4	$ 75.64
	OPIOID AGONISTS* Total**				**6**	**$ 99.30**
	THIAZIDES AND THIAZIDE-LIKE DIURETICS***	HYDROCHLOROT TAB 25MG	**30**	30	2	$ 10.18
	THIAZIDES AND THIAZIDE-LIKE DIURETICS* Total**				**2**	**$ 10.18**
7 Total					**18**	**$ 293.53**
9	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	**1**	1	3	$ 0.69
			2	1	3	$ 2.12
		ONDANSETRON TAB 4MG	**15**	5	1	$ 4.27
			18	4	2	$ 2.40
			30	10	1	$ 3.57
		ONDANSETRON TAB 4MG ODT	**12**	10	1	$ 13.58
	5-HT3 RECEPTOR ANTAGONISTS* Total**				**11**	**$ 26.63**
	ACE INHIBITORS***	LISINOPRIL TAB 40MG	**30**	30	5	$ 6.00
	ACE INHIBITORS* Total**				**5**	**$ 6.00**
	ALPHA-2 RECEPTOR ANTAGONISTS (TETRACYCLICS)***	MIRTAZAPINE TAB 30MG	**30**	30	1	$ 1.20
	ALPHA-2 RECEPTOR ANTAGONISTS (TETRACYCLICS)* Total**				**1**	**$ 1.20**
	ANALGESICS-SEDATIVES***	BUT/APAP/CAF CAP	**10**	2	1	$ 1.20
		BUT/APAP/CAF TAB	**30**	7	1	$ 1.20
	ANALGESICS-SEDATIVES* Total**				**2**	**$ 2.40**
	ANESTHETICS TOPICAL ORAL***	LIDOCAINE SOL 2% VISC	**40**	1	1	$ 1.04
	ANESTHETICS TOPICAL ORAL* Total**				**1**	**$ 1.04**
	ANTICONVULSANTS - MISC.***	GABAPENTIN CAP 300MG	**120**	30	1	$ 1.20
		TOPIRAMATE TAB 50MG	**60**	30	1	$ 1.20
	ANTICONVULSANTS - MISC.* Total**				**2**	**$ 2.40**
	ANTIFUNGALS - TOPICAL***	CICLOPIROX SOL 8%	**6.6**	30	1	$ 1.20
	ANTIFUNGALS - TOPICAL* Total**				**1**	**$ 1.20**
	ANTISPASMODICS***	DICYCLOMINE TAB 20MG	**20**	5	1	$ 1.20
	ANTISPASMODICS* Total**				**1**	**$ 1.20**
	BENZODIAZEPINE HYPNOTICS***	TEMAZEPAM CAP 15MG	**14**	14	1	$ 1.20

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
9	**BENZODIAZEPINE HYPNOTICS*** **	TEMAZEPAM CAP 30MG	**30**	30	1	$ 1.20
	BENZODIAZEPINE HYPNOTICS* Total**				**2**	**$ 2.40**
	BENZODIAZEPINES* **	ALPRAZOLAM TAB 0.5MG	**30**	30	1	$ 1.20
	BENZODIAZEPINES* Total**				**1**	**$ 1.20**
	BETA ADRENERGICS* **	PROAIR HFA AER	**8.5**	16	1	$ 3.60
				25	2	$ 7.20
	BETA ADRENERGICS* Total**				**3**	**$ 10.80**
	BETA BLOCKERS CARDIO-SELECTIVE* **	BYSTOLIC TAB 5MG	**30**	30	1	$ 3.60
	BETA BLOCKERS CARDIO-SELECTIVE* Total**				**1**	**$ 3.60**
	CALCIUM CHANNEL BLOCKERS* **	AMLODIPINE TAB 5MG	**30**	30	1	$ 1.20
	CALCIUM CHANNEL BLOCKERS* Total**				**1**	**$ 1.20**
	CENTRAL MUSCLE RELAXANTS* **	METHOCARBAM TAB 750MG	**180**	30	1	$ 1.20
	CENTRAL MUSCLE RELAXANTS* Total**				**1**	**$ 1.20**
	DIBENZOTHIAZEPINES* **	QUETIAPINE TAB 100MG	**60**	30	3	$ 3.60
		QUETIAPINE TAB 200MG	**30**	30	1	$ 1.20
		QUETIAPINE TAB 300MG	**30**	30	3	$ 3.60
	DIBENZOTHIAZEPINES* Total**				**7**	**$ 8.40**
	GASTROINTESTINAL STIMULANTS* **	METOCLOPRAM INJ 5MG/ML	**2**	1	1	$ 1.13
	GASTROINTESTINAL STIMULANTS* Total**				**1**	**$ 1.13**
	GLUCOCORTICOSTEROIDS* **	METHYLPRED PAK 4MG	**21**	6	1	$ 1.20
	GLUCOCORTICOSTEROIDS* Total**				**1**	**$ 1.20**
	H-2 ANTAGONISTS* **	FAMOTIDINE TAB 20MG	**30**	30	1	$ 1.20
	H-2 ANTAGONISTS* Total**				**1**	**$ 1.20**
	HUMAN INSULIN* **	LEVEMIR INJ FLEXPEN	**15**	15	1	$ 3.60
				30	1	$ 3.60
				62	1	$ 3.60
		LEVEMIR INJ FLEXTOUC	**15**	30	1	$ 3.60
	HUMAN INSULIN* Total**				**4**	**$ 14.40**
	HYDANTOINS* **	PHENYTOIN EX CAP 100MG	**90**	30	1	$ 1.20
			180	30	1	$ 1.20
	HYDANTOINS* Total**				**2**	**$ 2.40**
	HYDROCODONE COMBINATIONS* **	HYDROCO/APAP TAB 5-325MG	**12**	2	1	$ 1.20
			120	30	1	$ 1.20
	HYDROCODONE COMBINATIONS* Total**				**2**	**$ 2.40**
	IBS AGENT - GUANYLATE CYCLASE-C (GC-C) AGONISTS* **	LINZESS CAP 145MCG	**30**	30	1	$ 3.60
	IBS AGENT - GUANYLATE CYCLASE-C (GC-C) AGONISTS* Total**				**1**	**$ 3.60**
	NEEDLES & SYRINGES* **	BD PEN NEEDL MIS 31GX5/16	**100**	30	1	$ 3.60
		NOVOFINE MIS 32GX6MM	**100**	90	1	$ 3.60
	NEEDLES & SYRINGES* Total**				**2**	**$ 7.20**
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* **	IBUPROFEN TAB 600MG	**24**	8	1	$ 1.20
			28	7	1	$ 1.20
		IBUPROFEN TAB 800MG	**90**	30	1	$ 1.20
		NAPROXEN TAB 500MG	**20**	10	1	$ 1.20
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* Total**				**4**	**$ 4.80**
	OPHTHALMIC ANTIALLERGIC* **	EYE ITCH REL DRO 0.025%OP	**5**	20	1	$ 12.79
	OPHTHALMIC ANTIALLERGIC* Total**				**1**	**$ 12.79**
	OPIOID AGONISTS* **	HYDROMORPHON INJ 1MG/ML	**1**	1	1	$ 2.12
		HYDROMORPHON INJ 2MG/ML	**2**	1	1	$ 2.94
			3	1	2	$ 8.82
		METHADONE TAB 5MG	**60**	15	1	$ 1.20
			120	30	1	$ 1.20
		MORPHINE SUL INJ 4MG/ML	**1**	1	1	$ 1.87
		MORPHINE SUL INJ 5MG/ML	**1**	1	1	$ 1.01
			2	1	1	$ 2.02
		OXYCODONE TAB 15MG	**120**	30	1	$ 1.20
		TRAMADOL HCL TAB 50MG	**12**	2	1	$ 1.20
			60	15	1	$ 1.20
	OPIOID AGONISTS* Total**				**12**	**$ 24.78**
	OPIOID COMBINATIONS* **	OXYCOD/APAP TAB 10-325MG	**10**	2	1	$ 1.20
			60	10	1	$ 1.20
			90	30	1	$ 1.20
			120	30	1	$ 1.20
		OXYCOD/APAP TAB 5-325MG	**10**	5	1	$ 1.20
			60	10	1	$ 1.20
			90	15	1	$ 1.20

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
9	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 7.5-325	24	4	1	$ 1.20
	OPIOID COMBINATIONS* Total**				**8**	**$ 9.60**
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	2	1	1	$ 0.75
	POTASSIUM* Total**				**1**	**$ 0.75**
	PROTON PUMP INHIBITORS***	OMEPRAZOLE CAP 40MG	20	20	1	$ 1.20
	PROTON PUMP INHIBITORS* Total**				**1**	**$ 1.20**
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)***	DULOXETINE CAP 30MG	30	30	4	$ 4.80
	SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)* Total**				**4**	**$ 4.80**
	SODIUM***	SOD CHLORIDE INJ 0.9%	1000	1	1	$ 1.85
			2000	1	1	$ 3.71
	SODIUM* Total**				**2**	**$ 5.56**
	STEROID COMBINATIONS***	CELESTONE INJ SOLUSPAN	2	1	1	$ 14.40
	STEROID COMBINATIONS* Total**				**1**	**$ 14.40**
	SULFONYLUREAS***	GLIPIZIDE TAB 5MG	30	30	1	$ 1.20
	SULFONYLUREAS* Total**				**1**	**$ 1.20**
	TETRACYCLINES***	DOXYCYCL HYC CAP 100MG	14	7	1	$ 1.20
	TETRACYCLINES* Total**				**1**	**$ 1.20**
	TRICYCLIC AGENTS***	AMITRIPTYLIN TAB 50MG	30	30	1	$ 1.20
	TRICYCLIC AGENTS* Total**				**1**	**$ 1.20**
	VITAMIN D***	VITAMIN D CAP 50000UNT	4	28	1	$ 7.21
	VITAMIN D* Total**				**1**	**$ 7.21**
9 Total					**92**	**$ 193.89**
32	ACE INHIBITORS***	LISINOPRIL TAB 20MG	30	30	1	$ 1.20
		LISINOPRIL TAB 40MG	30	30	2	$ 2.40
	ACE INHIBITORS* Total**				**3**	**$ 3.60**
	ALPHA-2 RECEPTOR ANTAGONISTS (TETRACYCLICS)***	MIRTAZAPINE TAB 15MG	15	30	4	$ 4.80
	ALPHA-2 RECEPTOR ANTAGONISTS (TETRACYCLICS)* Total**				**4**	**$ 4.80**
	ALPHA-BETA BLOCKERS***	CARVEDILOL TAB 25MG	60	30	1	$ 1.20
	ALPHA-BETA BLOCKERS* Total**				**1**	**$ 1.20**
	ANALGESICS-SEDATIVES***	BUT/APAP/CAF TAB	30	5	1	$ 1.20
			60	15	1	$ 1.20
	ANALGESICS-SEDATIVES* Total**				**2**	**$ 2.40**
	ANTIADRENERGICS - CENTRALLY ACTING***	CLONIDINE DIS 0.1/24HR	4	30	3	$ 3.60
		CLONIDINE DIS 0.2/24HR	4	30	1	$ 1.20
		CLONIDINE DIS 0.3/24HR	4	30	2	$ 2.40
		CLONIDINE TAB 0.2MG	90	30	3	$ 3.60
	ANTIADRENERGICS - CENTRALLY ACTING* Total**				**9**	**$ 10.80**
	ANTIADRENERGICS - PERIPHERALLY ACTING***	DOXAZOSIN TAB 4MG	30	30	1	$ 1.20
	ANTIADRENERGICS - PERIPHERALLY ACTING* Total**				**1**	**$ 1.20**
	ANTICONVULSANTS - MISC.***	GABAPENTIN CAP 100MG	30	30	4	$ 4.80
	ANTICONVULSANTS - MISC.* Total**				**4**	**$ 4.80**
	ANTIDEPRESSANTS - MISC.***	BUPROPION TAB 100MG SR	60	30	3	$ 3.60
	ANTIDEPRESSANTS - MISC.* Total**				**3**	**$ 3.60**
	BENZISOXAZOLES***	RISPERIDONE TAB 1MG	30	30	4	$ 4.80
	BENZISOXAZOLES* Total**				**4**	**$ 4.80**
	BETA ADRENERGICS***	PROAIR HFA AER	8.5	25	4	$ 14.40
	BETA ADRENERGICS* Total**				**4**	**$ 14.40**
	BETA BLOCKERS CARDIO-SELECTIVE***	METOPROL TAR TAB 25MG	60	30	2	$ 2.40
		METOPROL TAR TAB 50MG	60	30	2	$ 2.40
		METOPROLOL TAB 50MG ER	60	30	3	$ 3.60
	BETA BLOCKERS CARDIO-SELECTIVE* Total**				**7**	**$ 8.40**
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 10MG	30	30	3	$ 3.60
	CALCIUM CHANNEL BLOCKERS* Total**				**3**	**$ 3.60**
	CENTRAL MUSCLE RELAXANTS***	CARISOPRODOL TAB 350MG	30	15	1	$ 1.20
			60	30	1	$ 1.20
	CENTRAL MUSCLE RELAXANTS* Total**				**2**	**$ 2.40**
	OPIOID AGONISTS***	OXYCODONE TAB 30MG	120	30	3	$ 3.60
	OPIOID AGONISTS* Total**				**3**	**$ 3.60**
	OPIOID ANTITUSSIVE-ANTIHISTAMINE***	PROMETH/COD SYP 6.25-10	240	12	1	$ 9.25
	OPIOID ANTITUSSIVE-ANTIHISTAMINE* Total**				**1**	**$ 9.25**
	PHOSPHATE BINDER AGENTS***	CALC ACETATE CAP 667MG	180	30	2	$ 2.40
		SEVELAMER TAB 800MG	90	30	2	$ 7.20
	PHOSPHATE BINDER AGENTS* Total**				**4**	**$ 9.60**
	PROTON PUMP INHIBITORS***	OMEPRAZOLE CAP 20MG	30	30	4	$ 4.80
	PROTON PUMP INHIBITORS* Total**				**4**	**$ 4.80**

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Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
32	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)***	FLUOXETINE CAP 10MG	30	30	4	$ 4.80
		FLUOXETINE CAP 20MG	30	30	4	$ 4.80
		SERTRALINE TAB 50MG	30	30	4	$ 4.80
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)*** Total				12	$ 14.40
	SEROTONIN MODULATORS***	TRAZODONE TAB 100MG	30	30	3	$ 3.60
	SEROTONIN MODULATORS*** Total				3	$ 3.60
	SURFACTANT LAXATIVES***	DOCQLACE CAP 100MG	60	30	1	$ 5.93
	SURFACTANT LAXATIVES*** Total				1	$ 5.93
	VASODILATORS***	HYDRALAZINE TAB 100MG	90	30	1	$ 1.20
	VASODILATORS*** Total				1	$ 1.20
32 Total					76	$ 118.38
41	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	2	1	2	$ 2.24
			4	1	1	$ 2.36
	5-HT3 RECEPTOR ANTAGONISTS*** Total				3	$ 4.60
	ANESTHETICS - MISC.***	DIPRIVAN INJ 10MG/ML	20	1	1	$ 2.45
	ANESTHETICS - MISC.*** Total				1	$ 2.45
	ANTISPASMODICS***	BENTYL INJ 10MG/ML	2	1	1	$ 46.91
	ANTISPASMODICS*** Total				1	$ 46.91
	BENZODIAZEPINES***	LORAZEPAM INJ 2MG/ML	1	1	1	$ 0.94
	BENZODIAZEPINES*** Total				1	$ 0.94
	BETA ADRENERGICS***	ALBUTEROL NEB 0.5%	0.5	1	2	$ 0.24
			1	1	1	$ 0.23
	BETA ADRENERGICS*** Total				3	$ 0.47
	BRONCHODILATORS - ANTICHOLINERGICS***	IPRATROPIUM SOL 0.02%INH	2.5	1	1	$ 0.21
			5	1	1	$ 0.42
	BRONCHODILATORS - ANTICHOLINERGICS*** Total				2	$ 0.63
	COBALAMINS***	CYANOCOBALAM INJ 1000MCG	1	1	3	$ 7.47
	COBALAMINS*** Total				3	$ 7.47
	GLUCOCORTICOSTEROIDS***	METHYLPR SS INJ 125MG	2	1	1	$ 6.92
	GLUCOCORTICOSTEROIDS*** Total				1	$ 6.92
	LOCAL ANESTHETICS - AMIDES***	LIDOCAINE INJ 1%	20	1	1	$ 1.23
	LOCAL ANESTHETICS - AMIDES*** Total				1	$ 1.23
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	KETOROLAC INJ 30MG/ML	1	1	1	$ 0.86
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*** Total				1	$ 0.86
	OPIOID AGONISTS***	MORPHINE SUL INJ 2MG/ML	1	1	1	$ 1.87
		MORPHINE SUL INJ 4MG/ML	1	1	1	$ 1.87
			2	1	1	$ 3.73
		MORPHINE SUL INJ 5MG/ML	1	1	2	$ 2.02
	OPIOID AGONISTS*** Total				5	$ 9.49
	PHENOTHIAZINES***	PROCHLORPER INJ 5MG/ML	2	1	2	$ 9.38
	PHENOTHIAZINES*** Total				2	$ 9.38
	SALICYLATES***	CHILD ASA CHW 81MG	2	1	1	$ 0.04
	SALICYLATES*** Total				1	$ 0.04
41 Total					25	$ 91.39
6	ADRENERGIC COMBINATIONS***	IPRATROPIUM/ SOL ALBUTER	540	30	1	$ 1.20
		SYMBICORT AER 160-4.5	10.2	30	1	$ 3.60
	ADRENERGIC COMBINATIONS*** Total				2	$ 4.80
	ANALGESICS-SEDATIVES***	BUT/APAP/CAF TAB	15	4	1	$ 1.20
	ANALGESICS-SEDATIVES*** Total				1	$ 1.20
	ANGIOTENSIN II RECEPTOR ANTAGONISTS***	LOSARTAN POT TAB 100MG	90	90	1	$ 1.20
	ANGIOTENSIN II RECEPTOR ANTAGONISTS*** Total				1	$ 1.20
	ANTICONVULSANTS - MISC.***	GABAPENTIN CAP 300MG	90	10	3	$ 3.60
				30	1	$ 1.20
	ANTICONVULSANTS - MISC.*** Total				4	$ 4.80
	ANTIHISTAMINES - PHENOTHIAZINES***	PROMETHAZINE TAB 25MG	60	30	1	$ 1.20
	ANTIHISTAMINES - PHENOTHIAZINES*** Total				1	$ 1.20
	ANTI-INFECTIVE AGENTS - MISC.***	METRONIDAZOL TAB 500MG	30	10	2	$ 2.40
	ANTI-INFECTIVE AGENTS - MISC.*** Total				2	$ 2.40
	ANTI-INFECTIVE MISC. - COMBINATIONS***	SMZ/TMP DS TAB 800-160	14	7	1	$ 1.20
			20	10	2	$ 3.75
			40	10	1	$ 1.20
	ANTI-INFECTIVE MISC. - COMBINATIONS*** Total				4	$ 6.15
	AZITHROMYCIN***	AZITHROMYCIN INJ 500MG	1	1	1	$ 6.12
		AZITHROMYCIN TAB 250MG	4	4	1	$ 1.20
	AZITHROMYCIN*** Total				2	$ 7.32

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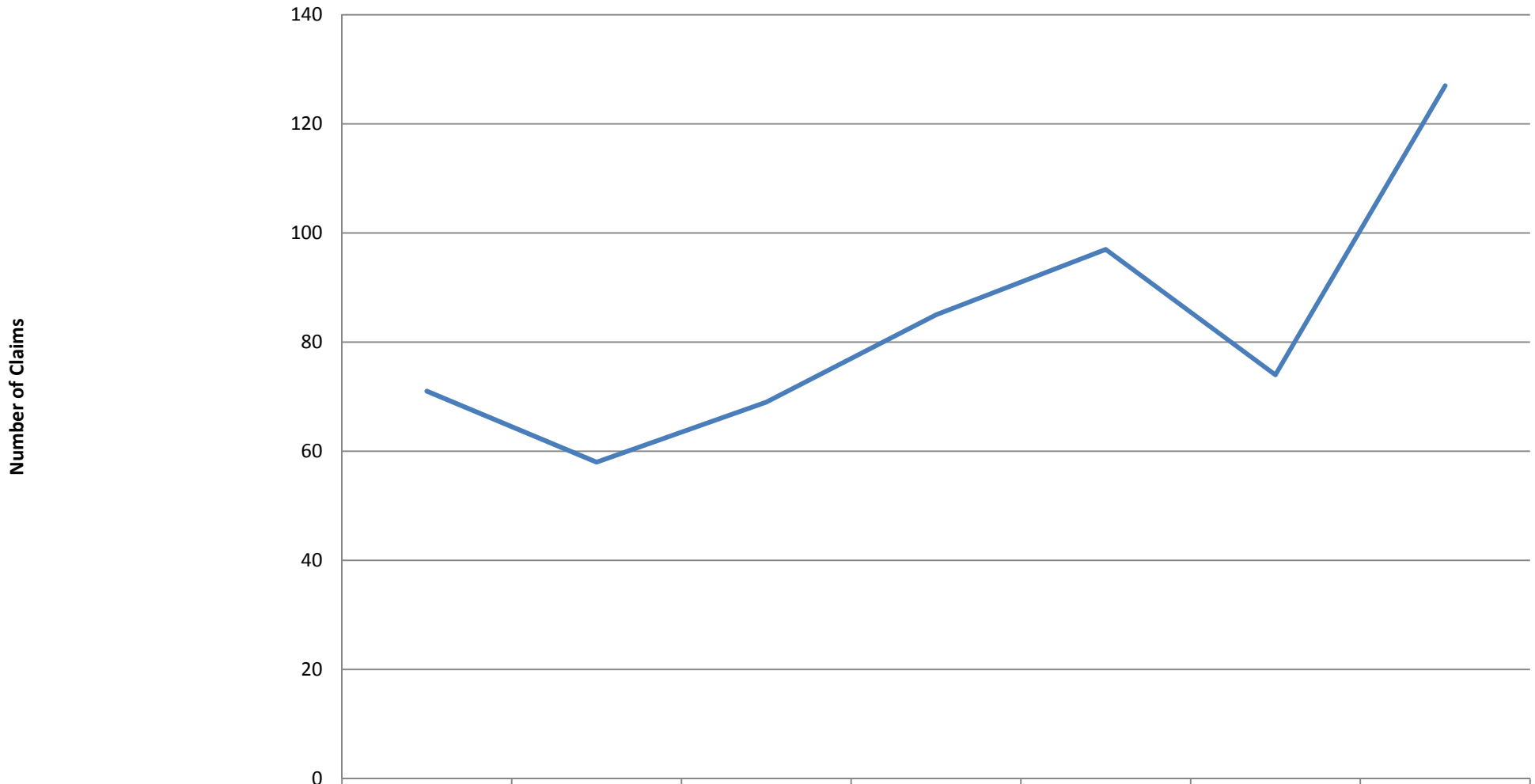
6	BENZODIAZEPINES***	ALPRAZOLAM TAB 0.5MG	60	20	1	$ 1.20
	BENZODIAZEPINES*** Total				1	$ 1.20
	BETA ADRENERGICS***	PROAIR HFA AER	17	16	1	$ 3.60
				25	1	$ 3.60
		XOPENEX HFA AER	30	30	3	$ 10.80
	BETA ADRENERGICS*** Total				5	$ 18.00
	CALCIUM CHANNEL BLOCKERS***	AMLODIPINE TAB 10MG	90	90	1	$ 1.20
	CALCIUM CHANNEL BLOCKERS*** Total				1	$ 1.20
	CEPHALOSPORINS - 3RD GENERATION***	CEFDINIR CAP 300MG	20	10	4	$ 4.80
	CEPHALOSPORINS - 3RD GENERATION*** Total				4	$ 4.80
	FLUOROQUINOLONES***	LEVOFLOXACIN TAB 750MG	10	10	2	$ 2.40
	FLUOROQUINOLONES*** Total				2	$ 2.40
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 10MG	120	30	1	$ 1.20
		PREDNISONE TAB 20MG	30	30	2	$ 2.40
			60	30	1	$ -
			90	30	1	$ 1.20
	GLUCOCORTICOSTEROIDS*** Total				5	$ 4.80
	LEUKOTRIENE RECEPTOR ANTAGONISTS***	MONTELUKAST TAB 10MG	90	90	1	$ 1.20
	LEUKOTRIENE RECEPTOR ANTAGONISTS*** Total				1	$ 1.20
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)***	NAPROXEN TAB 500MG	60	30	1	$ 1.20
	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*** Total				1	$ 1.20
	OPIOID AGONISTS***	METHADONE TAB 10MG	10	3	1	$ 1.20
		OXYCODONE TAB 10MG	50	9	1	$ 3.98
		OXYCODONE TAB 5MG	60	5	1	$ 1.20
	OPIOID AGONISTS*** Total				3	$ 6.38
	OPIOID COMBINATIONS***	ENDOCET TAB 5-325MG	40	4	1	$ 1.20
		OXYCOD/APAP TAB 10-325MG	1	1	1	$ 0.81
			120	20	1	$ 1.20
	OPIOID COMBINATIONS*** Total				3	$ 3.21
	POTASSIUM***	POT CL MICRO TAB 20MEQ ER	30	30	1	$ 1.20
	POTASSIUM*** Total				1	$ 1.20
	PROTON PUMP INHIBITORS***	OMEPRAZOLE CAP 40MG	30	30	3	$ 3.60
	PROTON PUMP INHIBITORS*** Total				3	$ 3.60
	TETRACYCLINES***	DOXYCYC MONO TAB 100MG	20	10	1	$ 1.20
	TETRACYCLINES*** Total				1	$ 1.20
	THIAZIDES AND THIAZIDE-LIKE DIURETICS***	HYDROCHLOROT TAB 25MG	90	90	1	$ 1.20
	THIAZIDES AND THIAZIDE-LIKE DIURETICS*** Total				1	$ 1.20
6 Total					49	$ 80.66
18	FOLIC ACID/FOLATES***	FOLIC ACID TAB 1MG	2	2	1	$ 4.80
			30	30	4	$ 21.52
	FOLIC ACID/FOLATES*** Total				5	$ 26.32
18 Total					5	$ 26.32
25	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	2	1	2	$ 0.90
		ONDANSETRON TAB 4MG ODT	1	1	1	$ 0.65
	5-HT3 RECEPTOR ANTAGONISTS*** Total				3	$ 1.55
	ANESTHETICS TOPICAL ORAL***	LIDOCAINE SOL 2% VISC	50	1	1	$ 1.79
	ANESTHETICS TOPICAL ORAL*** Total				1	$ 1.79
	GLUCOCORTICOSTEROIDS***	PREDNISONE TAB 10MG	120	30	1	$ -
	GLUCOCORTICOSTEROIDS*** Total				1	$ -
	H-2 ANTAGONISTS***	FAMOTIDINE TAB 20MG	1	1	1	$ 0.09
	H-2 ANTAGONISTS*** Total				1	$ 0.09
	LINCOSAMIDES***	CLINDAMYCIN CAP 150MG	2	1	1	$ 0.41
	LINCOSAMIDES*** Total				1	$ 0.41
	OPIOID AGONISTS***	HYDROMORPHON INJ 1MG/ML	1	1	2	$ 2.18
			2	1	1	$ 2.18
	OPIOID AGONISTS*** Total				3	$ 4.36
	OPIOID COMBINATIONS***	OXYCOD/APAP TAB 10-325MG	1	1	1	$ 0.81
	OPIOID COMBINATIONS*** Total				1	$ 0.81
	PROTON PUMP INHIBITORS***	OMEPRAZOLE CAP 20MG	1	1	1	$ 0.20
	PROTON PUMP INHIBITORS*** Total				1	$ 0.20
25 Total					12	$ 9.21
28	5-HT3 RECEPTOR ANTAGONISTS***	ONDANSETRON INJ 4MG/2ML	1	1	2	$ 0.46
		ONDANSETRON TAB 4MG	108	30	1	$ 2.55
	5-HT3 RECEPTOR ANTAGONISTS*** Total				3	$ 3.01
	DIAGNOSTIC TESTS***	ONETOUCH TES ULTRA BL	100	50	1	$ 4.16

Utilization of Top Hospital Admitted Members with Asthma

Pt #	MSC Drug Sub Class Name	Drug Label Name	Metric Decimal Qty	Days Supply	Count of Claims	Paid Amount
28	**DIAGNOSTIC TESTS*** Total**				**1**	**$ 4.16**
28 Total					**4**	**$ 7.17**
16	**BENZODIAZEPINES***	LORAZEPAM INJ 2MG/ML	**1**	1	1	$ 0.94
	BENZODIAZEPINES* Total**				**1**	**$ 0.94**
16 Total					**1**	**$ 0.94**
Grand Total					**2630**	**$ 779,965.31**

Sum of Count of Claims

Tussionex Utilization 06/2014 - 12/2014



	201406	201407	201408	201409	201410	201411	201412
HYDROCODONE POLISTIREX/CH	71	58	69	85	97	74	127
TUSSICAPS	1					1	

YearMonth Filled

Tussionex Utilization

YearMonth Filled	Product Name	Dosage Form	Count of Claims	Count of Members	Qty Disp	Days Supply	Paid Amt	Qty/Claim	Qty/Member
201406	TUSSICAPS	CP12	1	1	30	15	$ 280.16	30	30
201406	HYDROCODONE POLISTIREX/CH	LQCR	71	57	10,620.00	1,019	$ 5,393.36	150	186
201407	HYDROCODONE POLISTIREX/CH	LQCR	58	51	9,451.00	888	$ 4,531.68	163	185
201408	HYDROCODONE POLISTIREX/CH	LQCR	69	62	10,388.00	1,023	$ 5,030.38	151	168
201409	HYDROCODONE POLISTIREX/CH	LQCR	85	75	11,728.00	1,208	$ 5,912.02	138	156
201410	HYDROCODONE POLISTIREX/CH	LQCR	97	89	13,247.00	1,318	$ 6,550.85	137	149
201411	HYDROCODONE POLISTIREX/CH	LQCR	74	71	11,094.00	1,066	$ 5,429.78	150	156
201411	TUSSICAPS	CP12	1	1	30	15	$ 609.81	30	30
201412	HYDROCODONE POLISTIREX/CH	LQCR	127	119	15,846.00	1,539	$ 7,865.76	125	133

Top 10 Drug Group by Paid Amt

Q2 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	28,921	$ 7,424,205.97
12	ANTIVIRALS*	4,342	$ 7,289,800.64
85	HEMATOLOGICAL AGENTS - MISC.*	3,882	$ 4,727,980.68
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	38,939	$ 3,624,007.69
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	3,464	$ 2,951,808.49
27	ANTIDIABETICS*	25,734	$ 2,743,765.19
65	ANALGESICS - OPIOID*	70,305	$ 2,510,212.56
72	ANTICONVULSANTS*	39,275	$ 2,420,985.24
61	ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	10,673	$ 2,120,175.37
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	9,519	$ 2,098,378.82

Q3 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
12	ANTIVIRALS*	4,334	$ 7,831,875.91
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	28,851	$ 7,459,877.89
85	HEMATOLOGICAL AGENTS - MISC.*	3,700	$ 5,050,893.52
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	36,589	$ 3,491,464.48
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4,031	$ 3,442,320.47
27	ANTIDIABETICS*	24,791	$ 3,076,547.70
72	ANTICONVULSANTS*	39,051	$ 2,535,347.65
65	ANALGESICS - OPIOID*	71,642	$ 2,482,410.76
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	4,005	$ 2,351,578.94
61	ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	10,219	$ 2,115,073.48

Q4 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
12	ANTIVIRALS*	4,468	$ 8,504,634.14
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	27,128	$ 7,683,927.56
85	HEMATOLOGICAL AGENTS - MISC.*	3,372	$ 6,979,163.17
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	37,789	$ 3,711,803.05
27	ANTIDIABETICS*	23,521	$ 3,238,990.79
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	3,514	$ 2,928,075.06
72	ANTICONVULSANTS*	38,048	$ 2,690,144.60
65	ANALGESICS - OPIOID*	61,598	$ 2,362,958.40
61	ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	10,496	$ 2,204,887.73
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	3,724	$ 2,014,499.56

Top 10 Drug Group by Claim Count

Q2 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	70,305	$ 2,510,212.56
72	ANTICONVULSANTS*	39,275	$ 2,420,985.24
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	38,939	$ 3,624,007.69
58	ANTIDEPRESSANTS*	37,310	$ 808,755.36
36	ANTIHYPERTENSIVES*	33,125	$ 378,903.86
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	28,921	$ 7,424,205.97
27	ANTIDIABETICS*	25,734	$ 2,743,765.19
39	ANTIHYPERLIPIDEMICS*	24,996	$ 730,054.94
57	ANTIANXIETY AGENTS*	24,966	$ 196,771.03
49	ULCER DRUGS*	22,559	$ 999,167.38

Q3 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	71,631	$ 2,482,276.97
72	ANTICONVULSANTS*	39,050	$ 2,535,347.64
58	ANTIDEPRESSANTS*	37,932	$ 826,977.09
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	36,593	$ 3,491,467.74
36	ANTIHYPERTENSIVES*	32,250	$ 354,937.49
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	28,849	$ 7,459,859.59
57	ANTIANXIETY AGENTS*	25,921	$ 201,414.02
27	ANTIDIABETICS*	24,791	$ 3,076,547.70
39	ANTIHYPERLIPIDEMICS*	24,671	$ 820,516.83
49	ULCER DRUGS*	22,070	$ 1,026,492.05

Q4 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	61,598	$ 2,362,958.40
72	ANTICONVULSANTS*	38,048	$ 2,690,144.60
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	37,789	$ 3,711,803.05
58	ANTIDEPRESSANTS*	36,919	$ 837,021.47
36	ANTIHYPERTENSIVES*	31,101	$ 349,762.95
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	27,128	$ 7,683,927.56
57	ANTIANXIETY AGENTS*	23,977	$ 200,978.33
39	ANTIHYPERLIPIDEMICS*	23,655	$ 804,254.01
27	ANTIDIABETICS*	23,521	$ 3,238,990.79
49	ULCER DRUGS*	21,208	$ 1,079,722.12

Top 10 Drug Classes by Paid Amt

Q2 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
1235	HEPATITIS AGENTS**	384	$ 4,804,602.04
8510	ANTIHEMOPHILIC PRODUCTS**	113	$ 4,214,917.26
5925	QUINOLINONE DERIVATIVES**	4,152	$ 3,405,157.22
1210	ANTIRETROVIRALS**	2,376	$ 2,332,663.50
2710	INSULIN**	8,782	$ 2,104,928.74
4420	SYMPATHOMIMETICS**	25,601	$ 2,095,249.19
5907	BENZISOXAZOLES**	7,574	$ 1,610,765.98
7260	ANTICONVULSANTS - MISC.**	26,955	$ 1,590,703.86
6510	OPIOID AGONISTS**	28,381	$ 1,333,124.78
5915	DIBENZAPINES**	10,591	$ 1,279,205.70

Q3 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
1235	HEPATITIS AGENTS**	398	$ 5,224,584.34
8510	ANTIHEMOPHILIC PRODUCTS**	119	$ 4,519,700.74
5925	QUINOLINONE DERIVATIVES**	4,085	$ 3,445,502.22
1210	ANTIRETROVIRALS**	2,427	$ 2,496,796.37
2710	INSULIN**	8,300	$ 2,347,110.16
4420	SYMPATHOMIMETICS**	24,372	$ 2,090,374.30
7260	ANTICONVULSANTS - MISC.**	26,756	$ 1,682,719.06
5907	BENZISOXAZOLES**	7,177	$ 1,612,690.41
5915	DIBENZAPINES**	10,625	$ 1,279,998.43
6510	OPIOID AGONISTS**	29,413	$ 1,271,033.91

Q4 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	124	$ 6,483,141.59
1235	HEPATITIS AGENTS**	332	$ 5,947,397.39
5925	QUINOLINONE DERIVATIVES**	4,203	$ 3,636,167.83
2710	INSULIN**	7,686	$ 2,477,258.93
1210	ANTIRETROVIRALS**	2,245	$ 2,371,303.70
4420	SYMPATHOMIMETICS**	25,497	$ 2,148,741.41
7260	ANTICONVULSANTS - MISC.**	26,416	$ 1,761,055.45
5907	BENZISOXAZOLES**	6,765	$ 1,725,772.87
5915	DIBENZAPINES**	10,027	$ 1,250,108.53
6240	MULTIPLE SCLEROSIS AGENTS**	272	$ 1,238,233.66

Top 10 Drug Classes by Claim Count

Q2 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
6599	OPIOID COMBINATIONS**	41,456	$ 1,086,238.29
6510	OPIOID AGONISTS**	28,381	$ 1,333,124.78
7260	ANTICONVULSANTS - MISC.**	26,955	$ 1,590,703.86
4420	SYMPATHOMIMETICS**	25,601	$ 2,095,249.19
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	20,480	$ 405,189.09
3940	HMG COA REDUCTASE INHIBITORS**	20,126	$ 341,789.19
5710	BENZODIAZEPINES**	20,057	$ 131,945.68
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	18,980	$ 153,220.53
7510	CENTRAL MUSCLE RELAXANTS**	15,230	$ 228,810.08
3610	ACE INHIBITORS**	15,078	$ 85,099.26

Q3 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
6599	OPIOID COMBINATIONS**	41,662	$ 1,113,326.31
6510	OPIOID AGONISTS**	29,422	$ 1,271,156.49
7260	ANTICONVULSANTS - MISC.**	26,756	$ 1,682,719.06
4420	SYMPATHOMIMETICS**	24,369	$ 2,090,371.25
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	21,162	$ 408,697.98
5710	BENZODIAZEPINES**	21,039	$ 137,184.71
3940	HMG COA REDUCTASE INHIBITORS**	19,961	$ 351,213.63
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	19,439	$ 160,654.59
7510	CENTRAL MUSCLE RELAXANTS**	15,151	$ 240,050.41
3610	ACE INHIBITORS**	14,733	$ 84,073.37

Q4 2014

Class	Drug Class Name	Count of Claims	Pharmacy Paid
6599	OPIOID COMBINATIONS**	35,453	$ 1,028,967.39
7260	ANTICONVULSANTS - MISC.**	26,416	$ 1,761,055.45
6510	OPIOID AGONISTS**	25,600	$ 1,234,264.94
4420	SYMPATHOMIMETICS**	25,497	$ 2,148,741.41
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	20,575	$ 397,015.36
3940	HMG COA REDUCTASE INHIBITORS**	19,117	$ 353,605.23
5710	BENZODIAZEPINES**	19,078	$ 135,647.26
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	18,977	$ 167,907.49
7510	CENTRAL MUSCLE RELAXANTS**	14,722	$ 234,927.34
3610	ACE INHIBITORS**	14,065	$ 92,980.74

Top 50 Drugs by Amount - Q2 2014

Drug Code	Drug Name	Claim Count		Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
1235308000	SOFOSBUVIR	158	$	4,264,001.84	15	15
5925001500	ARIPIPRAZOLE	4,152	$	3,405,157.22	22	19
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	16	$	1,186,422.55	21,038	7
8510001000	ANTIHEMOPHILIC FACTOR (HUMAN)	5	$	1,035,035.76	173,456	30
2710400300	INSULIN GLARGINE	3,496	$	881,286.25	13	26
4420990270	FLUTICASONE-SALMETEROL	3,451	$	858,339.07	45	23
5915307010	QUETIAPINE FUMARATE	6,843	$	853,215.37	30	19
5940002310	LURASIDONE HCL	1,158	$	821,967.63	17	15
5907005010	PALIPERIDONE PALMITATE	570	$	761,417.77	1	23
3030001000	CORTICOTROPIN	9	$	741,988.80	8	14
4927002510	ESOMEPRAZOLE MAGNESIUM	3,711	$	741,589.46	24	22
9410003000	GLUCOSE BLOOD	6,066	$	724,839.05	71	21
4420101010	ALBUTEROL SULFATE	17,693	$	710,463.43	42	16
6510007510	OXYCODONE HCL	8,573	$	617,902.86	73	17
6599170210	HYDROCODONE-ACETAMINOPHEN	29,505	$	611,924.00	61	14
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	20	$	589,055.45	6,653	7
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	1	$	541,624.76	300,000	30
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	37	$	501,147.54	5,232	9
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2,576	$	493,582.07	26	25
6135303010	GUANFACINE HCL (ADHD)	1,716	$	493,077.05	22	19
6110990210	AMPHETAMINE-DEXTROAMPHETAMINE	2,973	$	464,896.72	30	20
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	408	$	463,105.48	22	22
6599000220	OXYCODONE W/ ACETAMINOPHEN	9,926	$	429,118.34	52	12
5907005000	PALIPERIDONE	478	$	424,671.90	21	16
7260005700	PREGABALIN	2,014	$	412,050.16	49	21
8580005000	ECULIZUMAB	18	$	403,523.28	6,069	1
7250001010	DIVALPROEX SODIUM	4,547	$	395,479.50	54	19
8240157000	PEGFILGRASTIM	94	$	395,218.42	1	1
6240552500	DIMETHYL FUMARATE	79	$	393,620.72	20	10
5818002510	DULOXETINE HCL	2,157	$	369,159.29	24	18
3010002000	SOMATROPIN	131	$	368,985.38	3	14
2710400500	INSULIN LISPRO (HUMAN)	1,344	$	358,868.24	11	22
2710400200	INSULIN ASPART	1,484	$	351,024.95	12	20
1235307710	SIMEPREVIR SODIUM	16	$	338,511.00	15	15
1210990330	EFAVIRENZ-EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	179	$	328,816.87	21	21
6110002510	LISDEXAMFETAMINE DIMESYLATE	1,631	$	321,958.08	23	23
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2,090	$	316,964.26	8	24
1910002010	IMMUNE GLOBULIN (HUMAN) IV	88	$	316,704.80	428	4
6629003000	ETANERCEPT	115	$	306,906.90	2	12
6140002010	METHYLPHENIDATE HCL	2,250	$	306,523.11	33	18
6240306045	INTERFERON BETA-1A	65	$	302,474.60	2	18
8310102010	ENOXAPARIN SODIUM	948	$	302,261.77	2	2
700007000	TOBRAMYCIN	59	$	292,750.78	180	19
6627001500	ADALIMUMAB	108	$	291,787.11	1	12
1210990430	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR	131	$	284,807.61	22	22
6510005510	MORPHINE SULFATE	7,021	$	281,962.93	27	11
2153253000	EVEROLIMUS	24	$	265,721.51	13	11
4530402000	DORNASE ALFA	100	$	248,066.64	41	14
7260003600	LACOSAMIDE	617	$	246,878.18	58	16
3090685000	IDURSULFASE	14	$	238,894.88	18	9

Top 50 Drugs by Amount - Q3 2014

Drug Code	Drug Name	Claim Count		Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
1235308000	SOFOSBUVIR	184.00	$	4,604,058.76	17	17
5925001500	ARIPIPRAZOLE	4,085.00	$	3,445,502.22	21	18
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	18.00	$	2,296,990.49	48,703	13
2710400300	INSULIN GLARGINE	3,252.00	$	964,196.18	12	25
3030001000	CORTICOTROPIN	14.00	$	935,563.72	5	7
5940002310	LURASIDONE HCL	1,182.00	$	856,355.39	15	13
4420990270	FLUTICASONE-SALMETEROL	3,222.00	$	844,417.24	42	22
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	23.00	$	832,808.69	6,681	6
5915307010	QUETIAPINE FUMARATE	6,847.00	$	826,606.07	28	18
5907005010	PALIPERIDONE PALMITATE	550.00	$	818,557.72	1	22
4927002510	ESOMEPRAZOLE MAGNESIUM	3,679.00	$	786,069.74	23	21
9410003000	GLUCOSE BLOOD	6,268.00	$	748,719.26	67	20
4420101010	ALBUTEROL SULFATE	16,740.00	$	713,262.54	37	16
6599170210	HYDROCODONE-ACETAMINOPHEN	29,340.00	$	619,000.21	59	14
8240157000	PEGFILGRASTIM	134.00	$	615,327.01	1	2
6510007510	OXYCODONE HCL	8,389.00	$	609,521.64	76	17
8510001000	ANTIHEMOPHILIC FACTOR (HUMAN)	2.00	$	563,891.02	236,250	30
6135303010	GUANFACINE HCL (ADHD)	1,681.00	$	546,177.48	22	19
1235307710	SIMEPREVIR SODIUM	33.00	$	498,641.92	23	23
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2,329.00	$	492,487.19	25	25
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	411.00	$	488,303.73	20	20
7260005700	PREGABALIN	1,996.00	$	452,189.99	47	20
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	51.00	$	446,853.86	3,474	8
6599000220	OXYCODONE W/ ACETAMINOPHEN	10,244.00	$	441,649.77	50	12
3090685000	IDURSULFASE	21.00	$	437,977.12	22	11
6110990210	AMPHETAMINE-DEXTROAMPHETAMINE	2,775.00	$	430,287.23	27	19
6240552500	DIMETHYL FUMARATE	84.00	$	414,248.21	21	11
8580005000	ECULIZUMAB	22.00	$	412,460.46	73	1
2710400500	INSULIN LISPRO (HUMAN)	1,257.00	$	405,780.87	11	21
2135307000	TRASTUZUMAB	108.00	$	393,806.76	1	1
7250001010	DIVALPROEX SODIUM	4,519.00	$	391,547.41	48	16
5907005000	PALIPERIDONE	440.00	$	388,302.22	19	15
2710400200	INSULIN ASPART	1,430.00	$	381,056.58	11	19
6629003000	ETANERCEPT	144.00	$	359,298.96	2	13
0700007000	TOBRAMYCIN	73.00	$	350,441.60	149	16
5818002510	DULOXETINE HCL	2,024.00	$	347,708.92	21	16
3010002000	SOMATROPIN	135.00	$	344,453.60	2	12
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2,022.00	$	338,108.73	8	24
8310102010	ENOXAPARIN SODIUM	1,091.00	$	330,376.20	2	2
1210990330	EFAVIRENZ-EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	171.00	$	319,656.05	17	17
1210990430	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR	139.00	$	315,527.09	19	19
2133502000	BEVACIZUMAB	265.00	$	313,803.32	8	1
6110002510	LISDEXAMFETAMINE DIMESYLATE	1,577.00	$	309,412.07	23	22
6140002010	METHYLPHENIDATE HCL	2,154.00	$	290,257.28	31	17
1910002010	IMMUNE GLOBULIN (HUMAN) IV	100.00	$	285,840.69	294	3
6510005510	MORPHINE SULFATE	7,917.00	$	282,200.24	21	9
4530402000	DORNASE ALFA	112.00	$	281,526.18	52	18
6627001500	ADALIMUMAB	101.00	$	278,509.23	1	12
6240306045	INTERFERON BETA-1A	56.00	$	269,038.25	2	17
2710400600	INSULIN DETEMIR	993.00	$	268,359.17	14	20

Top 50 Drugs by Amount - Q4 2014

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
5925001500	ARIPIPRAZOLE	4203	$ 3,636,167.83	21	18
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	26	$ 3,287,092.39	54,794	16
1235990240	LEDIPASVIR-SOFOSBUVIR	102	$ 2,956,433.92	16	16
1235308000	SOFOSBUVIR	99	$ 2,657,888.92	15	15
8510001026	ANTIHEMOPHILIC FACTOR (RECOMBINANT) PLASMA/ALBLUMIN FREE	19	$ 1,124,529.80	13,823	9
2710400300	INSULIN GLARGINE	3133	$ 1,039,653.64	12	25
1950206000	PALIVIZUMAB	407	$ 971,315.39	1	18
8510001000	ANTIHEMOPHILIC FACTOR (HUMAN)	5	$ 909,227.52	152,372	27
5907005010	PALIPERIDONE PALMITATE	586	$ 895,252.39	1	24
4927002510	ESOMEPRAZOLE MAGNESIUM	3847	$ 840,377.85	23	22
4420990270	FLUTICASONE-SALMETEROL	3145	$ 840,005.60	45	23
5915307010	QUETIAPINE FUMARATE	6610	$ 828,408.65	30	20
5940002310	LURASIDONE HCL	1104	$ 814,253.85	15	14
4420101010	ALBUTEROL SULFATE	18082	$ 753,958.27	42	16
9410003000	GLUCOSE BLOOD	5985	$ 727,299.29	70	21
6510007510	OXYCODONE HCL	7825	$ 563,217.49	73	18
6135303010	GUANFACINE HCL (ADHD)	1711	$ 553,254.34	20	17
3030001000	CORTICOTROPIN	17	$ 549,122.44	2	5
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2231	$ 508,666.85	26	26
8240157000	PEGFILGRASTIM	109	$ 506,187.12	1	3
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	50	$ 504,302.54	5,235	9
6599170210	HYDROCODONE-ACETAMINOPHEN	22615	$ 491,601.83	55	13
6599000220	OXYCODONE W/ ACETAMINOPHEN	10297	$ 483,437.76	51	12
7260005700	PREGABALIN	1916	$ 473,314.13	50	21
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	388	$ 469,187.54	20	20
2710400500	INSULIN LISPRO (HUMAN)	1241	$ 446,756.00	11	20
6240552500	DIMETHYL FUMARATE	87	$ 446,305.76	22	11
6110990210	AMPHETAMINE-DEXTROAMPHETAMINE	2869	$ 446,230.71	26	18
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	12	$ 417,607.27	9,138	8
5907005000	PALIPERIDONE	390	$ 409,331.27	21	16
7250001010	DIVALPROEX SODIUM	4267	$ 392,241.84	53	18
2710400200	INSULIN ASPART	1246	$ 382,606.01	11	20
6629003000	ETANERCEPT	139	$ 369,088.32	2	14
3010002000	SOMATROPIN	137	$ 367,750.01	2	11
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	1994	$ 359,869.68	8	24
8580005000	ECULIZUMAB	18	$ 348,665.58	95	1
3090685000	IDURSULFASE	17	$ 345,488.54	19	9
2135307000	TRASTUZUMAB	80	$ 344,697.38	1	2
0700007000	TOBRAMYCIN	72	$ 334,530.59	131	14
5818002510	DULOXETINE HCL	1893	$ 332,664.60	23	18
6110002510	LISDEXAMFETAMINE DIMESYLATE	1677	$ 326,933.74	23	23
1210990430	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR	135	$ 312,348.17	19	19
6140002010	METHYLPHENIDATE HCL	2225	$ 310,302.21	34	18
1210990330	EFAVIRENZ-EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	152	$ 308,339.02	19	18
6627001500	ADALIMUMAB	111	$ 300,211.89	1	15
1910002010	IMMUNE GLOBULIN (HUMAN) IV	94	$ 285,168.97	314	4
7260003600	LACOSAMIDE	599	$ 277,355.61	54	14
4530402000	DORNASE ALFA	108	$ 270,423.92	48	17
2710400600	INSULIN DETEMIR	862	$ 269,279.85	9	17
6510005510	MORPHINE SULFATE	6052	$ 256,449.38	30	12

Top 50 Drugs by Claim Count - Q2 2014

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	29505	$ 611,924.00	61	14
4420101010	ALBUTEROL SULFATE	17693	$ 710,463.43	42	16
3610003000	LISINOPRIL	13406	$ 70,242.02	30	27
5710001000	ALPRAZOLAM	11223	$ 88,503.87	51	21
7260003000	GABAPENTIN	10724	$ 183,761.71	72	23
6599000220	OXYCODONE W/ ACETAMINOPHEN	9926	$ 429,118.34	52	12
6610002000	IBUPROFEN	9549	$ 58,142.48	46	13
2810001010	LEVOTHYROXINE SODIUM	9500	$ 90,464.81	29	29
3400000310	AMLODIPINE BESYLATE	9436	$ 43,955.75	28	27
2725005000	METFORMIN HCL	9081	$ 62,368.98	48	24
6510007510	OXYCODONE HCL	8573	$ 617,902.86	73	17
3940007500	SIMVASTATIN	8011	$ 43,763.15	28	28
120001010	AMOXICILLIN	7300	$ 58,338.76	57	7
6510005510	MORPHINE SULFATE	7021	$ 281,962.93	27	11
5915307010	QUETIAPINE FUMARATE	6843	$ 853,215.37	30	19
6510009510	TRAMADOL HCL	6656	$ 54,984.63	63	16
5025006505	ONDANSETRON HCL	6516	$ 39,280.78	5	2
5812008010	TRAZODONE HCL	6507	$ 45,652.30	32	24
4450505010	MONTELUKAST SODIUM	6434	$ 153,673.03	22	22
5907007000	RISPERIDONE	6083	$ 143,339.99	35	20
9410003000	GLUCOSE BLOOD	6066	$ 724,839.05	71	21
3940001010	ATORVASTATIN CALCIUM	6061	$ 67,012.53	25	25
3320003010	METOPROLOL TARTRATE	5959	$ 26,736.88	40	22
6020408010	ZOLPIDEM TARTRATE	5925	$ 44,382.36	24	24
5816007010	SERTRALINE HCL	5662	$ 43,449.21	29	23
3720003000	FUROSEMIDE	5513	$ 21,316.18	30	24
4220003230	FLUTICASONE PROPIONATE (NASAL)	5447	$ 117,799.91	13	24
6410001000	ASPIRIN	5402	$ 18,693.90	20	19
4920002010	RANITIDINE HCL	5401	$ 49,877.48	47	23
7210001000	CLONAZEPAM	5288	$ 30,216.02	47	22
5816002010	CITALOPRAM HYDROBROMIDE	5210	$ 29,540.78	23	21
7510005010	CYCLOBENZAPRINE HCL	5207	$ 37,754.29	42	19
3090504000	DOXERCALCIFEROL	5137	$ 59,096.98	2	1
8240102000	EPOETIN ALFA	5132	$ 202,664.79	0	1
340001000	AZITHROMYCIN	4941	$ 70,636.15	8	4
5816004000	FLUOXETINE HCL	4767	$ 40,810.15	31	23
4155003000	LORATADINE	4758	$ 32,061.73	33	22
3620101010	CLONIDINE HCL	4750	$ 64,497.27	36	20
5710006000	LORAZEPAM	4740	$ 22,132.69	23	10
7250001010	DIVALPROEX SODIUM	4547	$ 395,479.50	54	19
2210004500	PREDNISONE	4518	$ 21,701.23	19	10
5925001500	ARIPIPRAZOLE	4152	$ 3,405,157.22	22	19
4927006000	OMEPRAZOLE	4147	$ 15,933.75	32	27
3760004000	HYDROCHLOROTHIAZIDE	4133	$ 19,162.82	28	27
5710004000	DIAZEPAM	3855	$ 19,643.93	43	19
3330000700	CARVEDILOL	3851	$ 24,015.93	47	23
4920003000	FAMOTIDINE	3761	$ 31,068.60	31	20
4927002510	ESOMEPRAZOLE MAGNESIUM	3711	$ 741,589.46	24	22
3615004020	LOSARTAN POTASSIUM	3571	$ 21,525.41	32	30
2710400300	INSULIN GLARGINE	3496	$ 881,286.25	13	26

Top 50 Drugs by Claim Count - Q3 2014

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	29338	$ 618,989.00	59	14
4420101010	ALBUTEROL SULFATE	16742	$ 713,263.14	37	16
3610003000	LISINOPRIL	13101	$ 68,700.96	30	25
5710001000	ALPRAZOLAM	11294	$ 92,530.23	50	21
7260003000	GABAPENTIN	10536	$ 185,170.10	71	22
6599000220	OXYCODONE W/ ACETAMINOPHEN	10244	$ 441,649.77	50	12
6610002000	IBUPROFEN	9664	$ 58,411.63	45	13
2810001010	LEVOTHYROXINE SODIUM	9481	$ 99,472.70	27	27
3400000310	AMLODIPINE BESYLATE	9119	$ 42,996.36	26	25
2725005000	METFORMIN HCL	8994	$ 66,856.80	53	26
6510007510	OXYCODONE HCL	8389	$ 609,521.64	76	17
6510005510	MORPHINE SULFATE	7911	$ 282,087.76	21	9
3940007500	SIMVASTATIN	7558	$ 43,174.73	28	28
5025006505	ONDANSETRON HCL	7365	$ 31,625.45	4	2
5915307010	QUETIAPINE FUMARATE	6847	$ 826,606.07	28	18
6510009510	TRAMADOL HCL	6636	$ 57,237.47	56	14
5812008010	TRAZODONE HCL	6625	$ 48,998.99	31	23
3940001010	ATORVASTATIN CALCIUM	6427	$ 71,736.04	23	23
9410003000	GLUCOSE BLOOD	6268	$ 748,719.26	67	20
3320003010	METOPROLOL TARTRATE	6017	$ 27,346.44	38	21
0120001010	AMOXICILLIN	5982	$ 46,071.50	51	6
4450505010	MONTELUKAST SODIUM	5915	$ 138,056.26	22	22
6020408010	ZOLPIDEM TARTRATE	5912	$ 43,644.50	23	23
6410001000	ASPIRIN	5859	$ 19,017.45	17	16
5907007000	RISPERIDONE	5831	$ 137,405.55	33	19
5816007010	SERTRALINE HCL	5788	$ 45,749.15	28	22
3720003000	FUROSEMIDE	5467	$ 21,636.80	27	21
5816002010	CITALOPRAM HYDROBROMIDE	5460	$ 30,281.53	24	22
5710006000	LORAZEPAM	5413	$ 22,429.53	19	9
4920002010	RANITIDINE HCL	5368	$ 50,383.36	45	22
7210001000	CLONAZEPAM	5240	$ 29,539.18	44	21
7510005010	CYCLOBENZAPRINE HCL	5121	$ 39,085.83	43	19
5816004000	FLUOXETINE HCL	4826	$ 46,273.14	29	22
4220003230	FLUTICASONE PROPIONATE (NASAL)	4722	$ 104,724.34	13	23
3620101010	CLONIDINE HCL	4597	$ 58,626.59	34	19
7250001010	DIVALPROEX SODIUM	4519	$ 391,547.41	48	16
4155003000	LORATADINE	4477	$ 29,125.42	30	21
2210004500	PREDNISONE	4309	$ 20,569.93	19	10
5925001500	ARIPIPRAZOLE	4085	$ 3,445,502.22	21	18
0340001000	AZITHROMYCIN	4053	$ 55,089.97	7	4
5710004000	DIAZEPAM	4046	$ 20,369.68	40	18
3760004000	HYDROCHLOROTHIAZIDE	4022	$ 18,784.13	26	26
3330000700	CARVEDILOL	3838	$ 23,158.82	44	21
4920003000	FAMOTIDINE	3729	$ 30,838.74	28	18
4120003010	DIPHENHYDRAMINE HCL	3721	$ 11,264.09	16	6
4927002510	ESOMEPRAZOLE MAGNESIUM	3679	$ 786,069.74	23	21
4927006000	OMEPRAZOLE	3603	$ 13,842.02	32	28
3615004020	LOSARTAN POTASSIUM	3561	$ 21,310.61	30	29
5025006500	ONDANSETRON	3425	$ 55,874.04	9	3
7260004300	LEVETIRACETAM	3399	$ 179,465.25	112	17

Top 50 Drugs by Claim Count - Q4 2014

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	22615	$ 491,601.83	55	13
4420101010	ALBUTEROL SULFATE	18082	$ 753,958.27	42	16
3610003000	LISINOPRIL	12423	$ 68,245.04	31	28
7260003000	GABAPENTIN	10661	$ 195,663.17	69	22
5710001000	ALPRAZOLAM	10565	$ 88,571.88	52	22
6599000220	OXYCODONE W/ ACETAMINOPHEN	10297	$ 483,437.76	51	12
6610002000	IBUPROFEN	9771	$ 60,767.95	47	13
2810001010	LEVOTHYROXINE SODIUM	9161	$ 98,696.16	28	28
3400000310	AMLODIPINE BESYLATE	8845	$ 43,406.79	27	26
2725005000	METFORMIN HCL	8707	$ 68,667.87	54	26
6510007510	OXYCODONE HCL	7825	$ 563,217.49	73	18
0120001010	AMOXICILLIN	7580	$ 63,406.59	63	6
3940007500	SIMVASTATIN	6960	$ 41,083.13	28	28
5915307010	QUETIAPINE FUMARATE	6610	$ 828,408.65	30	20
3940001010	ATORVASTATIN CALCIUM	6552	$ 77,301.22	26	26
5812008010	TRAZODONE HCL	6490	$ 50,704.17	32	24
5025006505	ONDANSETRON HCL	6235	$ 36,144.18	4	2
6510009510	TRAMADOL HCL	6213	$ 52,385.26	60	15
0340001000	AZITHROMYCIN	6125	$ 82,705.38	8	4
6510005510	MORPHINE SULFATE	6052	$ 256,449.38	30	12
9410003000	GLUCOSE BLOOD	5985	$ 727,299.29	70	21
5816007010	SERTRALINE HCL	5928	$ 48,325.71	27	22
3320003010	METOPROLOL TARTRATE	5831	$ 28,162.87	39	21
4450505010	MONTELUKAST SODIUM	5810	$ 141,311.22	21	21
6020408010	ZOLPIDEM TARTRATE	5619	$ 41,533.66	24	24
5907007000	RISPERIDONE	5413	$ 129,270.64	34	20
4920002010	RANITIDINE HCL	5352	$ 49,978.57	47	23
4220003230	FLUTICASONE PROPIONATE (NASAL)	5174	$ 117,045.11	12	23
6410001000	ASPIRIN	5128	$ 19,171.16	21	21
5816002010	CITALOPRAM HYDROBROMIDE	5056	$ 28,941.53	25	24
7510005010	CYCLOBENZAPRINE HCL	5030	$ 41,770.39	44	20
7210001000	CLONAZEPAM	4995	$ 29,860.87	46	22
3720003000	FUROSEMIDE	4769	$ 20,189.38	28	22
5816004000	FLUOXETINE HCL	4610	$ 51,135.58	29	22
3620101010	CLONIDINE HCL	4493	$ 54,750.27	38	21
4155003000	LORATADINE	4468	$ 30,270.52	33	21
5710006000	LORAZEPAM	4422	$ 25,378.35	24	11
2210004500	PREDNISONE	4417	$ 22,078.42	16	8
7250001010	DIVALPROEX SODIUM	4267	$ 392,241.84	53	18
5925001500	ARIPIPRAZOLE	4203	$ 3,636,167.83	21	18
5710004000	DIAZEPAM	3886	$ 19,821.21	43	19
4927002510	ESOMEPRAZOLE MAGNESIUM	3847	$ 840,377.85	23	22
3760004000	HYDROCHLOROTHIAZIDE	3809	$ 18,404.43	27	27
3615004020	LOSARTAN POTASSIUM	3589	$ 22,712.87	31	30
3330000700	CARVEDILOL	3549	$ 23,253.15	48	24
5025006500	ONDANSETRON	3443	$ 55,252.51	9	3
7720203200	CHOLECALCIFEROL	3428	$ 18,152.96	26	22
4920003000	FAMOTIDINE	3338	$ 26,771.27	31	19
7260004000	LAMOTRIGINE	3302	$ 189,153.92	45	21
7260004300	LEVETIRACETAM	3279	$ 175,214.12	110	17

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between Apr 1, 2014 and Jun 30, 2014

Jan 13, 2015
1:44:06 PM

Claims Summary:

RxCLAIM Status	Total Rxs	% of Total Rxs	Total Plan Paid	Total Member Paid
Paid	738,771	63.7%	$57,714,244.95	$0.00
Rejected	319,562	27.6%	$31,447,993.83	$0.00
Reversed	100,919	8.7%	-$13,052,639.94	$0.00
Totals	1,159,252	100%	$76,109,598.84	$0.00

DUR Information Summary:

		Total DURs		DURs on Paid Rxs		DURs on Rejected Rxs		DURs on Reversed Rxs	
DUR Type	Clinical Level	Count	% of All DURs	Count	% of DUR Type	Count	% of DUR Type	Count	% of DUR Type
TD - Therapeutic Duplication	0 - NS	67,470	23.1%	49,762	73.8%	7,960	11.8%	9,748	14.4%
LR - Underuse Precaution	0 - NS	55,312	19.0%	49,817	90.1%	0	0.0%	5,495	9.9%
ID - Ingredient Duplication	2 - Mod	48,928	16.8%	11,300	23.1%	34,444	70.4%	3,184	6.5%
DD - Drug-Drug Interaction	1 - Maj	38,723	13.3%	30,915	79.8%	3,608	9.3%	4,200	10.8%
HD - High Dose Alert	0 - NS	30,389	10.4%	24,688	81.2%	209	0.7%	5,492	18.1%
LD - Low Dose Alert	0 - NS	29,400	10.1%	24,320	82.7%	0	0.0%	5,080	17.3%
MN - Insufficnt Duration Alert	0 - NS	18,447	6.3%	13,215	71.6%	0	0.0%	5,232	28.4%
MX - Excessive Duration Alert	0 - NS	2,992	1.0%	2,707	90.5%	0	0.0%	285	9.5%
PA - Drug-Age Precaution	1 - Maj	70	0.0%	66	94.3%	0	0.0%	4	5.7%
SX - Drug Gender Alert	1 - Maj	1	0.0%	1	100.0%	0	0.0%	0	0.0%
Total All DURs		291,732	100.0%	206,791	70.9%	46,221	15.8%	38,720	13.3%

* DUR Information Summary results are sorted by Total DUR count in descending order
* Some Rx claims could have multiple DUR messages. And there could be multiple instances of the same DUR message on a Rx claim
* The Count and % of DUR Type for Paid, Rejected and Reversed Rxs are based on DUR Type totals for each row

DD - Drug-Drug Interaction

Rank	Top Drug Drug Interaction	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	CARISOPRODOL - ALPRAZOLAM	Message Only	1,096	$8,397.67	$7.66	$0.00	28.0	77.1	157	38	$463.16
2	OXYCODONE HCL - CARISOPRODOL	Message Only	567	$26,804.66	$47.27	$0.00	26.6	115.4	43	25	$808.21
3	OXYCODONE - CARISOPRODOL	Message Only	486	$4,198.77	$8.64	$0.00	28.1	83.5	73	37	$316.68
4	SIMVASTATIN - FENOFIBRATE	Message Only	442	$14,430.21	$32.65	$0.00	33.9	34.3	45	27	$1,137.04
5	OXYCOD/APAP - CARISOPRODOL	Message Only	344	$2,433.03	$7.07	$0.00	26.6	73.4	73	21	$96.77
6	OXYCODONE/ACETAMINOPHEN - CARISOPRODOL	Message Only	359	$20,315.88	$56.59	$0.00	23.9	99.6	30	20	$731.56
7	OMEPRAZOLE - CLOPIDOGREL	Message Only	333	$1,017.28	$3.05	$0.00	38.8	40.3	50	23	$92.65
8	METHADONE - ALPRAZOLAM	Message Only	348	$3,037.31	$8.73	$0.00	26.1	70.2	32	22	$110.01
9	SPIRONOLACT - LISINOPRIL	Message Only	308	$1,620.56	$5.26	$0.00	34.3	38.9	38	44	$117.80
10	SPIRONOLACTONE - LISINOPRIL	Message Only	306	$2,993.02	$9.78	$0.00	34.7	38.1	43	39	$244.79
All Others			26,326	$1,737,226.10	$65.99	$0.00	24.1	47.6	3,024	3,904	$210,263.93
DD - Drug-Drug Interaction			30,915	$1,822,474.49	$58.95	$0.00	24.9	51.1	3,608	4,200	$214,382.60

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

HD - High Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HECTOROL	GERIATRIC MAX DLY = 1.28UN	Message Only	2,157	$34,118.71	$15.82	$0.00	1.0	2.5	0	54	$812.91
2	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	875	$26,667.10	$30.48	$0.00	13.0	102.6	0	30	$1,144.48
3	POLYETHYLENE GLYCOL 3350	ADULT MAX DLY = 17.00 UN	Message Only	616	$16,497.08	$26.78	$0.00	28.1	569.2	0	46	$1,078.42
4	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	503	$1,746.43	$3.47	$0.00	1.0	4.3	0	56	$192.96
5	POLYETHYLENE GLYCOL 3350	PEDIATRIC MAX DLY = 17.00UN	Message Only	480	$13,546.47	$28.22	$0.00	28.6	542.8	0	67	$1,974.11
6	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	478	$1,252.22	$2.62	$0.00	29.3	29.9	0	29	$42.52
7	VENOFER	GERIATRIC MAX DLY = 3.57UN	Message Only	384	$25,472.88	$66.34	$0.00	1.0	13.5	0	22	$1,140.77
8	DIPHENHYDRAMINE HCL	GERIATRIC MAX DLY = 1.00UN	Message Only	183	$454.08	$2.48	$0.00	1.0	2.6	0	108	$293.07
9	POLYETHYLENE GLYCOL 3350	GERIATRIC MAX DLY = 17.00UN	Message Only	221	$1,268.07	$5.74	$0.00	29.2	553.5	0	42	$408.85
10	DEXAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 6.50UN	Message Only	163	$978.53	$6.00	$0.00	1.0	21.6	0	36	$185.85

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

RXT6050D - Summarized DUR Activity Report

Between Apr 1, 2014 and Jun 30, 2014

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
All Others				18,628	$5,885,072.07	$315.93	$0.00	11.6	263.4	209	5,002	$1,027,438.84
HD - High Dose Alert				24,688	$6,007,073.64	$243.32	$0.00	11.4	233.4	209	5,492	$1,034,712.78

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

ID - Ingredient Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 10-325MG	Hard Reject	4	$130.59	$32.65	$0.00	21.2	90.0	1,398	0	$0.00
2	EPOGEN	EPOGEN INJ 2000/ML	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	1,213	0	$0.00
3	EPOGEN	EPOGEN INJ 3000/ML	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	982	0	$0.00
4	EPOGEN	EPOGEN INJ 10000/ML	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	710	0	$0.00
5	EPOGEN	EPOGEN INJ 4000/ML	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	619	0	$0.00
6	OXYCODONE/ ACETAMINOPHEN	OXYCOD/APAP TAB 10-325MG	Hard Reject	4	$188.56	$47.14	$0.00	12.5	52.5	463	0	$0.00
7	ZOLPIDEM TARTRATE	ZOLPIDEM TAB 10MG	Hard Reject	1	$5.78	$5.78	$0.00	30.0	30.0	459	0	$0.00
8	SODIUM CHLORIDE	SOD CHLORIDE INJ 0.9%	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	451	0	$0.00
9	ALPRAZOLAM	ALPRAZOLAM TAB 2MG	Hard Reject	1	$6.38	$6.38	$0.00	7.0	14.0	427	0	$0.00
10	ALPRAZOLAM	ALPRAZOLAM TAB 1MG	Hard Reject	2	$15.27	$7.64	$0.00	18.5	55.5	381	0	$0.00
All Others				11,288	$1,568,683.29	$138.97	$0.00	26.7	105.1	27,341	3,184	$902,219.02
ID - Ingredient Duplication				11,300	$1,569,029.87	$138.85	$0.00	26.7	105.1	34,444	3,184	$902,219.02

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LD - Low Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	1,103	$465.23	$0.42	$0.00	1.4	1.3	0	816	$244.11
2	EPOGEN	GERIATRIC MIN DLY = .13UN	Message Only	1,182	$3,333.24	$2.82	$0.00	1.0	0.1	0	0	$0.00
3	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	568	$401.49	$0.71	$0.00	1.1	1.0	0	193	$129.53
4	ZOFRAN ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	520	$4,407.52	$8.48	$0.00	1.0	1.0	0	231	$1,796.27
5	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	484	$2,435.71	$5.03	$0.00	34.0	33.7	0	62	$277.58
6	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	426	$2,643.50	$6.21	$0.00	30.7	2.8	0	47	$289.46
7	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	368	$2,477.25	$6.73	$0.00	31.6	49.9	0	43	$255.41
8	IPRATROPIUM BROMIDE/ALBUT	GERIATRIC MIN DLY = 12.00UN	Message Only	251	$1,079.25	$4.30	$0.00	4.0	26.3	0	154	$246.62
9	METFORMIN HCL	GERIATRIC MIN DLY = 1.70UN	Message Only	285	$509.69	$1.79	$0.00	36.4	36.2	0	91	$80.86
10	CITALOPRAM HYDROBROMIDE	ADULT MIN DLY = 2.00 UN	Message Only	336	$2,018.79	$6.01	$0.00	29.4	29.3	0	26	$142.52
All Others				18,797	$1,625,606.86	$86.48	$0.00	22.6	51.0	0	3,417	$302,828.41
LD - Low Dose Alert				24,320	$1,645,378.53	$67.66	$0.00	20.2	42.1	0	5,080	$306,290.77

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LR - Underuse Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	90	$419.40	$4.66	$0.00	29.3	33.1	0	4	$23.14
2	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	71	$385.95	$5.44	$0.00	29.6	31.3	0	4	$18.04
3	LISINOPRIL	9 DAYS LATE REFILLING	Message Only	56	$307.33	$5.49	$0.00	29.2	32.9	0	3	$19.60
4	SIMVASTATIN	7 DAYS LATE REFILLING	Message Only	53	$316.53	$5.97	$0.00	29.6	29.6	0	4	$24.63
4	LEVOTHYROXINE SODIUM	8 DAYS LATE REFILLING	Message Only	49	$357.87	$7.30	$0.00	31.2	30.6	0	8	$59.65
6	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	53	$274.90	$5.19	$0.00	29.1	30.0	0	3	$14.18
6	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	50	$258.77	$5.18	$0.00	29.4	29.4	0	6	$26.16
8	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	46	$673.08	$14.63	$0.00	27.4	87.8	0	6	$120.58
9	MONTELUKAST SODIUM	7 DAYS LATE REFILLING	Message Only	43	$1,082.60	$25.18	$0.00	30.0	30.0	0	8	$145.75
9	PROAIR HFA	8 DAYS LATE REFILLING	Message Only	43	$1,830.67	$42.57	$0.00	22.7	9.3	0	8	$324.54
All Others				49,263	$3,911,321.95	$79.40	$0.00	28.4	51.6	0	5,441	$540,734.73
LR - Underuse Precaution				49,817	$3,917,229.05	$78.63	$0.00	28.4	51.4	0	5,495	$541,511.00

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MN - Insufficnt Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HECTOROL	MIN. DAYS THERAPY = 7	Message Only	2,442	$15,673.04	$6.42	$0.00	1.0	1.0	0	81	$586.59
2	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	477	$121.58	$0.25	$0.00	1.1	1.6	0	372	$27.71
3	PROTONIX	MIN. DAYS THERAPY = 7	Message Only	374	$1,261.96	$3.37	$0.00	1.1	1.1	0	308	$749.03
4	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	374	$122.74	$0.33	$0.00	1.1	1.8	0	267	$52.55
5	LIPITOR	MIN. DAYS THERAPY = 7	Message Only	270	$2,282.44	$8.45	$0.00	1.0	1.2	0	211	$1,901.14
6	CLONIDINE HCL	MIN. DAYS THERAPY = 7	Message Only	322	$259.37	$0.81	$0.00	1.4	3.1	0	155	$27.12
7	NICOTINE	MIN. DAYS THERAPY = 7	Message Only	276	$544.18	$1.97	$0.00	1.0	1.0	0	185	$360.62
8	FUROSEMIDE	MIN. DAYS THERAPY = 7	Message Only	246	$330.25	$1.34	$0.00	1.7	2.5	0	202	$80.39
9	AMLODIPINE BESYLATE	MIN. DAYS THERAPY = 7	Message Only	237	$162.23	$0.68	$0.00	1.2	1.4	0	172	$68.65
10	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	247	$107.73	$0.44	$0.00	1.2	1.2	0	157	$36.03
All Others				7,950	$318,111.30	$40.01	$0.00	3.0	18.4	0	3,122	$75,820.62
MN - Insufficnt Duration Alert				13,215	$338,976.82	$25.65	$0.00	2.3	11.6	0	5,232	$79,710.45

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MX - Excessive Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	480	$9,871.33	$20.57	$0.00	25.2	351.0	0	53	$1,234.91
2	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	216	$5,294.70	$24.51	$0.00	12.5	19.8	0	10	$154.01
3	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	180	$2,164.90	$12.03	$0.00	3.1	3.2	0	4	$66.55
4	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	169	$2,904.85	$17.19	$0.00	26.1	107.7	0	6	$96.00
5	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	150	$47,147.96	$314.32	$0.00	2.2	2.2	0	19	$6,099.71
6	PHENAZOPYRIDINE HCL	MAX DAYS THERAPY = 2	Message Only	144	$1,673.40	$11.62	$0.00	5.0	15.5	0	8	$139.86
7	TRAMADOL HYDROCHLORIDE/AC	MAX DAYS THERAPY = 5	Message Only	95	$1,975.47	$20.79	$0.00	22.7	80.7	0	11	$209.06
8	MAPAP	MAX DAYS THERAPY = 10	Message Only	88	$490.18	$5.57	$0.00	26.0	103.7	0	3	$19.46
9	CEFDINIR	MAX DAYS THERAPY = 10	Message Only	84	$5,339.74	$63.57	$0.00	15.0	67.7	0	4	$252.56
10	DOCUSATE SODIUM & SENNA S	MAX DAYS THERAPY = 14	Message Only	59	$333.77	$5.66	$0.00	30.6	57.0	0	4	$16.71
All Others				1,042	$230,148.65	$220.87	$0.00	28.0	93.3	0	163	$192,121.75
MX - Excessive Duration Alert				2,707	$307,344.95	$113.54	$0.00	21.3	117.2	0	285	$200,410.58

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

PA - Drug-Age Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	30	$214.48	$7.15	$0.00	13.6	117.4	0	1	$6.18
2	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	12	$70.89	$5.91	$0.00	8.1	78.8	0	0	$0.00
3	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	8	$48.72	$6.09	$0.00	13.2	84.4	0	0	$0.00
4	MULTI-VITAMINS	AGE LESS THAN 10	Message Only	2	$5.82	$2.91	$0.00	30.0	30.0	0	2	$5.82
5	GNP ESSENTIAL ONE DAILY	AGE LESS THAN 19	Message Only	3	$16.08	$5.36	$0.00	30.0	30.0	0	0	$0.00
5	MULTI-VITAMINS	AGE LESS THAN 19	Message Only	3	$15.15	$5.05	$0.00	30.0	30.0	0	0	$0.00
5	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	3	$13.07	$4.36	$0.00	3.3	53.3	0	0	$0.00
5	PROMETHAZINE/CODEINE	AGE LESS THAN 4	Message Only	2	$13.44	$6.72	$0.00	13.5	105.0	0	1	$4.95
9	MULTIPLE VITAMINS	AGE LESS THAN 10	Message Only	1	$3.19	$3.19	$0.00	30.0	30.0	0	0	$0.00
9	THERA/BETA-CAROTENE	AGE LESS THAN 19	Message Only	1	$5.93	$5.93	$0.00	30.0	30.0	0	0	$0.00
All Others				1	$23.98	$23.98	$0.00	5.0	20.0	0	0	$0.00
PA - Drug-Age Precaution				66	$430.75	$6.53	$0.00	14.4	88.4	0	4	$16.95

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

SX - Drug Gender Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	BICALUTAMIDE	GENERAL CONTRAINDICATION	Message Only	1	$16.84	$16.84	$0.00	30.0	30.0	0	0	$0.00
SX - Drug Gender Alert				1	$16.84	$16.84	$0.00	30.0	30.0	0	0	$0.00

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

TD - Therapeutic Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	2,695	$50,363.44	$18.69	$0.00	16.3	65.5	0	348	$2,467.58
2	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,213	$5,633.44	$4.64	$0.00	4.5	17.2	0	795	$1,839.03
3	OXYCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,535	$58,836.78	$38.33	$0.00	13.6	59.9	0	234	$2,099.08
4	OXYCODONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,364	$67,622.26	$49.58	$0.00	21.7	97.5	0	136	$2,296.13
5	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	957	$6,501.69	$6.79	$0.00	5.7	22.4	0	511	$1,732.12
6	TRAMADOL HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,003	$8,346.56	$8.32	$0.00	20.9	90.1	0	94	$384.41
7	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	1,002	$22,324.78	$22.28	$0.00	27.0	42.7	0	63	$1,079.33
8	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	866	$13,705.25	$15.83	$0.00	25.8	41.7	0	89	$1,003.42
9	ALPRAZOLAM	BENZODIAZEPINES	Message Only	850	$5,883.04	$6.92	$0.00	23.6	59.6	0	101	$239.60
10	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	644	$2,642.83	$4.10	$0.00	30.6	35.5	0	207	$340.27
All Others				37,633	$4,219,500.07	$112.12	$0.00	23.2	59.2	7,960	7,170	$594,618.57
TD - Therapeutic Duplication				49,762	$4,461,360.14	$89.65	$0.00	21.9	58.6	7,960	9,748	$608,099.54

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Primary Start Date:	Apr 1, 2014
Primary End Date:	Jun 30, 2014
Relative Date Description:	N/A
Select Report Group By:	Product
Top Values Displayed:	10
Display Report Description:	Yes

Report Description

Report overview:

This report will be used to track concurrent DURs. The subsequent information will also be used to assist clients in managing Hard Rejects, Soft Rejects as well as Message Only edits. Reversals are also included in the report.

Detail Line Description:

Column Name	Description
Summary Page:	
Claims Summary:	
RxCLAIM Status	The claims status associated with the RxCLAIM transaction. For this reoprt, a claim Status can be any one of the following values: P = Paid Status, X = Reversal Status, R = Rejected Status.
Total Rxs	The total number of Rxs.
% of Total Rxs	The percentage of the total number of Rxs.

Total Plan Paid	The Client Total Amount Due.
Total Member Paid	The Client Total Patient Pay Amount. The patient pay would include copays and all other charges paid by the member.

DUR Information Summary:

DUR Type	DUR Reason for Service Code and Description
Clinical Level	DUR (Drug Utilization Review). Indicates how significant the first conflict is. This field reflects the significance that the originating database assigned to it. 0 = Not specified, 1 = Major, 2 = Moderate, 3 = Minor
Total DURs	
Count	Total count of DUR edits. An Rx claim may have more than 1 DUR edit.
% of All DURs	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types.
DURs on Paid Rxs	
Count	Total count of DUR edits on paid Rx claims. A paid Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Paid Rx claims.
DURs on Rejected Rxs	
Count	Total count of DUR edits on rejected Rx claims. A rejected Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Rejected Rx claims.
DURs on Reversed Rxs	
Count	Total count of DUR edits on reversed Rx claims. A reversed Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Reversed Rx claims.

DUR Tabs:

Rank	Ranking is based on total number of Rxs (Paid + Rjected + Reversal) in descending order. A gap in sequence may occur if two or more rows tie (known as Olympic ranking).
Top Drug-Drug Interaction (DD Only)	Drug combination with a DD DUR code
Top Drug	Product Name
Therapy / Reason	DUR Free Text Message
DUR Response	DUR Responses are categorized as: H = Hard Reject, S = Soft Reject, any other code = Message Only
Total Paid Rxs	The total number of paid Rxs.
Total Plan Paid	The Client total amount due.
Avg Plan Paid / Rx	The average plan cost per Rx.

Avg Member Paid / Rx	The average member cost per Rx.
Avg Days Supply / Rx	The average days supply per Rx.
Avg Quantity / Rx	The average quantity per Rx.
Total Rejected Rxs	The total number of rejected Rxs.
Total Reversed Rxs	The total number of reversed Rxs.
Total Reversed Amount	The total amount of reversed Rxs.

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between Jul 1, 2014 and Sep 30, 2014

Jan 13, 2015
1:48:30 PM

Claims Summary:

RxCLAIM Status	Total Rxs	% of Total Rxs	Total Plan Paid	Total Member Paid
Paid	697,520	62.3%	$58,905,968.09	$0.00
Rejected	326,277	29.2%	$30,317,172.11	$0.00
Reversed	95,141	8.5%	-$12,110,667.86	$0.00
Totals	1,118,938	100%	$77,112,472.34	$0.00

DUR Information Summary:

		Total DURs		DURs on Paid Rxs		DURs on Rejected Rxs		DURs on Reversed Rxs	
DUR Type	Clinical Level	Count	% of All DURs	Count	% of DUR Type	Count	% of DUR Type	Count	% of DUR Type
TD - Therapeutic Duplication	0 - NS	64,761	23.8%	46,927	72.5%	7,437	11.5%	10,397	16.1%
LR - Underuse Precaution	0 - NS	57,271	21.1%	51,706	90.3%	0	0.0%	5,565	9.7%
ID - Ingredient Duplication	2 - Mod	44,974	16.6%	11,738	26.1%	29,723	66.1%	3,513	7.8%
DD - Drug-Drug Interaction	1 - Maj	38,368	14.1%	30,642	79.9%	3,280	8.5%	4,446	11.6%
LD - Low Dose Alert	0 - NS	26,454	9.7%	21,942	82.9%	0	0.0%	4,512	17.1%
HD - High Dose Alert	0 - NS	23,450	8.6%	19,417	82.8%	161	0.7%	3,872	16.5%
MN - Insufficnt Duration Alert	0 - NS	13,190	4.9%	8,991	68.2%	0	0.0%	4,199	31.8%
MX - Excessive Duration Alert	0 - NS	3,177	1.2%	2,841	89.4%	0	0.0%	336	10.6%
PA - Drug-Age Precaution	1 - Maj	35	0.0%	32	91.4%	0	0.0%	3	8.6%
Total All DURs		271,680	100.0%	194,236	71.5%	40,601	14.9%	36,843	13.6%

* DUR Information Summary results are sorted by Total DUR count in descending order
* Some Rx claims could have multiple DUR messages. And there could be multiple instances of the same DUR message on a Rx claim
* The Count and % of DUR Type for Paid, Rejected and Reversed Rxs are based on DUR Type totals for each row

DD - Drug-Drug Interaction

Rank	Top Drug Drug Interaction	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	CARISOPRODOL - ALPRAZOLAM	Message Only	1,015	$7,513.78	$7.40	$0.00	27.9	77.4	127	39	$246.18
2	OXYCODONE - CARISOPRODOL	Message Only	459	$4,221.21	$9.20	$0.00	28.4	81.8	72	20	$764.86
3	OXYCODONE HCL - CARISOPRODOL	Message Only	472	$23,227.78	$49.21	$0.00	27.0	114.9	45	15	$771.49
4	SIMVASTATIN - FENOFIBRATE	Message Only	425	$14,024.41	$33.00	$0.00	34.7	35.1	54	28	$1,505.70
5	TRAZODONE HCL - CITALOPRAM	Message Only	388	$2,961.46	$7.63	$0.00	29.0	36.1	47	20	$143.22
6	TRAZODONE - CITALOPRAM HYDROBROMIDE	Message Only	362	$1,897.17	$5.24	$0.00	28.5	30.5	40	20	$114.83
7	OXYCOD/APAP - CARISOPRODOL	Message Only	325	$2,309.58	$7.11	$0.00	26.5	74.7	42	15	$103.65
8	SPIRONOLACTONE - LISINOPRIL	Message Only	292	$2,548.04	$8.73	$0.00	35.4	38.0	45	42	$288.18
9	OXYCODONE/ACETAMINOPHEN - CARISOPRODOL	Message Only	332	$19,462.47	$58.62	$0.00	25.1	105.9	31	10	$432.64
10	METHADONE - ALPRAZOLAM	Message Only	331	$2,905.45	$8.78	$0.00	26.4	71.8	21	13	$72.03
All Others			26,241	$1,890,645.39	$72.05	$0.00	24.4	47.5	2,756	4,224	$303,981.81
DD - Drug-Drug Interaction			30,642	$1,971,716.74	$64.35	$0.00	25.0	50.6	3,280	4,446	$308,424.59

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

HD - High Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	865	$29,205.39	$33.76	$0.00	13.8	109.6	0	32	$915.67
2	POLYETHYLENE GLYCOL 3350	ADULT MAX DLY = 17.00 UN	Message Only	644	$17,323.73	$26.90	$0.00	27.9	560.2	0	64	$1,637.51
3	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	492	$1,823.73	$3.71	$0.00	1.0	4.2	0	58	$208.04
4	POLYETHYLENE GLYCOL 3350	PEDIATRIC MAX DLY = 17.00UN	Message Only	472	$13,605.98	$28.83	$0.00	28.3	546.6	0	76	$2,191.75
5	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	394	$1,205.59	$3.06	$0.00	29.4	29.4	0	12	$153.77
6	DIPHENHYDRAMINE HCL	GERIATRIC MAX DLY = 1.00UN	Message Only	162	$377.56	$2.33	$0.00	1.0	2.4	0	115	$261.09
7	GRANISETRON HCL	GERIATRIC MAX DLY = .85UN	Message Only	242	$27,250.72	$112.61	$0.00	1.0	5.9	0	4	$262.01
8	POLYETHYLENE GLYCOL 3350	GERIATRIC MAX DLY = 17.00UN	Message Only	193	$1,368.77	$7.09	$0.00	27.6	530.0	0	21	$157.62
9	DEXAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 6.50UN	Message Only	197	$947.76	$4.81	$0.00	1.0	14.8	0	9	$62.67
10	NEXIUM	ADULT MAX DLY = 1.00 UN	Message Only	168	$74,626.14	$444.20	$0.00	28.7	57.4	0	12	$4,579.59
All Others				15,588	$4,366,059.86	$280.09	$0.00	12.6	122.2	161	3,469	$767,342.09
HD - High Dose Alert				19,417	$4,533,795.23	$233.50	$0.00	13.5	141.6	161	3,872	$777,771.81

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

ID - Ingredient Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 10-325MG	Hard Reject	5	$146.93	$29.39	$0.00	14.8	79.2	1,394	0	$0.00
2	SODIUM CHLORIDE	SOD CHLORIDE INJ 0.9%	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	489	0	$0.00
3	ZOLPIDEM TARTRATE	ZOLPIDEM TAB 10MG	Hard Reject	1	$5.00	$5.00	$0.00	7.0	7.0	473	0	$0.00
4	OXYCODONE/ ACETAMINOPHEN	OXYCOD/APAP TAB 10-325MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	448	0	$0.00
5	ALPRAZOLAM	ALPRAZOLAM TAB 1MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	378	0	$0.00
6	ALPRAZOLAM	ALPRAZOLAM TAB 2MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	354	0	$0.00
7	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 5-325MG	Hard Reject	2	$17.23	$8.62	$0.00	2.0	12.5	351	0	$0.00
8	CARISOPRODOL	CARISOPRODOL TAB 350MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	307	0	$0.00
9	CLONAZEPAM	CLONAZEPAM TAB 1MG	Hard Reject	3	$18.79	$6.26	$0.00	23.3	50.0	298	0	$0.00
10	CLONAZEPAM	CLONAZEPAM TAB 0.5MG	Hard Reject	2	$12.15	$6.08	$0.00	30.0	60.0	293	0	$0.00
All Others				11,725	$2,364,423.61	$201.66	$0.00	26.6	139.0	24,938	3,513	$441,593.98
ID - Ingredient Duplication				11,738	$2,364,623.71	$201.45	$0.00	26.6	138.9	29,723	3,513	$441,593.98

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LD - Low Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	1,072	$429.58	$0.40	$0.00	1.7	1.6	0	678	$174.83
2	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	575	$407.31	$0.71	$0.00	1.2	1.1	0	200	$135.53
3	ZOFRAN ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	380	$8,084.66	$21.28	$0.00	1.0	1.0	0	179	$3,810.11
4	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	456	$2,342.27	$5.14	$0.00	34.8	34.4	0	50	$261.22
5	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	442	$2,716.08	$6.14	$0.00	30.6	2.7	0	39	$240.86
6	CITALOPRAM HYDROBROMIDE	ADULT MIN DLY = 2.00 UN	Message Only	396	$2,376.45	$6.00	$0.00	28.9	28.7	0	30	$187.61
7	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	388	$2,664.54	$6.87	$0.00	32.2	52.8	0	30	$221.62
8	ONDANSETRON HCL	ADULT MIN DLY = 2.00 UN	Message Only	336	$2,493.27	$7.42	$0.00	18.3	11.0	0	19	$154.48
9	PROPRANOLOL HCL	ADULT MIN DLY = 3.00 UN	Message Only	279	$1,569.26	$5.62	$0.00	27.4	48.8	0	19	$115.77
10	IPRATROPIUM BROMIDE/ALBUT	GERIATRIC MIN DLY = 12.00UN	Message Only	194	$562.58	$2.90	$0.00	4.1	23.2	0	103	$174.75
All Others				17,424	$1,921,720.99	$110.29	$0.00	23.7	54.6	0	3,165	$421,062.30
LD - Low Dose Alert				21,942	$1,945,366.99	$88.66	$0.00	22.1	46.7	0	4,512	$426,539.08

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LR - Underuse Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	LEVOTHYROXINE SODIUM	7 DAYS LATE REFILLING	Message Only	65	$534.96	$8.23	$0.00	29.6	29.6	0	4	$36.70
2	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	61	$292.54	$4.80	$0.00	29.6	31.6	0	2	$9.74
2	LISINOPRIL	9 DAYS LATE REFILLING	Message Only	61	$295.23	$4.84	$0.00	30.0	32.2	0	2	$9.45
4	METFORMIN HCL	7 DAYS LATE REFILLING	Message Only	57	$351.14	$6.16	$0.00	29.6	62.5	0	3	$13.23
5	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	54	$248.86	$4.61	$0.00	30.7	31.9	0	3	$18.13
6	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	53	$224.42	$4.23	$0.00	30.0	30.6	0	3	$13.40
7	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	51	$745.28	$14.61	$0.00	29.4	101.9	0	3	$83.24
8	SIMVASTATIN	7 DAYS LATE REFILLING	Message Only	48	$280.44	$5.84	$0.00	29.5	29.5	0	3	$9.14
9	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	48	$217.26	$4.53	$0.00	30.0	31.3	0	2	$6.25
10	PROAIR HFA	11 DAYS LATE REFILLING	Message Only	47	$2,336.55	$49.71	$0.00	19.4	8.9	0	1	$52.89
All Others				51,161	$4,099,564.81	$80.13	$0.00	28.8	51.0	0	5,539	$614,843.59
LR - Underuse Precaution				51,706	$4,105,091.49	$79.39	$0.00	28.8	50.9	0	5,565	$615,095.76

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MN - Insufficnt Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	395	$57.78	$0.15	$0.00	1.0	1.7	0	286	$24.81
2	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	376	$74.45	$0.20	$0.00	1.0	1.1	0	291	$56.32
3	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	283	$56.17	$0.20	$0.00	1.1	1.7	0	185	$12.28
4	CLONIDINE HCL	MIN. DAYS THERAPY = 7	Message Only	268	$188.88	$0.70	$0.00	1.3	3.0	0	144	$24.05
5	LEVOTHYROXINE SODIUM	MIN. DAYS THERAPY = 10	Message Only	302	$1,434.47	$4.75	$0.00	6.1	6.7	0	49	$95.91
6	CIPROFLOXACIN HCL	MIN. DAYS THERAPY = 5	Message Only	282	$769.46	$2.73	$0.00	2.0	3.6	0	63	$40.77
7	OLANZAPINE	MIN. DAYS THERAPY = 7	Message Only	242	$254.18	$1.05	$0.00	1.1	1.9	0	88	$96.82
8	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	Message Only	153	$84.40	$0.55	$0.00	1.1	1.3	0	167	$75.76
9	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	285	$8,130.73	$28.53	$0.00	8.6	131.2	0	24	$792.07
10		ING01 MIN DAYS THERAPY = 5	Message Only	297	$30,589.33	$102.99	$0.00	1.5	75.4	0	5	$668.47
All Others				6,108	$259,855.16	$42.54	$0.00	2.8	14.7	0	2,897	$61,409.17
MN - Insufficnt Duration Alert				8,991	$301,495.01	$33.53	$0.00	2.7	17.3	0	4,199	$63,296.43

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MX - Excessive Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	497	$10,926.16	$21.98	$0.00	25.5	331.3	0	55	$1,542.18
2	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	212	$5,277.51	$24.89	$0.00	12.1	18.7	0	10	$376.55
3	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	176	$59,899.28	$340.34	$0.00	2.2	2.2	0	32	$11,034.28
4	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	162	$2,007.79	$12.39	$0.00	3.2	3.2	0	7	$89.73
5	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	158	$3,032.41	$19.19	$0.00	25.4	98.9	0	10	$109.62
6	PHENAZOPYRIDINE HCL	MAX DAYS THERAPY = 2	Message Only	161	$3,037.11	$18.86	$0.00	5.3	16.3	0	5	$184.52
7	EPIPEN-JR 2-PAK	MAX DAYS THERAPY = 1	Message Only	92	$36,915.02	$401.25	$0.00	2.5	2.5	0	23	$8,825.47
8	TRAMADOL HYDROCHLORIDE/AC	MAX DAYS THERAPY = 5	Message Only	97	$2,263.70	$23.34	$0.00	19.5	86.4	0	12	$238.64
9	MAPAP	MAX DAYS THERAPY = 10	Message Only	99	$548.59	$5.54	$0.00	26.7	100.1	0	3	$16.89
10	DOCUSATE SODIUM & SENNA S	MAX DAYS THERAPY = 14	Message Only	69	$407.91	$5.91	$0.00	31.3	63.4	0	7	$47.50
All Others				1,118	$180,679.86	$161.61	$0.00	28.0	91.7	0	172	$76,809.56
MX - Excessive Duration Alert				2,841	$304,995.34	$107.35	$0.00	20.8	110.2	0	336	$99,274.94

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

PA - Drug-Age Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	11	$83.12	$7.56	$0.00	7.1	95.5	0	0	$0.00
2	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	10	$62.59	$6.26	$0.00	10.3	76.9	0	0	$0.00
3	PROMETHAZINE VC PLAIN	AGE LESS THAN 4	Message Only	3	$48.72	$16.24	$0.00	12.0	100.0	0	0	$0.00
3	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	3	$17.77	$5.92	$0.00	8.7	75.0	0	0	$0.00
5	INFANRIX	AGE GREATER THAN 64	Message Only	1	$43.74	$43.74	$0.00	1.0	1.0	0	1	$43.74
5	MULTI-VITAMIN	AGE LESS THAN 10	Message Only	1	$5.55	$5.55	$0.00	30.0	30.0	0	1	$5.55
5	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	2	$10.32	$5.16	$0.00	8.0	85.0	0	0	$0.00
8	MULTI-VITAMINS	AGE LESS THAN 10	Message Only	0	$0.00	$0.00	$0.00	0.00	0.00	0	1	$5.05
8	PROMETHAZINE/CODEINE	AGE LESS THAN 4	Message Only	1	$7.00	$7.00	$0.00	8.0	120.0	0	0	$0.00
PA - Drug-Age Precaution				32	$278.81	$8.71	$0.00	9.3	83.3	0	3	$54.34

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

TD - Therapeutic Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	2,522	$47,444.36	$18.81	$0.00	15.7	63.4	0	313	$1,943.15
2	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,281	$4,966.26	$3.88	$0.00	3.5	11.9	0	864	$1,820.48
3	OXYCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,508	$53,732.57	$35.63	$0.00	13.3	55.9	0	298	$2,106.36
4	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	975	$5,907.75	$6.06	$0.00	5.3	21.3	0	522	$1,545.12
5	OXYCODONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,322	$67,187.47	$50.82	$0.00	22.4	99.9	0	151	$2,512.61
6	TRAMADOL HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,006	$8,569.20	$8.52	$0.00	21.0	88.4	0	93	$485.23
7	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	1,022	$22,452.57	$21.97	$0.00	27.6	41.9	0	76	$1,603.59
8	ALPRAZOLAM	BENZODIAZEPINES	Message Only	818	$5,848.11	$7.15	$0.00	24.1	61.6	0	81	$232.12
9	LORAZEPAM	BENZODIAZEPINES	Message Only	629	$2,040.83	$3.24	$0.00	11.5	24.9	0	240	$244.11
10	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	610	$2,421.62	$3.97	$0.00	29.5	32.7	0	247	$269.35
All Others				35,234	$4,565,444.88	$129.57	$0.00	23.6	59.7	7,437	7,512	$714,197.15
TD - Therapeutic Duplication				46,927	$4,786,015.62	$101.99	$0.00	21.8	58.2	7,437	10,397	$726,959.27

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Primary Start Date:	Jul 1, 2014
Primary End Date:	Sep 30, 2014
Relative Date Description:	N/A
Select Report Group By:	Product
Top Values Displayed:	10
Display Report Description:	Yes

Report Description

Report overview:

This report will be used to track concurrent DURs. The subsequent information will also be used to assist clients in managing Hard Rejects, Soft Rejects as well as Message Only edits. Reversals are also included in the report.

Detail Line Description:

Column Name	Description
Summary Page:	
Claims Summary:	
RxCLAIM Status	The claims status associated with the RxCLAIM transaction. For this reoprt, a claim Status can be any one of the following values: P = Paid Status, X = Reversal Status, R = Rejected Status.
Total Rxs	The total number of Rxs.
% of Total Rxs	The percentage of the total number of Rxs.

Total Plan Paid	The Client Total Amount Due.
Total Member Paid	The Client Total Patient Pay Amount. The patient pay would include copays and all other charges paid by the member.

DUR Information Summary:

DUR Type	DUR Reason for Service Code and Description
Clinical Level	DUR (Drug Utilization Review). Indicates how significant the first conflict is. This field reflects the significance that the originating database assigned to it. 0 = Not specified, 1 = Major, 2 = Moderate, 3 = Minor
Total DURs	
Count	Total count of DUR edits. An Rx claim may have more than 1 DUR edit.
% of All DURs	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types.
DURs on Paid Rxs	
Count	Total count of DUR edits on paid Rx claims. A paid Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Paid Rx claims.
DURs on Rejected Rxs	
Count	Total count of DUR edits on rejected Rx claims. A rejected Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Rejected Rx claims.
DURs on Reversed Rxs	
Count	Total count of DUR edits on reversed Rx claims. A reversed Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Reversed Rx claims.

DUR Tabs:

Rank	Ranking is based on total number of Rxs (Paid + Rjected + Reversal) in descending order. A gap in sequence may occur if two or more rows tie (known as Olympic ranking).
Top Drug-Drug Interaction (DD Only)	Drug combination with a DD DUR code
Top Drug	Product Name
Therapy / Reason	DUR Free Text Message
DUR Response	DUR Responses are categorized as: H = Hard Reject, S = Soft Reject, any other code = Message Only
Total Paid Rxs	The total number of paid Rxs.
Total Plan Paid	The Client total amount due.
Avg Plan Paid / Rx	The average plan cost per Rx.

Avg Member Paid / Rx	The average member cost per Rx.
Avg Days Supply / Rx	The average days supply per Rx.
Avg Quantity / Rx	The average quantity per Rx.
Total Rejected Rxs	The total number of rejected Rxs.
Total Reversed Rxs	The total number of reversed Rxs.
Total Reversed Amount	The total amount of reversed Rxs.

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between Oct 1, 2014 and Dec 31, 2014

Jan 13, 2015
3:14:33 PM

Claims Summary:

RxCLAIM Status	Total Rxs	% of Total Rxs	Total Plan Paid	Total Member Paid
Paid	669,114	64.9%	$62,158,754.84	$0.00
Rejected	283,325	27.5%	$40,969,480.24	$0.00
Reversed	78,736	7.6%	-$13,791,232.46	$0.00
Totals	1,031,175	100%	$89,337,002.62	$0.00

DUR Information Summary:

		Total DURs		DURs on Paid Rxs		DURs on Rejected Rxs		DURs on Reversed Rxs	
DUR Type	Clinical Level	Count	% of All DURs	Count	% of DUR Type	Count	% of DUR Type	Count	% of DUR Type
LR - Underuse Precaution	0 - NS	56,821	22.8%	51,327	90.3%	0	0.0%	5,494	9.7%
TD - Therapeutic Duplication	0 - NS	56,687	22.7%	42,122	74.3%	7,414	13.1%	7,151	12.6%
ID - Ingredient Duplication	2 - Mod	45,384	18.2%	11,688	25.8%	30,589	67.4%	3,107	6.8%
DD - Drug-Drug Interaction	1 - Maj	35,093	14.1%	28,606	81.5%	3,487	9.9%	3,000	8.5%
LD - Low Dose Alert	0 - NS	23,888	9.6%	20,293	85.0%	0	0.0%	3,595	15.0%
HD - High Dose Alert	0 - NS	18,352	7.4%	16,142	88.0%	180	1.0%	2,030	11.1%
MN - Insufficnt Duration Alert	0 - NS	8,863	3.6%	6,291	71.0%	0	0.0%	2,572	29.0%
MX - Excessive Duration Alert	0 - NS	4,242	1.7%	3,872	91.3%	0	0.0%	370	8.7%
PA - Drug-Age Precaution	1 - Maj	44	0.0%	38	86.4%	0	0.0%	6	13.6%
Total All DURs		249,374	100.0%	180,379	72.3%	41,670	16.7%	27,325	11.0%

* DUR Information Summary results are sorted by Total DUR count in descending order
* Some Rx claims could have multiple DUR messages. And there could be multiple instances of the same DUR message on a Rx claim
* The Count and % of DUR Type for Paid, Rejected and Reversed Rxs are based on DUR Type totals for each row

DD - Drug-Drug Interaction

Rank	Top Drug Drug Interaction	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	CARISOPRODOL - ALPRAZOLAM	Message Only	840	$6,502.86	$7.74	$0.00	28.0	76.7	126	38	$290.04
2	OXYCODONE HCL - CARISOPRODOL	Message Only	416	$20,277.30	$48.74	$0.00	27.8	116.5	36	14	$632.71
3	OXYCODONE - CARISOPRODOL	Message Only	384	$3,785.02	$9.86	$0.00	29.2	83.1	56	16	$113.24
4	SIMVASTATIN - FENOFIBRATE	Message Only	341	$13,612.82	$39.92	$0.00	33.6	33.8	69	25	$825.85
5	TRAZODONE HCL - CITALOPRAM	Message Only	368	$3,581.28	$9.73	$0.00	30.1	38.0	35	19	$409.20
6	OXYCODONE/ACETAMINOPHEN - CARISOPRODOL	Message Only	343	$22,217.59	$64.77	$0.00	26.5	109.1	45	25	$2,024.38
7	OXYCOD/APAP - CARISOPRODOL	Message Only	312	$2,273.16	$7.29	$0.00	28.4	77.6	53	20	$133.71
8	TRAZODONE HCL - QUETIAPINE	Message Only	329	$2,274.11	$6.91	$0.00	27.0	38.8	34	11	$39.15
9	TRAZODONE - CITALOPRAM HYDROBROMIDE	Message Only	317	$1,817.02	$5.73	$0.00	29.7	31.8	38	17	$94.21
10	SPIRONOLACT - LISINOPRIL	Message Only	287	$1,532.79	$5.34	$0.00	37.0	41.6	40	19	$68.53
All Others			24,669	$2,075,769.24	$84.14	$0.00	25.5	48.5	2,955	2,796	$259,493.91
DD - Drug-Drug Interaction			28,606	$2,153,643.19	$75.29	$0.00	26.0	51.2	3,487	3,000	$264,124.93

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

HD - High Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	569	$18,788.06	$33.02	$0.00	14.5	114.9	0	33	$1,566.09
2	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	342	$1,080.45	$3.16	$0.00	29.9	29.9	0	16	$42.00
3	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	299	$1,376.39	$4.60	$0.00	1.0	4.3	0	48	$205.77
4	POLYETHYLENE GLYCOL 3350	ADULT MAX DLY = 17.00 UN	Message Only	246	$6,513.82	$26.48	$0.00	28.1	555.3	0	25	$609.58
5	POLYETHYLENE GLYCOL 3350	PEDIATRIC MAX DLY = 17.00UN	Message Only	166	$4,752.82	$28.63	$0.00	28.4	545.6	0	24	$711.73
6	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	181	$339,231.09	$1,874.20	$0.00	26.6	1.5	0	6	$11,520.48
7	MIDAZOLAM HCL	GERIATRIC MAX DLY = .70UN	Message Only	179	$922.92	$5.16	$0.00	1.0	5.7	0	2	$1.80
8	CELESTONE-SOLUSPAN	GERIATRIC MAX DLY = 1.50UN	Message Only	168	$4,704.38	$28.00	$0.00	1.0	4.0	0	2	$91.41
9	ONDANSETRON ODT	ADULT MAX DLY = 3.00 UN	Message Only	140	$3,472.78	$24.81	$0.00	6.7	26.4	0	26	$684.61
10	IBUPROFEN	ADULT MAX DLY = 4.00 UN	Message Only	159	$964.99	$6.07	$0.00	7.5	35.6	0	3	$19.34
All Others				13,693	$2,862,054.62	$209.02	$0.00	13.8	122.2	180	1,845	$466,409.78
HD - High Dose Alert				16,142	$3,243,862.32	$200.96	$0.00	14.0	123.2	180	2,030	$481,862.59

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

ID - Ingredient Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 10-325MG	Hard Reject	5	$191.13	$38.23	$0.00	17.8	108.0	1,161	0	$0.00
2	OXYCODONE/ ACETAMINOPHEN	OXYCOD/APAP TAB 10-325MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	497	0	$0.00
3	ZOLPIDEM TARTRATE	ZOLPIDEM TAB 10MG	Hard Reject	2	$11.56	$5.78	$0.00	30.0	30.0	468	0	$0.00
4	ALPRAZOLAM	ALPRAZOLAM TAB 1MG	Hard Reject	1	$6.22	$6.22	$0.00	8.0	30.0	425	0	$0.00
5	SODIUM CHLORIDE	SOD CHLORIDE INJ 0.9%	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	425	0	$0.00
6	TRAMADOL HCL	TRAMADOL HCL TAB 50MG	Hard Reject	1	$7.87	$7.87	$0.00	7.0	56.0	409	0	$0.00
7	ALPRAZOLAM	ALPRAZOLAM TAB 2MG	Hard Reject	0	$0.00	$0.00	$0.00	0.00	0.00	389	0	$0.00
8	PROAIR HFA	PROAIR HFA AER	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	336	0	$0.00
9	GABAPENTIN	GABAPENTIN CAP 300MG	Soft Reject	0	$0.00	$0.00	$0.00	0.00	0.00	326	0	$0.00
10	CLONAZEPAM	CLONAZEPAM TAB 1MG	Hard Reject	2	$12.14	$6.07	$0.00	22.5	45.0	312	0	$0.00
All Others				11,677	$3,171,850.00	$271.63	$0.00	27.3	184.9	25,841	3,107	$401,953.35
ID - Ingredient Duplication				11,688	$3,172,078.92	$271.40	$0.00	27.3	184.8	30,589	3,107	$401,953.35

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LD - Low Dose Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	687	$316.15	$0.46	$0.00	1.9	1.8	0	413	$119.25
2	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	526	$331.40	$0.63	$0.00	1.3	1.1	0	150	$99.46
3	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	450	$2,332.30	$5.18	$0.00	35.2	34.9	0	28	$147.25
4	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	379	$2,331.73	$6.15	$0.00	30.9	2.7	0	35	$222.44
5	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	371	$2,629.55	$7.09	$0.00	30.1	49.4	0	30	$217.85
6	CITALOPRAM HYDROBROMIDE	ADULT MIN DLY = 2.00 UN	Message Only	360	$2,163.19	$6.01	$0.00	28.7	28.7	0	34	$210.27
7	IPRATROPIUM BROMIDE/ALBUT	GERIATRIC MIN DLY = 12.00UN	Message Only	251	$727.47	$2.90	$0.00	3.4	18.6	0	122	$118.75
8	ZOFRAN ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	253	$5,312.95	$21.00	$0.00	1.0	1.0	0	79	$1,683.49
9	ONDANSETRON HCL	ADULT MIN DLY = 2.00 UN	Message Only	290	$2,292.97	$7.91	$0.00	19.4	12.0	0	26	$204.48
10	PROPRANOLOL HCL	ADULT MIN DLY = 3.00 UN	Message Only	249	$1,402.02	$5.63	$0.00	28.6	52.4	0	17	$97.59
All Others				16,477	$1,953,705.72	$118.57	$0.00	24.4	57.8	0	2,661	$344,409.31
LD - Low Dose Alert				20,293	$1,973,545.45	$97.25	$0.00	23.0	50.3	0	3,595	$347,530.14

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

LR - Underuse Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	83	$417.20	$5.03	$0.00	29.3	32.1	0	5	$26.14
2	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	62	$350.02	$5.65	$0.00	30.6	34.5	0	8	$38.71
3	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	61	$319.22	$5.23	$0.00	29.6	29.4	0	3	$18.83
4	SIMVASTATIN	7 DAYS LATE REFILLING	Message Only	60	$411.82	$6.86	$0.00	30.0	30.2	0	3	$26.06
4	LISINOPRIL	9 DAYS LATE REFILLING	Message Only	59	$298.49	$5.06	$0.00	30.0	32.8	0	4	$19.57
6	LEVOTHYROXINE SODIUM	7 DAYS LATE REFILLING	Message Only	59	$430.53	$7.30	$0.00	30.0	29.2	0	3	$45.62
7	LISINOPRIL	10 DAYS LATE REFILLING	Message Only	48	$251.56	$5.24	$0.00	29.5	31.4	0	3	$17.09
8	PROAIR HFA	11 DAYS LATE REFILLING	Message Only	47	$2,189.89	$46.59	$0.00	21.7	9.2	0	3	$303.09
9	PROAIR HFA	7 DAYS LATE REFILLING	Message Only	48	$2,145.10	$44.69	$0.00	24.2	8.9	0	1	$101.03
9	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	43	$226.41	$5.27	$0.00	30.0	30.7	0	6	$39.38
All Others				50,757	$4,368,294.68	$86.06	$0.00	28.6	51.2	0	5,455	$612,086.93
LR - Underuse Precaution				51,327	$4,375,334.92	$85.24	$0.00	28.6	50.9	0	5,494	$612,722.45

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MN - Insufficnt Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	361	$10,712.14	$29.67	$0.00	9.0	133.8	0	33	$532.98
2	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	204	$36.38	$0.18	$0.00	1.0	1.1	0	174	$36.16
3		ING01 MIN DAYS THERAPY = 5	Message Only	319	$39,236.46	$123.00	$0.00	1.6	30.3	0	20	$1,882.43
4	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	168	$56.20	$0.33	$0.00	1.1	1.4	0	130	$12.56
5	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	177	$61.98	$0.35	$0.00	1.2	1.9	0	116	$30.41
6	LEVOTHYROXINE SODIUM	MIN. DAYS THERAPY = 10	Message Only	255	$1,095.30	$4.30	$0.00	6.1	6.1	0	23	$26.41
7	LEVETIRACETAM	MIN. DAYS THERAPY = 14	Message Only	258	$2,727.23	$10.57	$0.00	6.8	32.3	0	9	$49.49
8	OLANZAPINE	MIN. DAYS THERAPY = 7	Message Only	141	$143.98	$1.02	$0.00	1.1	1.8	0	112	$96.58
9	SULFAMETHOXAZOLE/ TRIMETHO	MIN. DAYS THERAPY = 5	Message Only	198	$606.85	$3.06	$0.00	1.9	7.1	0	46	$103.41
10	NICOTINE	MIN. DAYS THERAPY = 7	Message Only	130	$252.57	$1.94	$0.00	1.0	1.0	0	99	$193.84
All Others				4,080	$216,057.53	$52.96	$0.00	3.0	21.2	0	1,810	$49,507.07
MN - Insufficnt Duration Alert				6,291	$270,986.62	$43.08	$0.00	3.3	24.9	0	2,572	$52,471.34

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

MX - Excessive Duration Alert

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	1,410	$10,860.05	$7.70	$0.00	30.3	65.3	0	96	$771.11
2	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	281	$6,588.74	$23.45	$0.00	11.6	19.2	0	32	$842.14
3	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	250	$6,184.26	$24.74	$0.00	26.5	266.6	0	40	$1,093.64
4	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	176	$2,244.10	$12.75	$0.00	3.4	3.5	0	13	$220.55
5	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	147	$2,697.43	$18.35	$0.00	25.6	106.7	0	7	$167.32
6	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	129	$47,831.30	$370.79	$0.00	2.2	2.2	0	20	$9,375.33
7	MAPAP	MAX DAYS THERAPY = 10	Message Only	126	$714.27	$5.67	$0.00	26.3	108.8	0	2	$10.98
8	PHENAZOPYRIDINE HCL	MAX DAYS THERAPY = 2	Message Only	107	$1,972.62	$18.44	$0.00	4.4	13.7	0	5	$168.59
9	TRAMADOL HYDROCHLORIDE/AC	MAX DAYS THERAPY = 5	Message Only	96	$2,156.62	$22.46	$0.00	18.7	71.2	0	7	$124.34
10	CEFDINIR	MAX DAYS THERAPY = 10	Message Only	79	$4,349.15	$55.05	$0.00	15.2	73.6	0	2	$171.62
All Others				1,071	$176,568.42	$164.86	$0.00	27.1	77.6	0	146	$69,786.55
MX - Excessive Duration Alert				3,872	$262,166.96	$67.71	$0.00	24.1	75.3	0	370	$82,732.17

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

PA - Drug-Age Precaution

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	13	$92.08	$7.08	$0.00	10.2	101.5	0	0	$0.00
2	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	10	$62.76	$6.28	$0.00	11.2	98.0	0	2	$16.94
3	PROMETHAZINE/CODEINE	AGE LESS THAN 4	Message Only	6	$40.70	$6.78	$0.00	16.8	108.3	0	1	$7.00
4	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	4	$35.07	$8.77	$0.00	9.5	70.0	0	2	$14.27
5	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	2	$12.43	$6.22	$0.00	4.0	75.0	0	1	$4.00
6	PROMETHEGAN	AGE LESS THAN 4	Message Only	2	$28.74	$14.37	$0.00	3.5	10.0	0	0	$0.00
7	PROMETHAZINE VC PLAIN	AGE LESS THAN 4	Message Only	1	$16.74	$16.74	$0.00	12.0	90.0	0	0	$0.00
PA - Drug-Age Precaution				38	$288.52	$7.59	$0.00	10.8	91.8	0	6	$42.21

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

TD - Therapeutic Duplication

Rank	Top Drug	Therapy / Reason	DUR Response	Total Paid Rxs	Total Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx	Total Rejected Rxs	Total Reversed Rxs	Total Reversed Amount
1	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,821	$37,623.27	$20.66	$0.00	17.6	72.2	0	191	$2,475.74
2	OXYCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,243	$50,036.55	$40.25	$0.00	14.7	62.1	0	192	$2,633.25
3	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	810	$5,999.26	$7.41	$0.00	5.9	22.4	0	421	$1,521.96
4	OXYCODONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,120	$55,871.84	$49.89	$0.00	23.3	106.7	0	102	$2,629.58
5	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	1,028	$22,621.49	$22.01	$0.00	27.2	41.5	0	80	$1,064.36
6	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	709	$4,307.57	$6.08	$0.00	5.9	19.5	0	376	$1,015.45
7	TRAMADOL HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	884	$7,519.90	$8.51	$0.00	19.8	84.4	0	61	$354.80
8	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	750	$11,964.83	$15.95	$0.00	26.7	43.6	0	73	$779.76
9	ALPRAZOLAM	BENZODIAZEPINES	Message Only	753	$5,707.04	$7.58	$0.00	25.4	63.7	0	56	$241.66
10	METHADONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	657	$10,795.01	$16.43	$0.00	27.4	135.9	0	27	$523.53
All Others				32,347	$4,474,070.44	$138.31	$0.00	24.9	62.7	7,414	5,572	$720,213.34
TD - Therapeutic Duplication				42,122	$4,686,517.20	$111.26	$0.00	23.6	63.5	7,414	7,151	$733,453.43

* Rankings are based on the following order: Total Rxs (Paid + Rejected + Reversed) descending, total Rejected Rxs descending and Top Drug/Client Rider ascending.

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Primary Start Date:	Oct 1, 2014
Primary End Date:	Dec 31, 2014
Relative Date Description:	N/A
Select Report Group By:	Product
Top Values Displayed:	10
Display Report Description:	Yes

Report Description

Report overview:

This report will be used to track concurrent DURs. The subsequent information will also be used to assist clients in managing Hard Rejects, Soft Rejects as well as Message Only edits. Reversals are also included in the report.

Detail Line Description:

Column Name	Description
Summary Page:	
Claims Summary:	
RxCLAIM Status	The claims status associated with the RxCLAIM transaction. For this reoprt, a claim Status can be any one of the following values: P = Paid Status, X = Reversal Status, R = Rejected Status.
Total Rxs	The total number of Rxs.
% of Total Rxs	The percentage of the total number of Rxs.

Total Plan Paid	The Client Total Amount Due.
Total Member Paid	The Client Total Patient Pay Amount. The patient pay would include copays and all other charges paid by the member.

DUR Information Summary:

DUR Type	DUR Reason for Service Code and Description
Clinical Level	DUR (Drug Utilization Review). Indicates how significant the first conflict is. This field reflects the significance that the originating database assigned to it. 0 = Not specified, 1 = Major, 2 = Moderate, 3 = Minor
Total DURs	
Count	Total count of DUR edits. An Rx claim may have more than 1 DUR edit.
% of All DURs	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types.
DURs on Paid Rxs	
Count	Total count of DUR edits on paid Rx claims. A paid Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Paid Rx claims.
DURs on Rejected Rxs	
Count	Total count of DUR edits on rejected Rx claims. A rejected Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Rejected Rx claims.
DURs on Reversed Rxs	
Count	Total count of DUR edits on reversed Rx claims. A reversed Rx claim may have more than 1 DUR edit.
% of DUR Type	The percentage is based on the total number of each unique DUR Type divided by the total number of all DUR Types on Reversed Rx claims.

DUR Tabs:

Rank	Ranking is based on total number of Rxs (Paid + Rjected + Reversal) in descending order. A gap in sequence may occur if two or more rows tie (known as Olympic ranking).
Top Drug-Drug Interaction (DD Only)	Drug combination with a DD DUR code
Top Drug	Product Name
Therapy / Reason	DUR Free Text Message
DUR Response	DUR Responses are categorized as: H = Hard Reject, S = Soft Reject, any other code = Message Only
Total Paid Rxs	The total number of paid Rxs.
Total Plan Paid	The Client total amount due.
Avg Plan Paid / Rx	The average plan cost per Rx.

Avg Member Paid / Rx	The average member cost per Rx.
Avg Days Supply / Rx	The average days supply per Rx.
Avg Quantity / Rx	The average quantity per Rx.
Total Rejected Rxs	The total number of rejected Rxs.
Total Reversed Rxs	The total number of reversed Rxs.
Total Reversed Amount	The total amount of reversed Rxs.