BRIAN SANDOVAL
*Governor*

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# NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

## AGENDA

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| **Date of Posting:** | **January 2, 2017** |
| **Date of Revision:** | **January 5, 2018** |
| **Date of Meeting:** | **Thursday, January 25, 2018 at 5:15 PM** |
| **Name of Organization:** | **The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP), Drug Use Review (DUR) Board** |
| **Place of Meeting:** | **Hyatt Place Reno – Tahoe Airport**<br>**1790 E. Plumb Lane**<br>**Reno, NV 89502**<br>**Phone: (775) 826-2500** |
| **Webinar Registration:** | **https://optum.webex.com/optum/onstage/g.php?MTID=e99bcf29e25e940176440dc3f0bbfad9c**<br><br>**Or go to www.webex.com and enter the Event Number listed below.**<br><br>**Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.** |
| **Event Number:** | **646 593 142**<br><br>**Click "Join Now"**<br>**Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet.** |

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**Phone: (763) 957-6300**
**Event: 646 593 142**

## 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 October 19, 2017.

b. Status Update by the DHCFP.

c. **For Possible Action**: Review and Approve updated DUR Bylaws.

**4. Clinical Presentations**

a. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for deutetrabenazine (Austedo®).

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.

b. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for betrixaban (Bevyxxa ®).

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.

c. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for belimumab (Benlysta®).

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 possible adoption of updated prior authorization criteria and/or quantity limits for Hepatitis C Direct-Acting Antiviral agents.

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.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Immunomodulator agents.

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.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Opioid-Induced Constipation Agents.

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.

**5. Public Comment on any DUR Board Requested Report**

**6. DUR Board Requested Reports**

a. Utilization of medications with Orphan Designation.

i. Discussion by the Board and review of utilization data.
ii. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

b. Opioid utilization – Members under age 18 years.

i. Discussion by the Board and review of utilization data.
ii. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

c. Opioid Utilization – Top prescriber and member.

i. Discussion by the Board and review of utilization data.

ii. **For Possible Action**: Requests for further evaluation or proposed clinical criteria to be presented at a later date.

**7. Public Comment on any Standard DUR Report**

**8. Standard DUR Reports**

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q1 2011, Q2 2017 and Q3 2017 (by Payment and by Claims).
ii. Top 50 Drugs of Q1 2011, Q2 2017 and Q3 2017 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR)

i. Review of Q1 2011, Q2 2017 and Q3 2017.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR)

i. Status of previous quarter.
ii. Status of current quarter.
iii. Review and discussion of responses.

**9. 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.

**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 five minutes.**

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**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 copy of the meeting materials will be mailed to you. Requests and/or written comments may be sent to Robyn Heddy 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 accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at cmclach@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Colleen McLachlan at (775) 684-3722.**

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# DRUG USE REVIEW BOARD

## Meeting Minutes

**Date of Meeting:** **Thursday, October 19, 2017 at 5:15 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:** **Hyatt Place Reno-Tahoe Airport**
**1790 E. Plumb Ln**
**Reno, NV 89502**
**Phone: (775) 826-2500**

**Event Number:** **315 214 493**

**Phone: 1-763-957-6300**
**Event: 315 214 493**

## Attendees

**Board Members (Present)**
Paul Oesterman, Pharm.D.
James Marx, MD
Michael Owens, MD
Marta Bunuel, MD

**Board Members (Absent)**
David England, Pharm.D.
Chris Shea, Pharm.D.
Jennifer Wheeler, Pharm.D.
Michael Casal, MD

**Reno**

**DHCFP:**
Darrell Faircloth, Deputy Attorney General
Holly Long, Social Services Program Specialist
Duane Young, Chief, DHCFP

**DXC:**
Beth Slamowitz, Pharm.D.

**OptumRx:**
Carl Jeffery, Pharm.D.

**Public:**
Niren Shah, PTC Bio
Don Moran, Teva
Deron Grothe, Teva
Nera Hartman, Neurocrine
Lisa Stroup, Neurocrine
Mark Swartz, GSK
Christy Lemons, Orexo

**Teleconference:**
Joanna Jacob, Ferrari
Stephanie Ferrell, DXC
Anastacia Marvi, DXC
Johnna Young, DXC
Jeannine Murray, Anthem
Ryan Bitton, HPN



**AGENDA**

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

The meeting called to order at 5:39PM.

Paul Oesterman, Chair: We're going to go ahead and call the meeting of the Drug Utilization Review Board to order. We'll start off with a roll call.

Beth Slamowitz: Beth Slamowitz, DXC Technology

Duane Young: Duane Young DHCFP

Holly Long: Holly Long, DHCFP

Carl Jeffery: Carl Jeffery, OptumRx

Marta Bunuel: Marta Bunuel, Psychiatrist

Paul Oesterman, Chair: Paul Oesterman, Pharmacist

Darrell Faircloth: Darrell Faircloth, Senior Deputy Attorney General's office

James Marx: James Marx, Physician, Las Vegas

Michael Owens: Mike Owens, Physician, Reno

Dr. Casal on the phone

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

Paul Oesterman, Chair: So we do have a quorum so we will go through our agenda and we'll start off by asking if anybody in the audience, either online or in person, who has any public comment on any matter on the agenda. If you have one specific agenda item you can make public comment at that time. Also just as a reminder public comment is limited to five minutes. Seeing no comment or hearing none... You know we do have one. Please provide us with your name and who you are with and your topic.

Christy Lemons: Absolutely. Good evening and thank you for the opportunity to be here tonight. My name is Christy Lemons, I am the National Account Director at Arexa Pharmaceuticals. I am here on behalf of requesting consideration around opioid dependence treatment. Specifically, given not only the known national epidemic, but also to consider the President's recent elevation of opioid dependence as a state of national emergency. I would like to read to you a brief statement by the President. President Trump's Commission on Combating Drug Addiction and the Opioid Crisis. Dated August 17, 2017. All FDA approved medication assisted treatment should be offered by authorized providers. Not just one or two of these approved options. These decisions of which medications to treatment used must be based upon what is best for the patient. I would like to hand out for your review a copy of ASAMS standards of care for the addiction specialists around opioid dependence and also thanks for your time and attention and ask you to consider parody for all opioid dependence treatments for this very important treatment area. Any questions?

Marta Bunuel: Just one. Is it all opiate and does it also include heroin and anything else that is an opiate, not just prescribed treatments to seek parity for all addiction treatment?

Christy Lemons: We refer to all opioid dependence treatment including Zubsolve and Suboxone and other generics and brand in that area.

James Marx: As the only Drug Utilization Review Board now, does that mean that all the Fee For Service and the managed Medicaid, do we all use the same criteria? Or do they get independent criteria to what we have here?

Duane Young: So, yes. They do have independent criteria so what this establishes going forward is they have to adopt whatever criteria we have here. So we may have to revisit certain drugs or certain criteria that we have done in the past.

## 3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from August 24, 2017

Paul Oesterman, Chair: We have the minutes from the August 24 meeting, they need to be reviewed and I will ask after a moment of review for a motion and second.

James Marx: I move to approve as submitted, Jim Marx.

Marta Bunuel: I second.

Paul Oesterman, Chair: We have a motion and a second, any discussion? Hearing and seeing none, I'll call for a question. All those who approve say Aye. Those oppose say nay, all abstaining. I was not in that meeting so I can't comment. They are approved.

b. Status Update by DHCFP

Paul Oesterman, Chair: We're going to start with our clinical presentations And Our First. Oh, Status.

Duane Young: Going to public hearing on next Wednesday will be the state plan amendment change to offer 12 months of contraceptives. This was done by our legislature and two bills of Assembly Bill 249 and Senate bill 233. Both protections around women's health. We will be one of the first states to offer a 12 month contraceptive package in the state plan. The policy will be a bit more intricate as it will allow for three months and then a renewal of six months and then after six months they can renew each year. It will be a stepped in policy. For the purpose of the state plan we only outline 12 months. Also going back to the workshop October 26 is the added services for adult podiatry, registered dietitians and medical nutrition therapy and then our gender reassignment surgery. Those will hopefully be added to the state plan beginning January 1st as well as we were given budget authority during the last legislative session.

Marta Bunuel: Why is the birth control in three months then six months?

Duane Young: In order to get all the various insurance providers to sign off on it, they agreed that they do it phased in so that people can get three months supply initially and if they don't like it or they want to try something else and they can do that. So it would allow them some kind of choice before they're locked in for an entire year supply.

Paul Oesterman, Chair: So on the six months, will they only get six months at a time or three months because most of the time we do a 90 day fill?

Duane Young: They do 90 days until they are locked into the one that they like and then move to six months and then a year.

Michael Owens: Forgive me, is it only oral contraceptives. Do we cover intrauterine devices?

Duane Young: Yes, those are covered as well. So it's a little bit different with the implant.

Paul Oesterman, Chair: Same with that Depo-Provera I guess.

**4. Clinical Presentations**

a. **For Possible Action:** Discussion and possible adoption of prior authorization criteria and/or quantity limits for deutetrabenazine (Austedo®)

Paul Oesterman, Chair: We'll start with the Clinical presentations. Our first presentation is in regards to the discussion of a possible adoption of prior authorization criteria and or quantity limits for Austedo. We will ask if there is anyone in the audience. Please step up to the mic and introduce yourself. Your five minutes start when you start.

Don Moran: (Difficult to hear on recording) – I'm Don a pharmacist with medical affairs for Teva. Offered some observations, Austedo approved for Huntington's chorea, a rare condition with a progressive and fatal outcome. Also has a high rate of depression and suicide ideation. Five months later the FDA approve an indication for tardive dyskinesia. The coverage criteria are focused on the treatment of Huntington's disease, but excludes tardive dyskinesia. Requested the board also discuss the tardive dyskinesia indication.

Paul Oesterman, Chair: Thank you for your presentation. Just one word of caution. Right now we have in front of us the prior authorization for that one indication. The second indication which you're talking about was not on the agenda. I don't believe we can take action on that.

Darrell Faircloth: I believe you are correct. I'm not sure this is within what you've proposed to do. So let's agendize it for a later time. Because it would include other drugs as well.

Carl Jeffery: So it says that the agenda is just the drug name. It doesn't talk about any indications. So it has the indication for the tardive dyskinesia and it did come out after we put these guidelines together so that's why it's not in there. There is criteria under the Ingrezza tab for tardive dyskinesia that I would propose the board adopt also for Austedo because it would also qualify. I don't want to get you out of your comfort zone so if you rather us bring this back for the next time to talk about tardive dyskinesia or if the board is able to do it now.

Darrell Faircloth: If you can independently incorporate the criteria for this drug that seems appropriate. You did agendize this drug and limitations and approval criteria for this drug. I don't see a problem doing it that way.

Carl Jeffery: No there wouldn't be any other drug involved.

Don Moran: Thank you, my hope was for not seeing it on the agenda that meant the product would be excluded.

Carl Jeffery: Duane brought up a good point. Because we have to incorporate the MCO data with this too. We didn't give them an opportunity to opine on any kind of proposed criterion. We may bring this back next time and maybe it would be fairer. OK. So this time we are going to talk about the criteria for Huntington's chorea. I think and just for completeness sake what will happen is we'll tell the PA call center if they get requests for tardive dyskinesia there won't be any criteria, they will just approve it based on the requested indication. So we're transitioning to kind of a different format for the DUR Board because we're incorporating the MCO data too. In your binders there is proposed criteria from OptumRx on page 17. On the next page the criteria that one MCO that submitted and this is from Amerigroup. In the future we may have the other two additional criteria to incorporate together. Amerigroup had some exclusion criteria that would say that people would be excluded if they're suicidal or treated inadequately for depression or have hepatic

impairment or utilizing an MAOI. It comes down to a diagnosis of Huntington's chorea and is prescribed by or in consultation with a neurologist.

Holly Long: Did we also want to include the age 18 requirement?

Carl Jeffery: No I didn't say that but we can add that. My understanding of the diagnosis of Huntington's chorea is really not diagnosed until 40s or 50s anyway. So I don't know that it is that critical, but we can certainly put it in.

Paul Oesterman, Chair: For safety's sake I think it should be in there. In terms of the two criteria it appears the Amerigroup criteria encompasses everything the Optum criteria has plus some additional points like 18 years of age or older and contraindications.

Carl Jeffery: Amerigroup doesn't include the requirement for being a neurologist.

Paul Oesterman, Chair: I propose we approve the Amerigroup criteria with the addition that a neurologist has been consulted.

Carl Jeffery: We had our initial authorization would be for three months and then 12 months after that based on a response to therapy.

Paul Oesterman, Chair: This will be a small number of patients who will be getting this. I will ask for a motion and a second to approve the criteria that's on the page with the addition of the consultation with neurologist being bullet point three.

Marta Bunuel: So it doesn't need to be prescribed by a neurologist just in consultation with one.

Paul Oesterman, Chair: Right. Rural Nevada provides a few challenges.

Marta Bunuel: Yes.

James Marx: And initial authorization of three months.

Paul Oesterman, Chair: I'm good with 12 months.

James Marx: I so move.

Marta Bunuel: Second.

Paul Oesterman, Chair: We have a motion and we have a second any further discussion. We'll make sure Dr. Casal is still on the line.

Dr. Casal: Still Here.

Paul Oesterman, Chair: Okay. Speak up if you have any comments or questions. Any further discussion? Hearing none I will call for the question, all those in favor of the proposed criteria for Austedo indicate by saying aye. All opposed say nay. Motion carries.

James Marx: Is the Amerigroup utilization per quarter or year or what?

Carl Jeffery: That's a good question. They didn't specify. The page where you see the Amerigroup utilization go ahead and tear that out because you will need to reference that in the future because they put all their utilization on one page.

Duane Young: We asked them for a year.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Cerliponase Alfa (Brineura ®)

Paul Oesterman, Chair: Our Second product is discussing the possible adoption of prior authorization criteria and or quantity limits of the Brinuera product. Is there anybody in the audience or on the phone who wishes to address the board? Seeing none, we will go ahead and take a look at the criteria here, Carl.

Carl Jeffery: Again this is out of my realm of expertise. This is an extremely rare condition, late infantile neuronal ceroid lipofuscinosis type 2. Brinura is indicated to treat this. It's a rare brain disorder, I was trying to read and understand how it all works is kind of a dysfunction how the brain metabolizes lipids. Our criteria here I think we're a little bit more strict than the Amerigroup criteria. We just wanted to make sure we have some safeguards in place to be sure that this was not going to be used inappropriately or outside the indication. I don't know what the price is but I'm sure it's not cheap and it has to be given intrathecally every two weeks. It's not an easy medication to give. We don't have any claims for it yet. My proposed criteria which is somewhat problematic requires a lab test to diagnosis and confirm this TPP1 enzyme is detected by dry blood spot tests. The state currently does not reimburse for that test. So I don't know if that's in the works or I'm not sure how you're going to diagnose this without the gene test.

James Marx: This is an insurmountable barrier.

Beth Slamowitz: There are ways to get the test. They have to apply for it.

Carl Jeffery: Our criteria is just the diagnosis and then avoiding the contradiction. So if they have a VP shunt or any kind of intraventricular access and in consultation of neurologist with expertise in the diagnosis of this disorder. And then under the care of a physician knowledgeable in intraventricular administration. It does have to be given intrathecally in a three year old which I don't think is an easy task.

James Marx: The indication is to slow the process. So they are ultimately going to lose the ability to ambulate?

Carl Jeffery: That's my understanding of the disease progress. It just slows it

Marta Bunuel: Do you know how long it slows it? For years maybe.

Carl Jeffery: They have some studies that show that the clinical efficacy. They needed to study it for the whole 96 weeks to see any kind of significant change. And so it's not a real significant change.

Paul Oesterman, Chair: It's a five year extension phase starting.

Marta Bunuel: I wondered about this phrase before, "With expertise in the diagnosis." How does the neurologist demonstrate expertise? Is there criteria?

Carl Jeffery: I think it's a valid question. I think it's a concern because is it just a physician who read an article, does that qualify them as being an expert? How does the call center judge that? I think sometimes you just have to put trust in the prescriber's office that they know what they are doing.

Michael Owens: All these kids are going to come from large centers, Davis, Stanford, and UCSF. And then will be farmed out to [local specialists], these are kids that are going to be coming from study centers because that's where they are going to get diagnosed. All of those orders are going to come through and have a neurologist here in Reno but the origins of the medications are going to come from large teaching centers. You might find one that sneaks through miraculously.

Paul Oesterman, Chair: For now it seems that one of our concerns is to have the ability for the diagnostic test done but there are options for patients. That's not going to be a barrier to approving. Going out of sequence here, I would ask that for the next meeting, could we see some utilization data on these orphan drug products to see what kind of use there is? I feel like the Optum criteria is a little bit more finite and descriptive. Those include the criteria from Amerigroup. Can I get a motion to approve?

James Marx: I move to approve the Optum criteria.

Paul Oesterman, Chair: I will second it, is there any further discussion.

Marta Bunuel: When the disease is so rare and patients are put on treatments like this, do they also automatically get included and the information sent to perhaps one of the centers so the study can continue in a way?

Paul Oesterman, Chair: I would think not necessarily. If it was being conducted as an investigational agent then it should be provided at no charge by the company. That's something to see if patients for whom this is prescribed if they are in the clinical trial then that should not be impacting us. So we have a motion and a second. Any further discussion? Hearing none, I will call for the question. All those in favor of approval of the Optum presented criteria for the Brinuera product indicate so by saying aye. All opposed say nay. The motion carries.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Valbenazine (Ingrezza®)

Paul Oesterman, Chair: Okay, our next product that we are discussing is the valbenazine or Ingrezza. I will ask if there's anybody here in the audience, on the phone or in person. I know we have one in person here. So is there anybody on the phone wishing to discuss that. If not we will ask our guest in the audience to step forward.

Lisa Stroup: Thanks for having us here, my name is Lisa Stroup, I am the neuropsychologist and medical liaison with Nurocrine biosciences. Nurocrine is excited to hear approval of the first medication indicated for tardive dyskinesia in adults. Ingrezza is a new chemical entity. Covers

approval process. There was a discrepancy around the modifiers to the diagnosis, the DSM 5 is the gold standard for diagnosis. There are no modifiers in the DSM criteria.

Marta Bunuel: I'm assuming this would not be a first line medication. There are other things that we try in the meanwhile, aside from discontinuation. I'm not saying they don't work well. I'm just wondering.

Lisa Stroup: This is the first medication indicated for TD. So if you go to the guidelines, we are not in there yet. They were last updated in 2013, there was not a level A recommendation. Level B was for gingko biloba and clonazepam. There are no strong studies. APA was most recently updated in 2009, they suggested a second generation over a first and consider reduction of the dose, but there is some question with that recommendation. There was a recent epidemiological study looking at prevalence in first generation vs. second generations and second generation reduced and was better but did not eliminate TD.

Paul Oesterman, Chair: There are mixed reviews for the use of benztropine, it is not an approved indication, however we still see it fairly widely. Are there any studies comparing and contrasting the two products?

Lisa Stroup: No, we actually allowed patients on benztropine. The interesting thing if you talk to a movement disorder neurologist, they typically advise that benztropine could be contraindicated in a hyperkinetic movement disorder. In something like Parkinson's in a hypokinetic disorder, benztropine would be expected to reduce those symptoms, but the evidence is not there to support its use. We did go ahead and include and do some sub-analysis. When broken down by those on benztropine vs. not, the ones on benztropine had a more robust response.

Paul Oesterman, Chair: There's no black box warning?

Lisa Stroup: No and nor were there any signals seen in our trials for increased depressive symptoms or suicidal ideation.

Michael Owens: For tardive dyskinesia, so this is a not a permanent illness?

Lisa Stroup: It often is. If you take a patient off all their dopamine blocking agents, you can still see this indefinitely.

Michael Owens: Okay, all right.

Marta Bunuel: Over time it seems to be related to the amount of exposure, length of time and total dose exposure. At least is seems to be once they start showing.

Michael Owens: Discontinued medications that kind of thing doesn't help?

Marta Bunuel: If you catch it quickly, some people certainly do stop it. Now you're in this dilemma, are you going to go to Clozapine or Seroquel or one of these other ones that are not strong on the dopamine blockade or are more specific or at least in terms of their striatal dopamine blockade. They've probably been tried of many things already, is my guess. How bad is their psychosis,

what is the impact on them perhaps. And people around them versus letting them have the movement disorder.

Michael Owens: For prior authorization we always ask, have you tried this and this and this. So if you really don't have much room for argument for trying a couple different medications and get back with us.

Lisa Stroup: Once you have gone through the hard work of stabilizing a patient, to be asked to reduce or destabilize the patient is a big ask. Discusses trial including how the movement disorders were rated.

Michael Owens: Are there and indications for Tourette's?

Lisa Stroup: We are just starting a phase 2 study in pediatrics. To date, we had a phase two in adults and pediatrics. Both failed to hit, especially in the pediatric trial, but there were some benefits so we are starting a new trial this month in ages 6 to 17.

Holly Long: I have a question. A couple of the other states included in their PA criteria that they require chart notes confirming no suicidal thoughts or violent behavior or has stable psychiatric symptoms and we don't have that.

Lisa Stroup: I'm not sure what that is a response to. It may be a black box warning on other medications. We didn't' rule out a rule history of suicidal or psychiatric symptoms. About 40% of the sample had a history of suicidal ideation. The patients in the trials did not show any changes in their psychiatric stability over the 48 weeks of the trials.

Paul Oesterman, Chair: There are pieces and parts from both criteria that are good. I would like to see a blend of the two where we use the diagnosis based on the DSM 5 criteria, the duration of treatment from Amerigroup criteria is good. The contraindications are pretty similar. The Amerigroup criteria did not include the patient not being a candidate for a trial dose reduction or discontinuation of the offending medication.

Carl Jeffery: Yeah I think it's worth consideration. It's going to be the exception. But if they have a patient and they can probably do without this they stop it and their symptoms get better, fantastic. I know it's going to be rare but if one out of 100 can do without it.

Paul Oesterman, Chair: Do we have consensus here for the blended criteria?

Carl Jeffery: On the screen, we're going to use the DSM 5 criteria for a diagnosis of tardive dyskinesia.

Paul Oesterman, Chair: And I like the A and B components from Amerigroup.

Carl Jeffery: And then the patient is 18 years or older. So one of the following the patient has persistent symptoms of tardive dyskinesia despite a trail dose reduction tapering or discontinuation, or the patient is not a candidate for a trial reduction tapering or discontinuation and prescribed in consultation with a neurologist or psychiatrist.

Paul Oesterman, Chair: Yes. And this is one I think the initial authorization of three months makes sense.

Michael Owens: Is there any wiggle room on the age restrictions?

Carl Jeffery: Do you really see TD in under 18?

Marta Bunuel: I don't have extensive experience with children, the atypicals are usually the ones to be approved first for them, and so the incidence in theory is less. I don't know all the study data. But I think it would be pretty unlikely to see a child, but I don't know if there are other studies that show something else.

Lisa Stroup: We don't have data for children. Tardive dyskinesia increases with age and exposure. There are cases and it does happen, but we do not have data for the pediatrics.

Carl Jeffery: You can see on the screen the criteria from a and b from Amerigroup. Everything else look good?

Paul Oesterman, Chair: We have a request for a motion to approve the revised and updated criteria for valbenazine.

Marta Bunuel: Motion to approve.

James Marx: Second.

Paul Oesterman, Chair: We have a motion and a second. Any further discussion? Hearing and seeing none, we will call for the question, all those in favor say aye, all those oppose say nay. The motion carries.

d. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Safinamide (Xadago®)

Paul Oesterman, Chair: Our next topic is the discussion and possible adoption of updated prior authorization criteria and or quantity limits of safinamide or Xadago. Do we have any public comment, in the audience or via phone? Hearing none, we will go ahead with the criteria.

Carl Jeffery: Xadago is indicated for Parkinson's disease who experience an off episode. The study participants had to have an off-episode for at least one hour. They have the freezing episodes. They had some strict criteria about what else needs to be with it, it needs to have a dopamine agent and that is why we wanted to bring it to the board to make sure these patients are not getting this as a monotherapy where is wouldn't be effective. That reflects our criteria, they have a diagnosis of Parkinson's disease, and they will continue on their dopamine agent and have 1.5 hours of off-period per day.

Paul Oesterman, Chair: The Amerigroup has their list of preferred and non-preferred agents. Does that mirror what we have?

Carl Jeffery: We don't have this class in our preferred drug list, so they are technically all preferred.

Paul Oesterman, Chair: I would like to request we look at these at the next meeting to bring consistency between the two groups.

Carl Jeffery: The P&T handles the preferred and non-preferred.

Paul Oesterman, Chair: OK, I would like to recommend the P&T handle this class.

Carl Jeffery: Okay, we have some of these. We have the pramipexole and ropinirole in a class. It is something the MCO's are still allowed to have their own preferred drug list, they are not required to follow ours.

Paul Oesterman, Chair: To me this is an example of we are going to have a difficult time with a single criteria. If you look at Amerigroup's approval criteria, you can't incorporate that into ours.

Carl Jeffery: I don't know how that incorporates with their PDL. If they have a requirement to try two preferred agents before getting a non-preferred, and we don't have that requirement, I'm not sure how that will work.

Duane Young: Whatever criteria we adopt, they won't require the true preferred.

Carl Jeffery: They couldn't require two agents first, so that would essentially be preferred.

Duane Young: What they do on their cost containment is a little different. Technically if we adopt criteria they do not have to have two fails, they would have to abide by that.

Darrell Faircloth: Are all the preferred generics? Is that the basis of their differentiation?

Paul Oesterman, Chair: No, they have some generics as non-preferred. They already have this product as a non-preferred agent. Where does apo-morphine stand on our formulary?

Carl Jeffery: We don't have that class, so it would be open access.

Paul Oesterman, Chair: Do we know in their trials how long it took to notice improvement?

Carl Jeffery: I don't remember seeing that. It was a 24 week study.

Paul Oesterman, Chair: It seems like there are several contraindications including opioids, SNRI's and TCA's. I have a feeling a lot of these patients will be on these medications.

Carl Jeffery: The contraindications have been added, the member is not on opioids, SNRI, TCA's.

Paul Oesterman, Chair: This is one of these drugs that if we don't add criteria it becomes blanket open access. My personal feeling is to have some kind of criteria and it should be relatively strict. I see a lot of potential as it being added on and widely misused or having the potential. I wish the manufacture had a representative here.

Marta Bunuel: What would you propose then like you have to try certain drugs first?

Carl Jeffery: We can take this to the P&T and have added in the class of the preferred drug list and maybe require step through some other agents. I suppose we could lump all the Parkinson's drugs in one class.

Paul Oesterman, Chair: Since the trial was 24 weeks, I would lean toward a 3 month initial authorization to make sure it is effective. As a recap for the Board, if we do not approve criteria of some kind, then the product becomes cart Blanche available for use. It is important for us to establish criteria that can be modified at a future meeting, but I think we do need to address with some kind of criteria. I am open to anything.

Carl Jeffery: I have recapped the changes on the screen, diagnosis of Parkinson's disease, levodopa or other dopaminergic treatments will be continued and patient reports greater than 1.5 hours per day of off-period and patient not on an opioids, MAOI, SNRI, TCA, cyclobenzaprine or methylphenidate/amphetamine, St. John's Wort or dextromethorphan. The initial authorization will be for three months.

Marta Bunuel: The Parkinson's patients I see, they have a high incidence of depression. What are the risks when we use with SNRI's, do we have any sense of how risky it is when combined? I'm just thinking it might be a problem. I'm wondering how risky combining these really is.

Carl Jeffery: It is essentially an MOAI, it is the same risk with mixing an MOAI with any of the other agents. Similar to selegiline to treat Parkinson's as well.

Paul Oesterman, Chair: I will ask for a motion and second to approve our revised criteria as shown on the screen.

James Marx: Motion to approve.

Michael Owens: Second.

Paul Oesterman, Chair: Any further discussion? Hearing none, I will call for the question, all those in favor or accepting the criteria say aye, those opposed say nay, the motion carries. We can again review the usage of this product moving forward.

Carl Jeffery: There were not any claims of this so far.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Deflazacort (Emflaza®)

Paul Oesterman, Chair: Our next topic is discussion and possible adoption of updated prior authorization criteria and or quantity limits for Deflazacort or Emflaza. Anybody in the audience or on line to address this? We do have someone in the audience.

Niren Shah: I'm Niren Shaw, I am a MSL at PTC Therapeutics. PTC therapeutics is company focused on rare orphan conditions for two decades now. With a deep focus on Duchenne muscular dystrophy. I appreciate the fair and balanced review and based on pivotal study one and two. PTC acquired Emflaza because we felt it was an important treatment for Duchenne. DMD is a

progressive and fatal disorder. Patients in the early phases lose muscle mass and as they get older lose the ability to walk. By teenage years become wheelchair bound. In late teens they acquire pulmonary dysfunction that often leads to their demise. The data used to approve Deflazacort was based on studies conducted in the 80's and 90's, we decided to move them to old data set that were collected by independent investigators. By using new outcome measure, we find there is a striking difference between other agents. We looked at active DMD, a phase three study compared to placebo, the patients were all on corticosteroids. We found that Deflazacort has a 36 meter improvement. The threshold from the FDA for meaningful benefit is about 30 meters. I would like to share the data, it is in a slide format.

Carl Jeffery: Is it something we can post publicly?

Niren Shah: Not yet.

Carl Jeffery: Sorry, it isn't something we can distribute to the board without being able to post publicly.

Niren Shah: I'm happy to take any questions.

Paul Oesterman, Chair: Looks like the criteria is very similar between Optum and Amerigroup. With one difference being the duration of prednisone treatment being 6 months in the Amerigroup criteria.

Carl Jeffery: I was going to recommend a change, I think it is a good idea to have a minimum trial of prednisone.

Paul Oesterman, Chair: One thing on the Amerigroup criteria, section 4 and item D, weight gain is likely a side effect of prednisone. If used in a five year old they will be gaining weight anyway, how do you attribute that to the medication?

Niren Shah: That is a good question, we looked at real world data, Deflazacort has been in Europe for a number of years, there was a program called the UK Master's program allowing some US citizens to get it. We found that physicians found these patients typically don't change dosing as they get older.

Marta Bunuel: Does it take six months to show the side effects of prednisone? The patients I have seen it is fairly quickly they show neuropsychiatric effects.

Niren Shah: We feel the same way. Most of our patients who have this PA criteria typically have complaints within the first couple weeks. It is mostly behavioral. Other adverse events are usually up to six months.

Holly Long: The other states that provided criteria to me also had a six month duration, but none said why they chose that duration.

Carl Jeffery: I think the requirement should be a fair trial. As long as it is a significant attempt. If prednisone works, all the better.

Paul Oesterman, Chair: The Emflaza is a synthetic steroid, how do the side effects compare to other steroids?

Niren Shah: Most studies compare to steroids, Deflazacort is shown to have less behavioral side effects, less weight gain, it doesn't affect the metabolic compared to prednisone. Deflazacort is associated with a higher incidence of cataracts.

Paul Oesterman, Chair: Are the side effect differences clinically significant?

Niren Shah: They were not measured that way, so it is hard to say. As a patient gains weight, they are higher risk of facture since they have brittle bones anyway. So just something to consider.

Carl Jeffery: On the bottom of page 58 shows the adverse events. Cushinoid appearance, increase weight, upper respiratory tract infection, cough.

Paul Oesterman, Chair: Ok, that is verses placebo, not prednisone.

Carl Jeffery: Right, they are similar to the prednisone. Is it a pro drug to a steroid?

Niren Shah: It is.

Marta Bunuel: Can we say that since there are some side effects that are later in onset, can the criteria reflect that? If there are neuropsychiatric symptoms from prednisone that present early, they would not have to continue?

Paul Oesterman, Chair: Would the three month timeframe capture that? Or do you need something shorter?

Marta Bunuel: When I see problems with prednisone, it is pretty early on with neuropsychiatric side effects. It usually presents within weeks or days.

Carl Jeffery: Could you say three month trial unless neuropsychiatric symptoms within one month?

Marta Bunuel: Could we break it up to something to what we see more clinically in general?

Paul Oesterman, Chair: Is there a difference in the neuropsychiatric response from steroids in peds vs adults?

Marta Bunuel: I don't have the knowledge. I know aggression is one, and they certainly see it in adults. Children may be acting out and may not be due to the steroid initially. Maybe a little more time than a couple weeks.

Paul Oesterman, Chair: We can always change it down the road if we need to.

Niren Shah: I can address the peds vs adults. A lot of the boys with DMD also have a spectrum of autism. It is interesting with the side effects, the level of irrationality is a little higher in these boys. When you do see it, it is clear. When it is in adults you can still see it. We had a case study where a boy with OCD got much worse with prednisone.

Marta Bunuel: I think we should take into consideration the aggression and especially if these boys also have autism. We don't have a lot of medications to treat autism and if the prednisone is going to make it worse, I would want them off it.

Carl Jeffery: Would you consider neuropsychiatric symptoms a contraindication for prednisone use? I'm just trying to think of some terminology we can use.

Marta Bunuel: The problem is when you take off prednisone, you are adding a bunch of other stuff to control other symptoms. I think the better choice is to remove the prednisone rather than start other medications. Children that have autistic spectrum disorder, they don't act predictably to medications.

There don't seem to be guidelines to say which medications first. The children I have worked with have been very aggressive. It is very hard for everyone in the family.

Paul Oesterman, Chair: Do we know why Utah went with three months?

Holly Long: They didn't provide that information.

Niren Shah: They didn't say anything, they just put three months.

Holly Long: The other states that sent information listed six months, Utah was the only state with three months and nobody had details as to why. The individual had a six month trial, contraindication or intolerance to a six month trial of oral prednisone.

Marta Bunuel: And intolerance isn't defined. So then we get some wiggle room.

Carl Jeffery: Right now we have a patient has had a trial of at least three months of prednisone or intolerance to prednisone.

Marta Bunuel: I think that sounds reasonable.

Paul Oesterman, Chair: Do we need to expand beyond prednisone to include prednisolone with is the liquid form.

Carl Jeffery: I think all the studies were done with prednisone, so I'm not sure.

Holly Long: I have one state that says both prednisone and prednisolone.

Paul Oesterman, Chair: I think if we include that it saves the call center some possible headaches.

Carl Jeffery: Or equivalent steroid dose since we do list the specific prednisone dose. I updated the criteria on the screen to read for at least 3 months or intolerance.

Marta Bunuel: It doesn't define a timeframe.

Paul Oesterman, Chair: At any point at which they have an intolerance to the prednisone, then there is no time requirement. Do we have any other discussion before we look for a motion and

second for the revised criteria? Then I will ask for a motion and second to approve the revised criteria.

Marta Bunuel: So move.

James Marx: Second.

Voting: Ayes across the board, the motion carries.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Omalizumab (Xolair®)

Paul Oesterman, Chair: Our next item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for omalizumab or Xolair. Do we have any public comment?

Carl Jeffery: This will be a fast one. All we are doing is changing the age. They got an updated indication for six years old instead of 12 years old. The red-lined version of Chapter 1200 on page 61. All we did was update the criteria to read the recipient must be six years of age or older instead of 12.

Paul Oesterman, Chair: Anybody on the board have anything to discuss?

Michael Owens: So moved.

James Marx: Second.

Voting: Ayes across the board, the motion carries.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for codeine and tramadol use in children.

Paul Oesterman, Chair: Our next item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for codeine and tramadol use in children. Do we have any public comment? I think the board members should have received the supplemental information for codeine and tramadol in children. It was from the dental provider response. Dr. Capurro who is the Nevada State Dental Health Officer has sent this additional information from the dental perspective. When looking at the usage of these products, it appears some was from dental practitioners. And it is being used off label for pain management in pediatric patients. Carl, do you want to go over the information?

Carl Jeffery: This is very timely. I was on a call with our commercial formulary group, and they are rolling out all the opioid cough syrups where they will not allow for anyone under 12, not obese, does not have severe lung disease or have sleep apnea, is not undergoing tonsillectomy or

adenoidectomy and the lowest effective dose for the shortest duration is being requested. We have quantity limits for the codeine related products. We don't have those applied to the tramadol related products. I think it should be just for one fill or one month. This would only apply for members under 18. But nobody under the age of 12 would be approved.

Paul Oesterman, Chair: I think this is consistent with the standard of practice for where these products are not approved for under the age of 12.

James Marx: there was an article a few days ago showing ibuprofen was just as effective as morphine for post op pain. Morphine was not superior to ibuprofen.

Paul Oesterman, Chair: The chart on page 80, we see that 11 and under, the primary agent is acetaminophen with codeine elixir.

Carl Jeffery: We have almost just as many claims in the zero to five group in the same time-frame.

Paul Oesterman, Chair: I wonder if some of this wasn't used for the anti-tussive properties. My question for the medical practitioners, would they want to include any tramadol quantity limits, we already have the codeine quantity limits.

Carl Jeffery: You could not allow tramadol for under 18, there really isn't that much use.

Paul Oesterman, Chair: You take away the codeine, I think you would see shift to tramadol rather than ibuprofen.

Holly Long: Colorado implemented a 400mg daily limit for tramadol.

Paul Oesterman, Chair: That is a pretty hefty dose.

Carl Jeffery: I was going to suggest 200mg daily for kids, that would be four tabs a day, for a seven day limit.

Holly Long: Arkansas has a limit of less than 17 years of age for tramadol. Tramadol/APAP is done separately, only indicated for five days or less for management of acute pain. Ages 16 or less will reject at the point of sale. They added some age edits at their last DUR.

Paul Oesterman, Chair: My thoughts are under 12, no, between 13 and 17, 200mg max and a five day limit for tramadol. Contraindicated if there is an SSRI on their profile? What is the lethal dose of tramadol?

James Marx: I never use it, so I'm not sure.

Paul Oesterman, Chair: I'm just thinking if we give them four tablets per day for 5 days, is that enough to cause problems if they took all of them.

James Marx: I suppose there would be some serotonin syndrome symptoms, but I don't suspect it would be deadly.

Beth Slamowitz: It says toxic dose starts at 500mg.

James Marx: A single dose of 500mg, at what age group.

Beth Slamowitz: A toxic dose starts at 500mg for the immediate release.

Paul Oesterman, Chair: I don't think we should cover any of the extended release product.

Beth Slamowitz: I would think a lot of these kids are getting it for tonsillectomy. Like Dr. Marx stated, using ibuprofen and acetaminophen are just as effective. I don't think it is necessary for children under 12 to have access to these agents.

James Marx: I think there are better options.

Paul Oesterman, Chair: Right now, under 12 would not be able to get either.

Carl Jeffery: Do you also want to include the tramadol with acetaminophen? I neglected to include that on the sheet.

Paul Oesterman, Chair: Yes. Authorization for one month hypothetically, they get a prescription with four refills…

Carl Jeffery: The way I thought it would happen, the authorization would be for one month, but they would only get one fill in that timeframe.

James Marx: Is this for antitussives or is this for pain?

Carl Jeffery: We don't know for sure what they are using it for. From the reports from the last meeting, a lot of the prescribers were ER doctors.

James Marx: I think seven days is more than adequate.

Carl Jeffery: I think there are better antitussives.

Marta Bunuel: If you're talking about kids, they may abuse it.

Paul Oesterman, Chair: Are we in agreement with these criteria with the inclusion of the tramadol limit of 200mg and a max of 5 days and no extended release and this would also include the products in combination with acetaminophen. And a one fill only. Do we have a motion to approve the criteria as presented on the screen with the modifications just made?

James Marx: Should we look at the opioids in general? I don't think we have pressed the whole issue, we should broaden our scope. I don't have a problem approving this motion, but we should drill down deeper.

Carl Jeffery: There are no restrictions for other opioids, they might move to hydrocodone. I think it is a good idea to roll out to all opioids.

Paul Oesterman, Chair: So I did hear approval of the motion.

James Marx: I think this is just a temporary solution, I move we approve as presented.

Marta Bunuel: Second.

Paul Oesterman, Chair: The only discussion is that at the next meeting we look at some of the other controlled substances and make that an agenda item.

Voting: Ayes across the board, the motion carries.

**5. Public Comment on any DUR Board Requested Report**

Paul Oesterman, Chair: Do we have any public comment on any of the board requested reports? No, we will go to the board requested reports. The first one is looking at the anticonvulsant medications used for children and adolescents.

**6. DUR Board Requested Reports**

Carl Jeffery: This was a difficult report to match up with the diagnosis. The request was to see why the anticonvulsant was being used in children. I ran a list of all the recipients that had a prescription for an anticonvulsant and sent to the medical side and they gathered the diagnosis codes for those members and pulled their primary diagnosis. That is what you see here compiled in the number of primary diagnosis. The pharmacy claims data and the medical claims data doesn't match because they are submitted at different times and there is nothing to match them up. So you can't really pair them up. So this is the best I could come up with. You get down to the forth one down, you get convulsions, the top three are just artifacts, I don't think they have anything to do with anticonvulsants. If you have a child on an anticonvulsant, they go to the doctor for a well child check they get their immunizations. It has nothing to do with the doctor writing, they probably just renewed their anticonvulsant. It is impossible to tease that out of that data. They start getting into some behavior issues, they start to make sense.

Paul Oesterman, Chair: I think one of the concerns is that we have so many drugs with multiple indications, they may be on an anticonvulsant classified drug, and they may be using it for something totally different.

Carl Jeffery: Especially the way our criteria is now, if they are over five years old, they can get one anticonvulsant without any PA. They could be using for sleep, and we would not know.

Marta Bunuel: Certainly there are a lot of these are being used in familiar ways, behavior, mood disorders, autistic disorders because of behavior issues. Migraines are also treated with these drugs. I have seen Topamax for weight loss, but most are neurological or psychiatric.

Carl Jeffery: Is there anything else you would like to see with this or some kind of analysis?

Paul Oesterman, Chair: I know in the past one of the concerns was children in foster care vs. children in care homes.

Carl Jeffery: Those reports are on the next page, starting page 82. We broke down the different programs the recipients are enrolled in. The number of claims and number of members.

Paul Oesterman, Chair: I looks to me that the number of claims per member, the ratio is pretty consistent across the board. The members in foster care are not greater than the regular program. This is very telling. Your efforts are paying off.

Carl Jeffery: I tried to get the number of how many kids are in each program but I wasn't confident in my numbers, but the majority of the children will be in the first CHAP program. I don't think you will see as many in the disable programs, but those that are in there are likely to have a need for anticonvulsants. It is encouraging to see the foster kids, they are up there, maybe a higher percentage than the average population, but it is not through the roof. In the other charts, the program is broken down by age. They go through phases for which medications each program is on. For CHAP utilization, antidepressants are favored and then antipsychotics start to creep up after age 11. In the foster kids, the antipsychotics are up there even with the antidepressants and six to 11 you have a lot more antipsychotics. It is interesting to see the changes as you go through the programs. As expected, the independent living has a lot of anticonvulsants.

Paul Oesterman, Chair: This is a good report, thank you.

Carl Jeffery: The last page breaks it down for all programs for the children and psychotropic utilization.

Paul Oesterman, Chair: Do we have any follow-up requests or questions regarding these reports? We will move to our opioid utilization report. The report on page 88, those are trends, I think this is good news, it looks like they are all trending on the downward side.

Carl Jeffery: May 15, 2017, we implemented the quantity limits for the opioids where we limit to 60 mg morphine equivalents, seven days supply or 13 fills in a rolling 12 months. I'm surprised how little pushback from the provider community we have had.

Michael Owens: I think it makes everyone happy. In our clinic and you inherit patients that say they have been on opioids. The FBI coming down and arresting the physician has caused some changes in our clinic and we start to refer out to others that can manage their opioids. Patients are much less likely to push back if you can put the blame on someone else. It makes you a lot more comfortable as a provider. If I can get them to a lower level of opioids until they can see a pain specialist, it makes both me and the patient feel more comfortable. It has made it a lot easier for me.

Carl Jeffery: I have some friends in retail pharmacy. It may be the exception, but patients will get the Medicaid allowed amount and then pay cash for the rest. They are getting it one way or another, we are just not paying for it.

Marta Bunuel: Do we track who gets it? In Phoenix, they would flag them and notify us.

Carl Jeffery: I have asked the board of pharmacy to get some reports out of the PMP. They are pretty strict on what reports they let out and I will continue to work with them. If we could see a breakdown of who the payer is. We don't know when they pay cash, but the board of pharmacy does. I wonder if they could break it down to see who has a Medicaid claim and paid cash on the same day.

James Marx: There was always for the last 20 years, there was someone from Medicaid at the task force meetings. I don't think there was any intention to exclude that kind of data with a legitimate reason to have it. What you are looking for is de-identified data anyway. There is a meeting on November 9th at 9:00.

Duane Young: They have invited me, but I have not been able to attend past meetings.

James Marx: There have been for many years, a representative from Medicaid at those meetings.

Paul Oesterman, Chair: The top 10 opioids by quantity, there are not any surprised here. Maybe tramadol is higher than I thought.

Carl Jeffery: I thought there would be a shift to tramadol after the quantity limits were put on, but that didn't really happen. Page 90, the breakdown for the top prescriber is shown. I went back to just one year of data and we get a different list. The top is the same nurse practitioner in Las Vegas that we have been talking about. I think the Board of Pharmacy may have them on the watch list too. The fifth one down with the high expense, that is from the fentanyl lollipops that are so expensive. He has about 8 patients.

James Marx: I thought we had utilization criteria on there, didn't that have some effect?

Carl Jeffery: Yes, the criteria is still on there.

James Marx: I think it is limited to terminal patients.

Paul Oesterman, Chair: I think this is an opportunity to let this provider know where they stand. Maybe it is just fine.

Carl Jeffery: I don't think it would be a bad idea to send this chart to these physicians and let them know they are in the top 10.

Paul Oesterman, Chair: On page 91 we have the impact of the 90 day supply when that got rolled out.

Carl Jeffery: That was the end of February. March was the first full month and you see a big spike there and then every three months, in June and then a little spike in September. It is stabilizing a bit as we go on.

Paul Oesterman, Chair: One of my concerns is that two years out, the pharmacy paid amount should drop back down and be consistent.

Carl Jeffery: This isn't the total program spend, this is only the 90 day fills.

Paul Oesterman, Chair: Oh, total program spend would be interesting to see. Gradually over two years you would expect to see it come back down.

Carl Jeffery: Yeah, we can look at those numbers. We run them every month anyway. I did look at the total dispensing fee for pharmacies, it came back really funny and didn't have time to QA. It would be interesting to see how the average dispensing fee over time changes.

James Marx: What is going to be the impact of the CVS policy of limiting to seven days, how is that going to be handled?

Carl Jeffery: What program is that?

James Marx: A few people were informed that CVS is only going to allow a seven day fill for opioids.

Michael Owens: Is that for new prescriptions only?

James Marx: No, for ongoing maintenance.

Beth Slamowitz: Yes they are going to limit all opioid prescription to seven days for certain conditions. It is for new patients.

Michael Owens: A lot of the requests are coming through, if you have been on the prescription for the past three months, you can get it. It is only for new prescriptions, for short-course therapy.

James Marx: I'm talking about the CVS policy.

Beth Slamowitz: It doesn't roll out until February 1st. It says patients that are new to pain therapy.

James Marx: So how is Medicaid going to deal with that? That means subsequent prescriptions will be on a seven day fill. That will quadruple the dispensing fee.

## 7. Public Comment on any Standard DUR Report

Paul Oesterman, Chair: Our standard DUR reports. Do we have any public comment?

## 8. Standard DUR Reports

Marta Bunuel: I have a question on the antipsychotics and antimanics and then psychotherapy and neurological agents. How are those separated out?

Carl Jeffery: The antipsychotics would be Abilify and Seroquel and Haldol. The antimanic are lithium. Tegretol falls within the anticonvulsant class even though it can be used as a psychotherapeutic. The psychotherapeutic and neurologic agents will have dopamine agents for Parkinson's.

Paul Oesterman, Chair: Do we have anything of significance going off patent coming up?

Carl Jeffery: Abilify went off patent, that was a big change, Strattera a few months ago, Crestor a few months ago. We do have two new Hep C agents are coming out fighting for best price. I think there is some room for case management for hemophilia. The state could probably hire a nurse for full time and easily pay for their salary.

Paul Oesterman, Chair: Was there a big change in membership between Q1 of 2017 and Q2? There appears to be the count of claims has really taken a big jump. On page 95, the anticonvulsants, it took a big jump in Q2. Opioid combos went up by 10,000.

Carl Jeffery: We can double check our numbers, the first two quarters have January and March that are big months and then the next big month is in July or August. The second quarter, April, May and June are big months. January and March are long months and beginning of the year and they have new insurance. Those are historically high months for number of claims.

Paul Oesterman, Chair: Top 50 looks pretty standard.

Carl Jeffery: Not a whole lot changes with those.

Beth Slamowitz: Just for a clarification for the CVS policy, it is the CVS PBM, it is all their clients that their policy will apply to. For commercial or Medicaid clients. Anyone that has CVS/Caremark for their pharmacy benefit manager. Express Scripts has done the same thing.

Carl Jeffery: You will see the same thing coming from Optum pretty soon. I think it is a pretty standard move coming from the PBMs.

Carl Jeffery: The question about the numbers not adding up, you can have more than one reject per claim. You can have a high dose alert and short duration on the same claim for example, that is why they don't add up to 100.

Paul Oesterman, Chair: These report still confuse me.

Marta Bunuel: The top drug interactions, what does it mean on this?

Carl Jeffery: This is the number of claims that have been submitted. Our system flagged the pharmacy and told the person filling the prescription. The pharmacy got a message, most of the time you have a technician that enters these and blows by these messages. Some have a hard stop, that requires a pharmacist to enter a code and indicate what action they took and enter a code. The claim would go through or they get the message and contact the prescriber and reverse the claim. These are helpful mostly when patients go to different pharmacies.

Paul Oesterman, Chair: Seems to me a lot of these messages are being done by a tech. Maybe we should look at some of these messages only and convert to hard stops so they have to act. All of them were message only.

Carl Jeffery: We really don't have many hard stops, like duplicates.

Paul Oesterman, Chair: On page 110, we have promethazine and age less than four, we got a message and they probably went right through it. In the past we have set up some criteria to prevent children from getting this.

Carl Jeffery: Some of these may not be where Medicaid is the primary, if they have another insurance that pays the claim, we follow the rules of the primary. We would have to look into those.

Paul Oesterman, Chair: I would like to spend some time at a future meeting looking at these in a little more detail so we can help provide quality care for our patients.

Carl Jeffery: Right, and make them more meaningful to the Board and the pharmacies. I don't know what the board is supposed to do with these reports. I will see what I can dig into.

James Marx: If there are so many messages being blown through, they may go through some significant messages and miss something serious.

Marta Bunuel: On page 112, some of these are single medications and there was a message, for what?

Paul Oesterman, Chair: TD is therapeutic duplication.

Carl Jeffery: If they are getting an extended release and immediate release, then it would flag.

Marta Bunuel: There are some other medication or some other form in their profile causing this to interact, I see.

Paul Oesterman, Chair: On page 137, therapeutic duplication, levothyroxine and thyroxine, it isn't uncommon to have a patient on both of those. But I would be concerned with a patient that is getting two strengths of medications, if we could tease those out, that would be a benefit. Knowing if the combination is deliberate or is it a transition is hard to tell.

James Marx: There is no way to call back a discontinued therapy when there is a change. A pharmacist doesn't have any way to get that medication back, so the member has both strengths.

Paul Oesterman, Chair: I have had a number of practitioners say to discontinue all prior medication.

James Marx: But that medication doesn't go anywhere.

Paul Oesterman, Chair: Speaking of which, the take back program is coming up. Do we have anything else we wish to discuss?

Carl Jeffery: For the retro-DUR, we have about 55 letters for the tramadol and codeine ready to go out to the prescribers. We can provide some education before we cut them off. We have some Hep C treatments for follow-up. A question to see why they didn't finish therapy and if they did, are they cured.

James Marx: Aren't those supposed to be through a specialty pharmacy and track those?

Carl Jeffery: They might, but they don't tell us. I don't think a lot of prescribers draw a follow-up viral load.

**9. Closing Discussion**

Paul Oesterman, Chair: We will ask for any public comment, hearing none. What is the next time and place for the meeting?

Carl Jeffery: January 25, 2018.

Duane Young: We will send a reminder and we are looking at some other options and times. If there are any changes we will reach out to you. We are looking at two locations. We had only one of the MCO's criteria, for January's meeting, we may need to move the time up.

Paul Oesterman, Chair: I think moving the time up is going to be difficult to those who are working.

Duane Young: We can keep it at this time, but we may be here until 9:30. When we add the other two MCO's criteria, it will take longer to review. One thing we can do is look to synthesize the criteria prior to the meeting and add some research from other States.

James Marx: Can we get Carl's criteria to the MCO and have them comment so we don't have contradictory and exclusionary criteria.

Duane Young: We will have a pre meeting and come up with some combined criteria.

James Marx: That way it is red-lined before we get to it.

Paul Oesterman, Chair: Ok, the meeting is adjourned.

Meeting adjourned at 8:22 PM.

**Nevada Medicaid**
**Austedo** (deutetrabenazine)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Austedo | deutetrabenazine |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Diagnosis of Huntington's Disease

Austedo (deutetrabenazine) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Recipient is 18 years of age or older **AND**
2. Diagnosis of chorea associated with Huntington's disease **AND**
3. Prescribed by or in consultation with a neurologist

**Initial Authorization: 3** months

**Reauthorization Duration:**

Authorization for continued use shall be reviewed at least every 12 months when the following criteria are met:

1. Documentation of positive clinical response to therapy

### Diagnosis of Tardive Dyskinesia

Austedo (deutetrabenazine) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Recipient is 18 years of age or older **AND**
2. Diagnosis of tardive dyskinesia confirmed by the following: **AND**
    a. At least 60 days of stable (drug, dose) neuroleptic medication exposure (either typical or first generation antipsychotic agents, atypical or second-generation antipsychotic agents, or certain dopamine receptor-blocking drugs used in treatment of nausea and gastroparesesis **AND**
    b. Presence of involuntary athetoid or choreiform movements lasting at least 30 days. **AND**

**3.** Prescribed by or in consultation with a neurologist or psychiatrist **AND**
**4.** One of the following:
   a. Patient has persistent symptoms of tardive dyskinesia despite a trial dose reduction, tapering, or discontinuation of the offending medication **OR**
   b. Patient is not a candidate for a trial dose reduction, tapering or discontinuation of the offending medication

**Reauthorization Duration:**

Authorization for continued use shall be reviewed at least every 12 months when the following criteria are met:

**1.** Documentation of positive clinical response to therapy

# Austedo Utilizaton

January 1, 2017 - December 31, 2017

Fee for Service Medicaid

| YearMonth Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201710 | AUSTEDO TAB 12MG | 1 | 1 | 7 | 14 | $ 1,161.40 |
| 201710 | AUSTEDO TAB 6MG | 1 | 1 | 7 | 14 | $ 777.80 |
| 201710 | AUSTEDO TAB 9MG | 1 | 1 | 7 | 14 | $ 873.70 |
| 201712 | AUSTEDO TAB 9MG | 1 | 1 | 30 | 120 | $ 7,408.60 |
| **Total** | | | | **51** | **162** | **$ 10,221.50** |

## INTRODUCTION

- Huntington disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and neuropsychiatric disturbances (*Coppen and Roos 2017*).
  - Motor dysfunction in HD may include involuntary movements (eg, chorea, dystonia, and tics) and voluntary movements (eg, bradykinesia, apraxia, and motor impersistence) (*Austedo dossier 2017, Coppen and Roos 2017*).
    - Choreic movements are rapid and unpredictable contractions of the facial muscles, trunk, and extremities which vary in frequency, intensity, and amplitude (*Austedo dossier 2017, Suchowersky 2016a*).
    - Chorea is a defining symptom at the time of diagnosis and typically develops early in the clinical onset of HD. Symptoms may gradually worsen over time and plateau or decline in late stages (*Armstrong and Miyasaki 2012, Suchowersky 2016a*).
    - Dystonia is characterized by sustained or intermittent muscle contractions which lead to abnormal posture of the trunk and extremities. It is more commonly observed in advanced disease stages (*Coppen and Roos 2017*).
    - Motor function slowly deteriorates as HD progresses, and chorea may eventually be replaced by bradykinesia and parkinsonism in advanced stages of the disease (*Suchowersky 2016a, Suchowersky 2016b*).
- HD affects an estimated 1 in 7300 individuals (approximately 43,000 people) in the United States. It is a rare and fatal autosomal dominant genetic disorder associated with onset in early adulthood and death within 20 years of symptom onset. The prevalence of chorea is estimated to be 50% in patients with new-onset HD (*Austedo dossier 2017, Austedo FDA Summary Review 2017*).
- Since there are no curative or disease-modifying therapies available for HD, the focus of treatment is on symptom management and supportive care to optimize quality of life (*Suchowersky 2016b*).
  - The most commonly prescribed medications in HD are neuroleptics and antidepressants. Neuroleptics are traditionally used off-label in HD to treat psychiatric symptoms (eg, agitation, psychosis) and suppress chorea. While there is an abundance of clinical experience with neuroleptics in reducing chorea, there is a lack of robust evidence from clinical trials supporting their use (*Armstrong and Miyasaki 2012, Suchowersky 2016b*).
  - Prior to the approval of deutetrabenazine, tetrabenazine was the only product FDA-approved for the treatment of chorea due to HD. Both tetrabenazine and deutetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors.
    - Deutetrabenazine is a chemically modified form of tetrabenazine with deuterium substituted for hydrogen at specific positions. Deuterium is a naturally occurring heavy isotope of hydrogen which creates stronger bonds that extend the half-life of deutetrabenazine. Compared to tetrabenazine, deutetrabenazine reaches comparable systemic exposure with smaller doses, longer treatment intervals, and lower peak concentrations (*Austedo dossier 2017*, *Coppen and Roos 2017*).
  - Many clinicians utilize neuroleptics (eg, olanzapine, risperidone) in the first-line setting for chorea associated with HD due to additional benefits in sleep dysfunction, mood disturbances, and weight maintenance. For patients with HD, neuropsychiatric symptoms typically have a greater impact on quality of life and functional disability than the motor or cognitive symptoms of the disease (*Austedo dossier 2017, Coppen and Roos 2017*).
- Tardive dyskinesia (TD) is a movement disorder resulting from exposure to dopamine receptor antagonists (DRAs), including typical and atypical antipsychotics, antiemetics, and metoclopramide. Approximately 20% to 50% of patients receiving antipsychotics develop TD (*Fernandez et al 2017*).
  - TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area. Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations *(Muller et al 2015, Rana et al 2013).*
  - Ingrezza (valbenazine), another VMAT2 inhibitor, was the first drug FDA-approved for TD in April 2017 (*Drugs@FDA 2017*). Deutetrabenazine received approval for this indication in August 2017.

- Differences between valbenazine and deutetrabenazine include once-daily dosing (vs. twice-daily dosing) and the absence of a boxed warning for depression and suicidality in patients with HD. Of note, valbenazine has not been studied in patients with HD (*Ingrezza prescribing information 2017*).
  - Prior to the approval of valbenazine and deutetrabenazine, guidelines suggested clonazepam, amantadine, and tetrabenazine were likely effective when used off-label for TD (*Bhidayasiri et al 2013*). The guidelines have yet to be updated to include the FDA-approved treatment options for TD.
- While deutetrabenazine has been designated a new molecular entity and an orphan drug, it was approved through the 505(b)(2) pathway with tetrabenazine as the Reference Listed Drug (RLD) (*Austedo FDA Summary Review 2017*).
  - The FDA issued a Complete Response Letter (CRL) for deutetrabenazine on May 27, 2016, which cited inadequate pharmacology studies identifying all major human metabolites of deutetrabenazine. The manufacturer was required to demonstrate that all major metabolites of deutetrabenazine were the same as those of tetrabenazine in order to bridge the nonclinical studies conducted for the RLD (*Austedo FDA Summary Review 2017*).
- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder

## INDICATIONS

- Deutetrabenazine is indicated for chorea associated with HD and for TD in adults (*Austedo prescribing information 2017*).

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

**Huntington Disease (HD)**

- The approval of deutetrabenazine was supported by the First-Time Use of Austedo in HD (First-HD) study conducted by the Huntington Study Group (HSG). The Phase 3, double-blind, multicenter, randomized controlled trial compared deutetrabenazine with placebo for 12 weeks, followed by a 1-week washout in 90 adults with HD (*HSG 2016*).
  - The study included patients with a Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score of at least 8 at baseline and a UHDRS total functional capacity score of at least 5 at screening.
    - The UHDRS is a widely accepted scale that has undergone extensive reliability and validity testing in HD. The TMC score ranges from 0 to 28, with higher scores indicating more severe chorea (*Coppen and Roos 2017, Geschwind and Paras 2016*).
    - Patients with untreated psychiatric illness, history of suicidal thoughts, prolonged QT interval, hepatic impairment, renal impairment, and dysphagia were excluded from the trial.
  - The primary endpoint was the change from baseline in UHDRS-TMC score; results for efficacy endpoints are summarized in **Table** below.
    - The placebo-adjusted mean change from baseline in TMC with deutetrabenazine was -2.5 points (95% confidence interval [CI], -3.7 to -1.3; $p < 0.001$).
    - In the deutetrabenazine group, the mean TMC scores improved by -4.4 points from 12.1 (95% CI, 11.2 to 12.9) to 7.7 (95% CI, 6.5 to 8.9) over 12 weeks. In the placebo group, mean TMC scores improved by -1.9 points from 13.2 (95% CI, 12.2 to 14.3) to 11.3 (95% CI, 10.0 to 12.5).
  - Four secondary endpoints were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 36-Item Short Form (SF-36) physical functioning subscale score, and Berg Balance Test (BBT). For the PGIC and CGIC, treatment success was defined as an answer of "much" or "very much" improved overall HD symptoms at Week 12.
    - The proportion of patients who reported treatment success on the PGIC was 31.1% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The proportion of clinicians who reported treatment success on the CGIC was 28.9% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The placebo-adjusted improvement in the SF-36 physical functioning subscale was 4.34 points with deutetrabenazine ($p = 0.03$).
    - BBT improvement observed with deutetrabenazine did not achieve statistical significance over placebo ($p = 0.14$).

- Additional pre-specified efficacy endpoints included the change in UHDRS total motor score (TMS) and the percentage change in TMC score. The TMS assesses all of the motor symptoms of HD (eg, chorea, dystonia, rigidity, bradykinesia), with higher scores indicating more severe motor impairment (*Austedo dossier 2017*).
  - The placebo-adjusted mean change from baseline in TMS with deutetrabenazine was -4.0 points (95% CI, -6.5 to -1.5; p = 0.002).
  - The placebo-adjusted percentage change from baseline in TMC with deutetrabenazine was -21% (95% CI, -30% to -11%; p < 0.001).
- In the First-HD study, the incidence of overall, psychiatric, and nervous system treatment-emergent adverse events (TEAEs) was similar between the deutetrabenazine and placebo groups.
  - While AEs were generally mild to moderate, AEs resulted in dose reductions for 3 patients (6.7%) in each group. Serious AEs resulted in drug suspension for 1 patient (2.2%) in each group.
  - Somnolence and diarrhea were reported more frequently with deutetrabenazine than with placebo.

**Table 1. First-HD Study Efficacy Results**

| Endpoint | DTBZ (n=45) | Placebo (n=45) | Difference (95% CI) | p-value |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| TMC Score*, LS mean (95% CI) | -4.4 (-5.3 to -3.6) | -1.9 (-2.8 to -1.1) | **-2.5** (-3.7 to -1.3) | **< 0.001** |
| **Secondary Endpoints** | | | | |
| PGIC Treatment Success†, n (%) | 23 (51) | 9 (20) | **31.1** (12.4 to 49.8) | **0.002** |
| CGIC Treatment Success†, n (%) | 19 (42) | 6 (13) | **28.9** (11.4 to 46.4) | **0.002** |
| SF-36 Physical Functioning Score*, LS mean (95% CI) | 0.7 (-2.0 to 3.4) | -3.6 (-6.4 to -0.8) | **4.3** (0.4 to 8.3) | **0.03** |
| BBT Score*, LS Mean (95% CI) | 2.2 (1.3 to 3.1) | 1.3 (0.4 to 2.2) | **1.0** (-0.3 to 2.3) | **0.14** |
| **Additional Pre-Specified Endpoints** | | | | |
| UHDRS TMS*, LS Mean (95% CI) | -7.4 (-9.1 to -5.6) | -3.4 (-5.1 to -1.6) | **-4.0** (-6.5 to -1.5) | **0.002** |
| TMC % Change*, LS Mean (95% CI) | -37 (-44 to -30) | -16 (-23 to -9) | **-21** (-30 to -11) | **< 0.001** |

Abbreviations: BBT, Berg Balance Test; CGIC, Clinical Global Impression of Change; CI, confidence interval; DTBZ, deutetrabenazine; LS, least squares; PGIC, Patient Global Impression of Change; TMC, total maximal chorea; TMS, total motor score; UHDRS, Unified Huntington Disease Rating Scale
*Change from baseline to end of maintenance therapy
†Treatment success at Week 12 was defined as “much improved” or “very much improved”

- The ongoing Alternatives for Reducing Chorea in HD (ARC-HD) study is a Phase 3, open-label, multicenter, long-term trial which evaluates the safety and efficacy of deutetrabenazine in 112 patients in 2 cohorts (*Austedo dossier 2017, Stamler 2016*).
  - The rollover cohort includes 75 patients from the First-HD study who underwent washout of deutetrabenazine or placebo. The switch cohort includes 37 patients previously on tetrabenazine who were switched overnight to deutetrabenazine at approximately half their previous tetrabenazine dose.
  - According to interim analyses, patients in the switch cohort demonstrated improved TMC from baseline with deutetrabenazine 8 weeks following conversion (-2.06 points; p = 0.0006). Improvements in TMC from baseline were also observed in the rollover cohort at Week 2 (-1.9; p < 0.0001; n = 58) and maintained through Week 28 (-4.4; p = 0.0055; n = 14). Common TEAEs included somnolence, falls, depression, and insomnia.

**Tardive Dyskinesia (TD)**

- The safety and efficacy of deutetrabenazine was established in the ARM-TD and AIM-TD trials, which were 12-week double-blind, placebo-controlled, multicenter, randomized controlled trials. Both studies evaluated the change from baseline in items 1 to 7 of the Abnormal Involuntary Movement Scale (AIMS) score as the primary efficacy endpoint. The AIMS total score ranges from 0 to 28, and a decreased score indicates improvement (*Anderson et al 2017, Fernandez et al 2017*).
  - The Phase 2/3 ARM-TD study randomized 117 adults with moderate to severe TD to receive deutetrabenazine titrated to an optimal dose or placebo. The mean dose of deutetrabenazine at the end of titration was 38.8 mg/day.

Significant reductions in TD were observed in patients who received deutetrabenazine compared to placebo (*Fernandez et al 2017*).
  - The LS mean AIMS score improved by -3.0 points in the deutetrabenazine group vs. -1.6 points in the placebo group (treatment difference -1.4; 95% CI, -2.6 to -0.2; p = 0.019).
  - Secondary endpoints included proportion of patients who experienced treatment success at week 12 on the CGIC and PGIC. Although CGIC and PGIC results were numerically higher for the deutetrabenazine group, the difference was not statistically significant.
  - The rates of AEs were similar between the deutetrabenazine and placebo groups, including depression and suicidal ideation.
- The Phase 3 AIM-TD study randomized 298 adults with TD to receive 1 of 3 fixed doses of deutetrabenazine (12, 24, or 36 mg/day) or placebo. Significant reductions in TD were observed in patients who received 24 or 36 mg of deutetrabenazine per day (*Anderson et al 2017*).
  - The LS mean AIMS score improved by -3.3, -3.2, -2.1, and -1.4 points in the deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo groups, respectively. The treatment difference was -1.9 points (95% CI, -3.09 to -0.79; p = 0.001) with deutetrabenazine 36 mg/day, -1.8 points (95% CI, -3.00 to -0.63; p = 0.003) with deutetrabenazine 24 mg/day, and -0.7 points (95% CI, -1.84 to 0.42; p = 0.217) with deutetrabenazine 12 mg/day.
  - The overall rate of AEs was similar between groups (51%, 44%, 49%, and 47% for deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo, respectively).
  - Rates of depression, depressed mood, and suicidal ideation were low in all treatment arms; no dose-response relationship was detected.

## CLINICAL GUIDELINES

**Huntington Disease (HD)**

- **American Academy of Neurology (AAN):** Pharmacologic treatment of chorea in HD (*Armstrong and Miyasaki 2012*)
  - Whether chorea requires treatment should be an individualized decision for providers and their patients with HD.
    - While some studies reported that improving chorea decreases disability or increases quality of life, other studies failed to show an association between chorea and functional decline in HD.
    - The impact of chorea on quality of life should be weighed against other issues, including mood disturbance, cognitive decline, AEs, and polypharmacy risks.
  - For HD chorea which requires pharmacological management, tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) are recommended.
    - Tetrabenazine likely provides very important antichoreic benefits, and riluzole 200 mg/day likely provides moderate benefits. The degree of benefit is unknown for amantadine.
    - Patients on tetrabenazine should be monitored for parkinsonism and depression/suicidality while patients on riluzole should be monitored for elevated liver enzymes.
  - Nabilone may be used for modest decreases in HD chorea, but there is insufficient evidence to recommend long-term use, particularly given concerns for abuse potential.
  - While neuroleptic agents (eg, clozapine) may be reasonable options with a historical suggestion of antichoreic benefit, formal recommendations are not provided due to a lack of studies with sufficient sample sizes and validated outcome measures.
  - The guideline has not been updated since the FDA approval of deutetrabenazine.

**Tardive Dyskinesia (TD)**

- **American Academy of Neurology (AAN):** Treatment of tardive syndromes (*Bhidayasiri et al 2013*)
  - Recommendations for tardive syndromes are summarized in Table 2 below.
  - The guideline has not been updated since the FDA approval of deutetrabenazine.

**Table 2. Guideline Recommendations for Tardive Syndromes**

| Level of evidence | Recommendation |
|---|---|
| **Level A**<br>(Recommendation must be done; high confidence in the evidence with high benefit and low risk) | None |

| | |
|---|---|
| **Level B**<br>(Recommendation should be done based on benefit/risk profile) | **Recommended**:<br>• Ginkgo biloba extract (EGb-761) for schizophrenia only<br>• Clonazepam, for short-term use<br><br>**Not recommended:**<br>• Diltiazem |
| **Level C**<br>(Recommendation may or might be done; lowest recommendation level considered useful within the scope of practice) | **Recommended**:<br>• Amantadine for short-term use<br>• Tetrabenazine<br><br>**Not recommended:**<br>• Galantamine |
| **Level U**<br>(Available evidence is insufficient to support or refute efficacy of an intervention) | • Withdrawal of dopamine receptor blocking agents (DRBAs)<br>• Switching from typical to atypical antipsychotics<br>• Acetazolamide plus thiamine<br>• Typical antipsychotics<br>• Atypical antipsychotics<br>• Electroconvulsive therapy<br>• Reserpine or α-methyldopa<br>• Bromocriptine<br>• Anticholinergic agents (other than galantamine)<br>• Biperiden discontinuation<br>• Antioxidants (vitamin E, vitamin B6, melatonin, selegiline, yi-gan san)<br>• Baclofen<br>• Levetiracetam<br>• Nifedipine<br>• Buspirone<br>• Botulinum toxin<br>• Pallidal deep-brain stimulation |

## SAFETY SUMMARY

- **Contraindications**
  - Deutetrabenazine is contraindicated in the following populations:
    - Patients with HD who are suicidal or have untreated or inadequately treated depression
    - Patients with hepatic impairment
    - Patients concurrently on monoamine oxidase inhibitors (MAOIs) or who have discontinued MAOI therapy within 14 days
    - Patients concurrently on reserpine or who have discontinued reserpine therapy within 20 days
    - Patients concurrently on tetrabenazine or valbenazine
- **Warnings/precautions**
  - **Boxed warning:** Depression and suicidality in patients with HD
    - Patients with HD have a greater risk of depression and suicidality. Treatment with deutetrabenazine may further increase this risk in patients with HD.
    - In the First-HD study, suicidal ideation was reported by 2% of patients treated with deutetrabenazine, compared to no patients on placebo. Depression was reported by 4% of patients treated with deutetrabenazine.

- Patients on deutetrabenazine should be closely monitored for worsening depression, suicidal thoughts, or unusual changes in behavior.
- Additional key warnings and precautions for deutetrabenazine include:
  - Clinical worsening (eg, decline in mood, cognition, rigidity, and functional capacity) and AEs (eg, sedation, depression, parkinsonism, akathisia, restlessness, cognitive decline) in patients with HD
    - The effect of deutetrabenazine on chorea should be periodically weighed against possible AEs to determine whether continued therapy is necessary. The underlying chorea may improve over the course of the disease, decreasing the need for pharmacologic therapy.
  - Neuroleptic malignant syndrome (NMS) in patients with HD and TD
    - NMS is a potentially fatal syndrome associated with hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. While NMS has not been observed with deutetrabenazine, it has been observed with its RLD, tetrabenazine. Deutetrabenazine should be discontinued immediately if NMS occurs.
  - Akathisia, agitation, and restlessness in patients with HD and TD
    - In the First-HD study, akathisia, agitation, or restlessness was reported by 4% of patients treated with deutetrabenazine and 2% of patients on placebo. In patients with TD, 2% of patients treated with deutetrabenazine and 1% of patients on placebo experienced these events.
  - Parkinsonism in patients with HD
    - Patients with HD often develop rigidity as part of their underlying disease progression. Drug-induced parkinsonism may cause more functional impairment than untreated chorea. Patients who develop parkinsonism during treatment with deutetrabenazine should reduce their dosage.
  - Sedation and somnolence
    - Sedation is a common dose-limiting AE with deutetrabenazine. In the First-HD study, 11% of patients treated with deutetrabenazine reported somnolence compared with 4% of patients on placebo.
  - QTc prolongation

- **Adverse effects**
  - The most common AEs (incidence > 8% and greater than placebo) with deutetrabenazine in the First-HD study included somnolence, diarrhea, dry mouth, and fatigue.
  - The most common AEs (incidence > 3% and greater than placebo) with deutetrabenazine in the TD studies included nasopharyngitis and insomnia.
- **Drug Interactions**
  - Deutetrabenazine is contraindicated in patients taking MAOIs, reserpine, tetrabenazine, or valbenazine.
  - Strong cytochrome P450 (CYP) 2D6 inhibitors increase the systemic exposure to metabolites of deutetrabenazine.
  - Concurrent use of tetrabenazines with neuroleptic drugs (ie, dopamine antagonists, antipsychotics) may increase risk for parkinsonism, NMS, and akathisia.
  - Concomitant use of deutetrabenazine with other drugs that are known to cause QT prolongation should be avoided.

## DOSING AND ADMINISTRATION

- The dose of deutetrabenazine is determined individually for each patient based on reduction of chorea or TD and tolerability.

**Table 3. Dosing and Administration**

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| Austedo (deutetrabenazine) | Tablets | Oral | Twice daily | Initial daily dose: 6 mg (HD) or 12 mg (TD)<br>Maximum daily dose: 48 mg<br>Titrated at weekly intervals by 6 mg per day<br>Administer with food |

See the current prescribing information for full details

## CONCLUSION

- Deutetrabenazine represents an additional oral therapeutic option for patients with TD or chorea associated with HD.

- For HD chorea, deutetrabenazine is comparable in safety and efficacy to its RLD, tetrabenazine. The use of both products in HD is limited by dose-related AEs (eg, somnolence, parkinsonism) and a boxed warning for depression and suicidality in a population that is already at a significantly increased risk.
  - Alternatives to tetrabenazine and deutetrabenazine include neuroleptics, which are more commonly used in clinical practice for HD. In addition to suppressing chorea, neuroleptics treat neuropsychiatric symptoms associated with HD.
- For TD, valbenazine is an alternative with the same mechanism of action and a once-daily dosing schedule compared to twice-daily deutetrabenazine.

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Publication Date: September 13, 2017

**Nevada Medicaid**
**Bevyxxa** (betrixaban)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Bevyxxa | betrixaban |

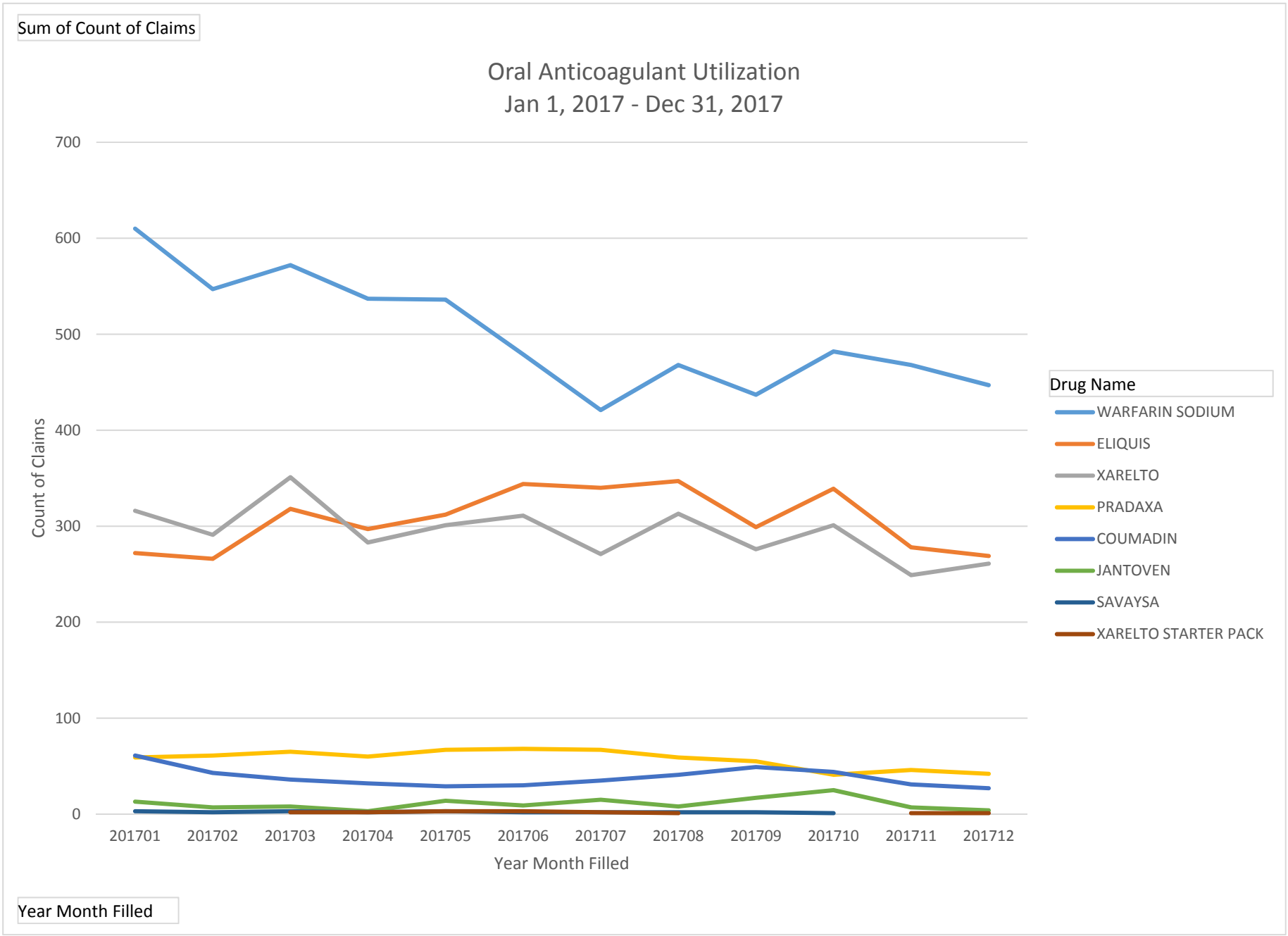
## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Prophylaxis of venous thromboembolism (VTE) :** Indicated for the treatment of prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

### Approval Criteria

1. Medication is used for prophylaxis of venous thromboembolism (VTE)
   **AND**
2. Patient is hospitalized for an acute medical illness (e.g., heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke)
   **AND**
3. Patient is at risk for thromboembolic complications due to moderate or severe restricted mobility and has other risk factors of VTE


Sum of Count of Claims
Oral Anticoagulant Utilization
Jan 1, 2017 - Dec 31, 2017
700
600
500
400
300
200
100
0
Count of Claims
201701
201702
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
Year Month Filled
Drug Name
WARFARIN SODIUM
ELIQUIS
XARELTO
PRADAXA
COUMADIN
JANTOVEN
SAVAYSA
XARELTO STARTER PACK
Year Month Filled

## INTRODUCTION

- The oral anticoagulants include BEVYXXA® (betrixaban), ELIQUIS® (apixaban), PRADAXA® (dabigatran), SAVAYSA® (edoxaban), XARELTO® (rivaroxaban), and warfarin (COUMADIN®, JANTOVEN®).
- Warfarin has been the principal oral anticoagulant for more than 60 years and has extensive, well established data demonstrating its safety and efficacy. However, warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- Four target-specific oral anticoagulants (TSOACs), ELIQUIS, PRADAXA, SAVAYSA, and XARLETO, are indicated for the reduction of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), otherwise known as events caused by a venous thromboembolism (VTE). PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE. PRADAXA, XARELTO, and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing hip replacement surgery and XARELTO and ELIQUIS have further indications for knee replacement surgery. BEVYXXA is the only agent in class indicated for patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- Atrial fibrillation (AF) is one of the most common cardiac arrhythmias in the US, affecting approximately 2.7 to 6.1 million people in 2010. AF has been associated with death either directly or cited as an underlying cause contributing to mortality. Stroke is the most concerning complication of AF. Before the widespread use of anticoagulants, and after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke (*Benjamin et al, 2017*). Approximately 5 to 8% of patients who require percutaneous coronary intervention (PCI) with stents have AF (*Gibson et al, 2016*).
- In patients with AF, oral anticoagulants are recommended for those who are at an intermediate or greater risk of stroke and selection should be based on individual patient characteristics (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).
- VTE encompasses both DVT and PE. The precise number of people affected is unknown, but it is estimated to affect ~900,000 US patients (*CDC, 2017*). Of those who suffer a DVT, approximately a third will have a recurrence within 10 years. Knee and hip replacement surgeries are associated with a high risk of VTE, which can lead to recurrent VTE events as well as post-thrombotic syndrome, and PE, which can be fatal. Without anticoagulant therapy, 40% to 50% of patients undergoing hip replacement surgery suffer VTE. This rises to 70% to 80% in hip fracture (*American Academy of Orthopaedic Surgeons [AAOS], 2011; Guyatt et al, 2012; Kearon et al, 2016*).
- Hospitalization is a risk factor for VTE with an estimated 22% of VTE occurrences following non-surgical hospital admissions (*Heit et al, 2002*). Additionally, an estimated 4.6 per 1000 admissions are complicated by symptomatic VTE, which can lead to a higher risk of morbidity and mortality (*Zakai et al, 2013*).
- Pharmacological anticoagulants available for the treatment of VTE (not due to orthopedic surgery) include parenteral anticoagulation (low molecular weight heparin [LMWH], fondaparinux, or intravenous [IV] or subcutaneous [SC] unfractionated heparin [UFH]) typically administered with warfarin, and the TSOACs (XARELTO, ELIQUIS, PRADAXA, or SAVAYSA) (*Guyatt et al, 2012; Kearon et al, 2016; Micromedex® 2.0, 2017*).
- Thromboprophylaxis is recommended to prevent VTE in patients undergoing total hip or knee replacement. Pharmacological anticoagulants available for the prophylaxis of VTE after orthopedic surgery include aspirin, LMWHs, warfarin, PRADAXA, and factor (F) Xa inhibitors (ARIXTRA® [fondaparinux], XARELTO, or ELIQUIS) (*AAOS, 2011; Guyatt et al, 2012*).
- The oral anticoagulants work through varied mechanisms of action. XARELTO, SAVAYSA, BEVYXXA, and ELIQUIS are selective FXa inhibitors, while PRADAXA is a direct thrombin inhibitor. Warfarin is a vitamin K antagonist (VKA) that works by interfering with the synthesis of vitamin K dependent clotting factors. Vitamin K, therefore, serves as a reversal agent for warfarin.

- In 2015, the first TSOAC reversal agent, PRAXBIND® (idarucizumab), was FDA-approved. PRAXBIND is indicated for the reversal of PRADAXA's anticoagulation effects as needed for emergency surgery, urgent procedures, and in life-threatening or uncontrolled bleeding (*PRAXBIND prescribing information, 2015*).
- There are no specific antidotes for BEVYXXA, ELIQUIS, SAVAYSA or XARELTO. ANDEXXA® (andexanet alfa) is an investigational agent that was submitted to the FDA for approval. Studies currently support use with ELIQUIS and XARELTO. In August 2016, the FDA issued a complete response letter (CRL) requesting additional information. In August 2017, Portola Pharmaceuticals announced that they re-submitted the biologics licensing application (BLA) addressing deficiencies noted in the CRL (*Portola Pharmaceuticals press release, 2017*).
- Another antidote, ciraparantag, is an intravenously administered small molecule which has demonstrated complete and sustained reversals of SAVAYSA and LOVENOX without rebound anticoagulation in Phase 2 trials and the reversal of PRADAXA, XARELTO, ELIQUIS, fondaparinux, and heparin ex vivo (*Perosphere press release, 2017*).

- Medispan class: Anticoagulants; Thrombin Inhibitors - Dabigatran; Coumarin Anticoagulants; Direct FXa Inhibitors

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| BEVYXXA (betrixaban) | - |
| ELIQUIS (apixaban) | - |
| PRADAXA (dabigatran) | - |
| SAVAYSA (edoxaban) | - |
| XARELTO (rivaroxaban) | - |
| COUMADIN, JANTOVEN (warfarin) | ✔ |

(*Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | BEVYXXA (betrixaban) | ELIQUIS (apixaban) | PRADAXA (dabigatran) | SAVAYSA (edoxaban) | XARELTO (rivaroxaban) | COUMADIN JANTOVEN (warfarin)† |
|---|---|---|---|---|---|---|
| Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement | | | | | | ✔ |
| Prophylaxis and treatment of venous thrombosis and its extension, PE | | | | | | ✔ |
| Reduce the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI | | | | | | ✔ |
| Reduce the risk of stroke and systemic embolism in patients with NVAF | | ✔ | ✔ | ✔ ‡ | ✔ | |
| Prophylaxis of DVT, which may lead to PE, in patients undergoing knee (TKR) or hip (THR) replacement surgery | | ✔ | | | ✔ | |
| Prophylaxis of DVT and PE in patients undergoing THR surgery | | | ✔ | | | |
| Treatment of DVT and PE | | ✔ | ✔ * | ✔ * | ✔ | |
| Reduction in the risk of recurrence of DVT and PE following initial therapy | | ✔ | ✔ | | ✔ | |
| Prophylaxis of VTE in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE | ✔ § | | | | | |

*Prior to treatment, patients should have been treated with parenteral anticoagulant for 5 to 10 days.
†Limitation of use: Warfarin has no direct effect on an established thrombus, nor does it reverse ischemic tissue damage.
‡Not indicated in NVAF patients with creatinine clearance (CrCL) > 95 mL/min due to increased rates of ischemic stroke.
§Limitation of use: Use has not been established in patients with prosthetic heart valves.

(*Prescribing information: BEVYXXA, 2017; COUMADIN, 2016; ELIQUIS, 2016; JANTOVEN, 2011; PRADAXA, 2015; SAVAYSA, 2016; XARELTO, 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Warfarin has been the principal oral anticoagulant for more than 60 years and the evidence demonstrating the safety and efficacy in Food and Drug Administration (FDA)-approved indications is well established (*Aguilar, 2005; Cundiff et al, 2006; DiNisio et al, 2012; Hutten, 2006; Lopes et al, 2013; Middeldorp et al, 2014; Salazar et al, 2010; Saxena, 2004; van der Heijden et al, 2001*).
- There is no direct comparator evidence of the TSOACs; therefore, caution should be exercised when drawing conclusions based on indirect data.

Non-valvular Atrial Fibrillation:

- Four large randomized controlled trials (RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48, and ROCKET AF) were the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively. Baseline populations varied for the PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials, with a mean proportion of 64%, 62%, 65%, and 55% time in therapeutic range (TTR) for warfarin patients and a mean baseline $CHADS_2$ score of 2.1, 2.1, 2.8, and 3.5, respectively (*Connolly et al, 2009; Connolly et al, 2011; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011*).
- The primary efficacy endpoint was stroke or systemic embolism, in which the following outcomes were reported:
  - PRADAXA was superior (relative risk [RR] for PRADAXA150 mg twice daily vs warfarin, 0.66 [95% confidence interval {CI}, 0.53 to 0.82], P < 0.001).
  - ELIQUIS was superior (Hazard ratio [HR] for ELIQUIS 5 mg twice daily vs warfarin, 0.79 [95% CI, 0.66 to 0.95], P = 0.01).
  - SAVAYSA was non-inferior (HR for SAVAYSA 60 mg once daily vs warfarin, 0.79 [97.5% CI, 0.63 to 0.99], P < 0.001; HR for SAVAYSA 30 mg once daily vs warfarin, 1.07 [97.5% CI, 0.87 to 1.31], P = 0.005).
  - XARELTO was non-inferior (HR for XARELTO 15 to 20 mg once daily vs warfarin, 0.88 [95% CI, 0.75 to 1.03], P < 0.001).
- In terms of safety, the following important outcomes were observed in trials:
  - All TSOACs had fewer intracranial hemorrhages (ICH) compared to warfarin.
  - For major bleeds, ELIQUIS and SAVAYSA were superior to warfarin (ELIQUIS HR, 0.69 [95% CI, 0.6 to 0.8], P < 0.001; SAVAYSA HR, 0.8 [95% CI, 0.71 to 0.91], P < 0.001) and PRADAXA and XARELTO were non-inferior to warfarin (PRADAXA RR, 0.93 [95% CI, 0.81 to1.07], P = 0.31; XARELTO HR, 1.04 [95% CI, 0.9 to1.2], P = 0.58).
  - For gastrointestinal (GI) bleeds, warfarin significantly out-performed PRADAXA, SAVAYSA, and XARELTO (PRADAXA RR, 1.5 [95% CI, 1.19 to 1.89], P < 0.001; SAVAYSA HR, 1.23 [95% CI, 1.02 to 1.5], P = 0.03; XARELTO HR, not reported [incidence, XARELTO 3.2% vs warfarin 2.2%], P < 0.001); however, ELIQUIS had a similar incidence of GI bleeds when compared to warfarin (ELIQUIS HR 0.89 [95% CI, 0.7 to 1.15], P = 0.37).
- In 2016, the Alere INRatio device, which was used in the ROCKET AF trial, was recalled due to the potential for falsely low INR results. An article from the British Medical Journal (BMJ) suggested that an independent assessment of trial data should be performed. Researchers from the FDA, Bayer, Johnson and Johnson, and the Duke Clinical Research Institute performed a post-hoc data analysis and concluded that the recalled devices did not have significant clinical effects on the primary efficacy and safety trial outcomes. The FDA and European Medicines Agency (EMA) concluded that any incorrect INR measures would have marginal effects on the study outcomes; therefore, they should not impact the safety or benefit-risk balance of XARELTO (*Cohen, 2016; EMA press release, 2016; FDA press release, 2016*)
- Extension trials and additional analyses were conducted for the thromboprophylaxis of NVAF and the following key results were demonstrated:
  - After 2.3 years of PRADAXA treatment, slightly higher rates of stroke and systemic embolism, in addition to increased rates of major bleeding were observed in the long-term trial, RELAY-ABLE, compared to the RE-LY trial, particularly in the FDA-approved 150 mg dose (*Connolly et al, 2013*).
  - One pre-specified secondary analysis of the ENGAGE AF-TIMI 48 trial demonstrated ischemic cerebrovascular event rates were similar with SAVAYSA 60 mg and warfarin, whereas SAVAYSA 30 mg was less effective than warfarin (*Giugliano et al, 2014*). Another pre-specified analysis found that patients with genetic variants of CYP2C9 and

VKORC1 derived a greater early safety benefit in bleeding rates with edoxaban over warfarin (*Mega et al, 2015*). An analysis of the ENGAGE-AF-TIMI 48 trial found that patients with valvular heart disease had an increased risk of death (P < 0.001), major adverse cardiovascular events (P < 0.001), and major bleeding (P = 0.02) than patients without valvular heart disease, but did not change the efficacy and safety result of the higher SAVAYSA dose vs warfarin (*De Caterina et al, 2017*).

- Data regarding GI adverse events and myocardial infarction with PRADAXA treatment have been conflicting. A subgroup analysis of GI adverse events found that PRADAXA demonstrated a statistically significant risk of non-bleeding upper GI effects, which also resulted in a statistically larger proportion of patients discontinuing PRADAXA due to these effects (*Bytzer et al, 2013*).
- A subgroup analysis demonstrated a nonsignificant increase in MI with PRADAXA compared to warfarin but other myocardial ischemic events were not increased. In addition, results revealed that treatment effects of PRADAXA were consistent in patients at higher and lower risk of myocardial ischemic events (*Hohnloser et al, 2012*). In contrast, a meta-analysis demonstrated that PRADAXA 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 VTE, ACS, short term prophylaxis of DVT) when compared against different controls (warfarin, enoxaparin, or placebo). It was not accompanied by an increase in mortality (*Uchino, 2012*).
- One observational cohort study of 134,000 Medicare patients was conducted by the FDA to compare PRADAXA to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within six months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. PRADAXA was found to be associated with a lower risk of ischemic stroke (HR, 0.8; 95% CI, 0.67 to 0.96), ICH (HR, 0.34; 95% CI, 0.26 to 0.46) and death (HR, 0.86; 95% CI, 0.77 to 0.96) vs warfarin. Risk for GI bleeding was higher for PRADAXA (HR, 1.28; 95% CI, 1.14 to 1.44) vs warfarin, and MI risk was similar (HR, 0.92; 95% CI, 0.78 to 1.08). Most results were similar to RE-LY; however, the MI risk was found to be similar between groups rather than an increased risk for PRADAXA as discovered in RE-LY. Also important to note, an increased risk of GI bleeds associated with PRADAXA was similar to the RE-LY study but differs from data found in the Mini Sentinel analysis which found less risk of GI bleeds with new users of PRADAXA vs warfarin (*FDA Drug Safety Communication, 2014*).

- In NVAF patients who require AF cardioversion, standard oral anticoagulant therapy generally consists of a warfarin-based regimen to prevent thrombosis. More recently, FXa inhibitors have been evaluated for this use. Caution should be exercised when interpreting results of these studies as both were underpowered to demonstrate statistically significant differences for efficacy and safety endpoints. Key results are as follows:
  - The X-VeRT trial randomized 1,504 patients with AF undergoing elective cardioversion to XARELTO dosed between 15 to 20 mg daily depending on renal function or a VKA in a 2:1 ratio. The primary endpoint (defined as a composite of stroke, transient ischemic attack, peripheral embolism, MI, and CV death) occurred in 0.5% of XARETO-treated patients vs 1% of VKA-treated patients. Additionally, the proportion of patients who had major bleeding were similar in the XARELTO and VKA treatment groups (0.6% vs 0.8%, respectively) (*Cappato et al, 2014*).
  - The ENSURE-AF trial randomized 2,199 NVAF patients undergoing cardioversion to SAVAYSA 30 to 60 mg daily vs an enoxaparin/warfarin regimen. The primary efficacy endpoint (defined as a composite of stroke, systemic embolic event, MI, or CV mortality) occurred in 0.5% of SAVAYSA-treated patients vs 1% of enoxaparin/warfarin-treated patients. Additionally, the proportion of patients who had a first major or clinically relevant non-major bleeding occurrence were similar (1% for each group) (*Goette et al, 2016*).

Triple anticoagulant therapy after cardiac procedures

- Some patients require triple anticoagulant therapy in cases of cardiac procedures, including PCI, which may be indicated in patients with AF with certain co-morbid diseases. There is limited evidence to guide appropriate treatment. Evidence has been controversial and often outcomes vary greatly according to the population studied requiring clinicians to balance the risk of thrombosis and ischemic stroke with that of potential bleeding. Studies have demonstrated that a $P2Y_{12}$ inhibitor plus aspirin are superior to warfarin in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent, but found oral anticoagulation was superior to dual antiplatelet therapy (DAPT) in reducing the risk of ischemic stroke in patients with AF (*Connolly et al, 2006; Cutlip et al, 1999; Gibson et al, 2016; Leon et al, 1998*).
  - Prior trials examining the use of oral anticoagulants vs DAPT post-procedurally has yielded mixed results. The ACTIVE-W trial found DAPT was inferior to warfarin for the prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking oral anticoagulation therapy; however, in the STARS trial, DAPT was superior to an oral anticoagulant for the prevention of thrombosis related to coronary stent insertion (*Connolly et al,*

*2006; Cutlip et al, 1999*). Most evidence with triple therapy has included warfarin and consists of small open-label (OL) RCTs or observational studies (*Dewilde et al, 2013; Fiedler et al, 2015*).
  - Recent American Heart Association (AHA) guidance recommends an assessment of CHA2DS2-VASc risk score to estimate the thromboembolic risk and the HASBLED risk score to estimate the hemorrhagic risk. The AHA recommends including the patient in a shared decision regarding the selection of DAPT vs triple therapy as well as the duration of therapy post-procedurally. Although the AHA acknowledges that both European and Canadian guidelines suggest TSOACs over warfarin for triple therapy, this has been based on lower quality observational data and post-hoc analyses (*Raval et al, 2017*). Current AHA guidance acknowledges that in spite of limited data, certain patients for whom it is difficult to reach and maintain therapeutic INR levels with warfarin may warrant the use of a TSOAC with DAPT (but not in combination with prasugrel or ticagrelor) after PCI (*Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017*).
- Studies are currently underway examining the benefits and risks of triple anticoagulant therapy. These studies, including the recently published PIONEER-AF-PCI trial and the ongoing RE-DUAL PCI, RT-AF, SAFE-A, and AUGUSTUS studies, will provide further insights into the use of a TSOAC with DAPT in patients undergoing PCI (*Cannon et al, 2016; Gao et al, 2015; Gibson et al, 2016; Hoshi et al, 2017; Ravel et al, 2017*). A number of studies have been conducted with three of the TSOACs which included triple therapy anticoagulant regimens for the treatment of secondary ACS prevention; however, this indication has not been FDA-approved and the percentage of patients who had concomitant AF has not been well documented:
  - ELIQUIS and PRADAXA have been studied in patients after an ACS via the APPRAISE trials and REDEEM trials, respectively. Trial outcomes resulted in minimal to no clinical benefit; however, an increased risk of harm was observed as bleeding events (*Alexander et al, 2009; Cornel et al, 2015; Ogawa et al, 2013; Oldgren et al, 2011*).
  - XARELTO has been studied at doses of 2.5 mg or 5 mg twice daily vs placebo in 15,526 patients with recent ACS and followed for approximately two years via the DB, PC, ATLAS trial. ACS patients were also administered DAPT therapy with a low-dose aspirin or thienopyridine (either clopidogrel or ticlopidine). XARELTO 2.5 mg twice daily dosing not only significantly reduced the primary endpoint (defined as the composite of death from CV causes, MI, or stroke; P = 0.02), but unlike the 5 mg dosing, the 2.5 mg dose also reduced the rate of death from CV or any cause (P = 0.002 for both). This benefit, however, was tempered by an increased risk of non-coronary artery bypass grafting (CABG) thrombolysis in myocardial infarction (TIMI) major bleeding (P < 0.001) and ICH (P = 0.04) vs placebo (*Mega et al, 2012*).
  - The recently conducted PIONEER-AF-PCI trial was a large, OL, randomized safety trial (N = 2,124) conducted in patients with NVAF undergoing PCI with stent placement and compared triple therapy strategies with XARELTO and warfarin. Patients were randomized to: (1) XARELTO 15 mg once daily plus clopidogrel 75 mg daily for 12 months, or (2) XARELTO 2.5 mg twice daily plus DAPT with a prespecified duration of 1, 6 or 12 months, or (3) warfarin plus DAPT with a prespecified duration of 1, 6 or 12 months. Patients administered XARELTO-based regimens had a lower risk of the primary safety endpoint of clinically significant bleeding (composite of major or minor TIMI bleeding or bleeding requiring medical attention) compared to warfarin (17.4% and 26.7%, respectively; P < 0.001). Clinically significant bleeding was driven by bleeding requiring medical attention. For the secondary efficacy endpoints, patients experienced no difference in major adverse CV events (defined as a composite of death from CV causes, MI, or stroke) or stent thrombosis compared to warfarin plus DAPT; however, caution should be exercised as the study was not powered for this outcome and clinical efficacy remains uncertain (*Gibson et al, 2015; Gibson et al, 2016*).

<u>VTE treatment</u>

- Six large, randomized controlled trials (RE-COVER, RE-COVER II, AMPLIFY, Hokusai-VTE, EINSTEIN-DVT and EINSTEIN-PE) evaluated the efficacy and safety of PRADAXA, ELIQUIS, SAVAYSA, and XARELTO vs warfarin, respectively, for the treatment of acute VTE (although PRADAXA and SAVAYSA trials had 5 to 10 days treatment with a parenteral anticoagulant prior to initiating treatment). Baseline populations for PRADAXA, ELIQUIS, SAVAYSA, and XARELTO trials varied greatly including the following characteristics (*Schulman et al, 2009; Schulman et al, 2009; Agnelli et al [a], 2013; Büller et al, 2013; Bauersachs et al, 2010; Büller et al, 2012; Prins et al, 2013*):
  - Patients aged ≥ 75 years ~10%, 14%, 13.5%, and 13 to 17%, respectively
  - Prior VTE ~22%, 16%, 18%, and 19 to 20%, respectively
  - Unprovoked VTE ~ 35%, 89.8%, 65.7%, and 62 to 64.5%, respectively
  - Cancer at baseline ~4.3%, 2.7%, 9.3%, and 5.2%, respectively
  - Duration of treatment: 6 months, 6 months, 3 to 12 months, and measures at 3, 6, and 12 months, respectively
  - TTR ~ 60%, 61%, 64%, and 58 to 63%, respectively

- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - For RE-COVER, recurrent VTE and related deaths occurred in 2.4% in the PRADAXA arm and 2.1% in the warfarin arm (P < 0.001 for non-inferiority). Major bleeding was similar (1.6% PRADAXA vs 1.9% warfarin), but more PRADAXA patients discontinued treatment due to adverse events (9%) compared to warfarin (6.8%; P < 0.05) (*Schulman et al, 2009*).
  - In RE-COVER II, symptomatic VTE or VTE- related deaths occurred in 2.3% of PRADAXA patients vs 2.2% of warfarin patients (P < 0.001 for non-inferiority). Major bleeding was similar; however, warfarin had significantly more overall bleeds in 22.1% of patients compared to 15.6% PRADAXA patients (P < 0.05) (*Schulman et al, 2014*).
  - In AMPLIFY, non-inferiority was met for the primary outcome of recurrent symptomatic VTE or death related to VTE in 2.3% ELIQUIS patients vs 2.7% conventional therapy patients (RR, 0.84; 95% CI, 0.6 to 1.18). Significantly more major bleeding was observed with conventional therapy (1.8%) compared to patients treated with ELIQUIS (0.6%) (*Agnelli et al [a], 2013*).
  - For Hokusai-VTE, SAVAYSA was non-inferior to warfarin for the prevention of recurrent VTE after treatment with parenteral anticoagulants (in 3.2% SAVAYSA vs 3.5% warfarin after 12 months follow-up; HR, 0.89; 95% CI, 0.7 to 1.13; P < 0.001 for non-inferiority). Significantly lower rates of major or clinically relevant non-major bleeding were observed in 8.5% of SAYVASA patients compared to 10.3% of warfarin patients (P = 0.004), but major bleeding was similar (P = 0.35) (*Büller et al, 2013*).
  - The results from EINSTEIN-DVT demonstrated XARELTO to be non-inferior to standard therapy (2.1% for XARELTO vs 3% for enoxaparin/VKA; P < 0.001 for non-inferiority) for symptomatic recurrent VTE. Identical rates (8.1%) of major or non-major clinically relevant bleeding were shown. Net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding favored XARELTO (reported in 2.9% XARELTO vs 4.2% enoxaparin/VKA patients; P = 0.03) (*Bauersachs et al, 2010*).
  - In EINSTEIN-PE, XARELTO was shown to be non-inferior to enoxaparin/VKA (2.1% XARELTO vs 1.8% enoxaparin/VKA; HR, 1.12; 95% CI, 0.75 to 1.68) for symptomatic recurrent VTE. The principal safety outcome, clinically relevant bleeding, occurred in 10.3% of XARELTO patients and 11.4% of standard therapy patients (HR, 0.9; 95% CI, 0.76 to 1.07; P = 0.23). Major bleeding was observed in 1.1% XARELTO patients and 2.2% in the standard-therapy group (HR, 0.49; 95% CI, 0.31 to 0.79; P = 0.003). Net clinical benefit occurred in 3.4% of XARELTO patients and 4% of standard therapy patients (HR, 0.85; 95% CI, 0.63 to 1.14; P = 0.28) (*Büller et al, 2012*).

Reduction in Recurrent VTE

- Four large randomized controlled trials (RE-MEDY, RE-SONATE, AMPLIFY-EXT, and EINSTEIN-EXT) were evaluated for the reduction in recurrent VTE and the basis for clinical efficacy and safety for PRADAXA, ELIQUIS, and XARELTO vs placebo, respectively (however, PRADAXA is the only agent compared to warfarin as observed in the RE-MEDY trial). Each trial was an extension of the acute VTE trials mentioned previously (*Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013*). The EINSTEIN CHOICE trial also evaluated the rate of recurrent VTE with long-term TSOAC treatment (*Weitz et al 2017*).
- The primary efficacy and safety endpoints also varied among trials. Important data include the following:
  - The RE-MEDY (comparing PRADAXA to warfarin) and RE-SONATE (comparing PRADAXA to placebo) trials had similar efficacy results with recurrent VTE reported in 1.8% PRADAXA vs 1.3% warfarin (P = 0.01 for non-inferiority) in the RE-MEDY trial and 0.4% PRADAXA vs 5.6% placebo (P < 0.001) in the RE-SONATE trial. However, RE-MEDY displayed lower major bleeding in the PRADAXA group (0.9% PRADAXA vs 1.8% warfarin; HR, 0.52; 95%, 0.27 to 1.02) compared to that of the RE-COVER trials (*Schulman et al, 2013*).
  - In AMPLIFY-EXT, extended treatment with ELIQUIS demonstrated superiority vs placebo in the reduction of the composite endpoint of symptomatic, recurrent VTE and death from any cause (8.8% placebo vs 1.7% for each ELIQUIS 2.5 and 5 mg groups). Across the trial, the rates of major bleeding were low and comparable (placebo 0.5% vs 0.2% and 0.1% for ELIQUIS 2.5 and 5 mg, respectively) (*Agnelli et al [b], 2013*).
  - In the EINSTEIN-EXT, XARELTO was superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs 7.1%; HR, 0.18; 95% CI, 0.09 to 0.39; P < 0.001). Rates of major bleeding were similar (0.7% vs 0%; P = 0.11). The outcome of net clinical benefit was significantly in favor of XARELTO, with symptomatic recurrent VTE plus major bleeding reported in 2% of XARELTO patients vs 7.1% of placebo patients (P < 0.001) (*Bauersachs et al, 2010*).
  - Recently, the EINSTEIN CHOICE trial (N = 3,365) evaluated the rates of recurrent VTE with a long duration of treatment with XARELTO 10 mg (N = 1,127), 20 mg (N = 1,107), or aspirin 100 mg (N = 1,131) once daily after 6 to 12 months of therapy. Patients in the XARELTO 10 and 20 mg groups had a significantly lower rate of recurrence of

VTE compared to aspirin 100 mg (1.2 vs 1.5 vs 4.4%; P < 0.001 for both XARELTO groups). The rates of major bleeding were similar between groups (0.4 vs 0.5 vs 0.3%, respectively). Of note, patients within the study were younger than a real world population; therefore, results may not be generalizable (*Weitz et al 2017*).

- Current guidelines recommend LMWH in patients who have recurrent VTE, including those currently stable on VKA or TSOAC therapy (*Kearon et al, 2016*).

VTE prophylaxis for total knee (TKR) and/or hip (THR) replacement surgery

- Nine large randomized, double blinded (DB) trials (RE-NOVATE and RE-NOVATE II [hip], RECORD 1 and 2 [hip], RECORD 3 and 4 [knee], ADVANCE 1 and 2 [knee], and ADVANCE 3 [hip]) were the basis for clinical efficacy and safety for PRADAXA, XARELTO, and ELIQUIS vs enoxaparin, respectively in VTE prophylaxis for TKR or THR surgeries. Duration of treatment, dose strength, and frequency varied for each group among trials.
- When evaluating anticoagulation therapies for patients undergoing THR or TKR endpoints use of the surrogate measure, asymptomatic DVT, detected by mandatory venography. The American College of Chest Physicians (ACCP) guidelines find this outcome unsatisfactory due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding. The guidelines provide suggestions to estimate reductions in symptomatic thrombosis; however, this is contingent on available evidence. Many studies rely on asymptomatic DVT events to determine differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates (*Guyatt et al, 2012*).
- Data from the THR trials found XARELTO and ELIQUIS to be superior to enoxaparin 40 mg once daily and PRADAXA to be non-inferior to enoxaparin 40 mg once daily when prescribed for orthopedic prophylaxis (*Eriksson et al, 2008; Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011; Kakkar et al, 2008; Lassen et al, 2010 [a]; Lassen et al, 2010 [b]*).
  - RE-NOVATE and RE-NOVATE II: The RE-NOVATE trial compared 150 and 220 mg of dabigatran to enoxaparin 40 mg per day and the RE-NOVATE II trial compared 220 mg of dabigatran to enoxaparin 40 mg per day in over 5,500 patients. In both trials, dabigatran was as effective as enoxaparin in reducing the risk of VTE and mortality after THR surgery (P for non-inferiority < 0.001). The incidence of major bleeding did not differ significantly among groups (enoxaparin 0.9% to 1.6% vs dabigatran 1.3% to 2%) (*Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011*).
  - ADVANCE-3: Apixaban 2.5 mg twice daily was superior to enoxaparin in approximately 5,400 patients in reducing the risk of VTE and mortality after THR surgery (P < 0.001). The incidence of adjudicated major bleeding events were similar between groups (enoxaparin 0.8% vs apixaban 0.7%) (*Lassen et al, 2010 [b]*).
  - RECORD 1: Rivaroxaban 10 mg once daily was superior to enoxaparin in approximately 5,600 patients for the combined endpoint of any DVT, nonfatal PE, or all-cause mortality up to day 42 for rivaroxaban and ranged from 1.1% to 2% compared to 3.7% to 9.3% for enoxaparin. Major VTE was decreased 0.2% to 0.6% with rivaroxaban compared with 2% to 5.1% with enoxaparin. The incidence of major bleeding was similar between groups (enoxaparin 0.1% vs rivaroxaban 0.3%; P = 0.18) (*Eriksson et al, 2008; Kakkar et al, 2008*).
- Studies in patients undergoing a TKR have conflicting results with evidence demonstrating superiority of XARELTO and ELIQUIS when compared to enoxaparin 40 mg dose. However, TKR studies evaluating the US enoxaparin recommended dose of 30 mg twice daily have demonstrated ELIQUIS to be inferior to enoxaparin for total VTE (RR, 1.02; 95% CI, 0.78 to 1.32; P for non-inferiority = 0.06) through the ADVANCE-1 trial (*Lassen et al, 2009*), and XARELTO has demonstrated superiority to enoxaparin for the primary efficacy endpoint (*Turpie et al, 2009*).
- It is important to note that guidelines favor LMWH over ARIXTRA, ELIQUIS, PRADAXA, XARELTO, or UFH (*AAOS, 2011; Guyatt et al, 2012*).

General VTE prophylaxis for the medically ill:

- Currently, BEVYXXA is the only oral anticoagulant specifically FDA-approved as prophylaxis in patients with restricted mobility from acute illness and other risk factors. The APEX trial was a randomized, DB trial which compared the safety and efficacy of an extended duration of BEVYXXA to a short duration of enoxaparin in patients who were hospitalized due to an acute illness and had risk factors for VTE. A total of 7,513 patients were randomized to BEVYXXA 160 mg orally on day 1, followed by 80 mg once daily for 35 to 42 days (and a subcutaneous placebo injection for 6 to 14 days) or to enoxaparin 40 mg administered subcutaneously once daily for 6 to 14 days (and an oral placebo tablet for 35 to 42 days). Patients with renal insufficiency received 50% of the dose for each medication. In the first cohort analyzed, patients with an elevated D-dimer level, the difference between BEVYXXA and enoxaparin on the primary composite of

asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42 did not reach statistical significance (6.9 vs 8.5%, respectively; RR, 0.81; 95% CI, 0.65 to 1; P = 0.054). In patients with an elevated D-dimer level or an age ≥ 75 years, the composite endpoint was reached in 5.6 vs 7.1%, respectively (RR, 0.8; 95% CI, 0.66 to 0.98; P = 0.03), and in the overall population, it was reached in 5.3 vs 7%, respectively (RR, 0.76; 95% CI, 0.63 to 0.92; P = 0.006). However, because the first test did not reach statistical significance, these subsequent outcomes were considered exploratory. In the overall population, there was no significant difference in the incidence of major bleeding through day 7 after discontinuation of therapy (0.7 vs 0.6%, respectively) (*Cohen et al, 2016*).
    - Additionally, BEVYXXA compared with enoxaparin significantly reduced the incidence of all cause strokes (0.54 vs. 0.97%, respectively; P = 0.032), ischemic strokes (0.48 vs 0.91%, respectively; P = 0.026), and a composite of all cause stroke or transient ischemic attack (0.65 vs 1.1%, respectively; P = 0.034) through 77 days of follow up (*Gibson et al, 2017*).
- For patients who are medically ill and at risk for a DVT or PE, two studies (ADOPT and MAGELLAN) have been conducted for ELIQUIS and XARELTO, respectively. Both TSOACs were compared to enoxaparin 40 mg daily for approximately 10 days to ELIQUIS 2.5 mg twice daily for 30 days and XARELTO 10 mg once daily for 35 days, respectively. The following efficacy and safety outcomes were reported in each trial:
    - ADOPT: ELIQUIS was demonstrated to be similar to enoxaparin for the primary endpoint of composite of total VTE and VTE-related death at 30 days (RR, 0.87; 95% CI, 0.62 to 1.23; P = 0.44) and at 90 days (RR, 1.06; 95% CI, 0.69 to 1.63; P = not reported). Enoxaparin treatment was associated with significantly less risk of bleeding compared to ELIQUIS (*Goldhaber et al, 2011*).
        - MAGELLAN: XARELTO was demonstrated to be as effective as enoxaparin for the primary endpoint of asymptomatic proximal or symptomatic VTE at day 10 (RR, 0.97; 95% CI, 0.71 to 1.31; P = 0.003 for non-inferiority) and superior to enoxaparin at day 35 (RR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02 for superiority). Enoxaparin treatment was associated with significantly less risk of bleeding compared to XARELTO (*Cohen et al, 2013*).
        - The clinical relevance of asymptomatic VTE is unknown in the MAGELLAN trial. The ADOPT trial included a number of endpoints, including the composite of VTE, PE, symptomatic DVT, or asymptomatic proximal leg DVT, and it is not clear if any of the individual measures were significantly different.

Safety in renal insufficiency:

- One meta-analysis of ten randomized controlled trials examined patients with mild to moderate renal insufficiency and AF, acute DVT/PE, or extended treatment of VTE who were administered recommended doses of TSOACs (e.g., ELIQUIS, PRADAXA, or XARELTO). The analysis of key outcomes demonstrated that TSOACs were non-inferior and had improved bleeding compared to conventional anticoagulant treatment with LMWH, VKA, LMWH followed by VKA, or aspirin therapy (*Sardar et al, 2014*).

## CLINICAL GUIDELINES

- In terms of current reputable guidelines, the following has been recommended:
    - For the prevention of stroke and systemic embolism in patients with NVAF, guidelines generally recommend oral anticoagulation in patients with NVAF at intermediate to high risk of stroke, or in certain patients with ≥ 1 moderate risk factors for stroke or thrombosis. TSOACs are considered to be a reasonable option in patients with native aortic valve disease, tricuspid valve disease, or mitral regurgitation, and in AF with a $CHA_2DS_2$-VASc score ≥ 2. Warfarin is generally recommended over the TSOACs, particularly for prosthetic or bioprosthetic valve thrombosis. Expert consensus guidelines stipulate that continuous uninterrupted VKA therapy has demonstrated lower bleeding risks vs interrupted treatment with heparin bridging for certain procedures such as pacemaker implants or implantable cardioverter defibrillators (ICD) in most NVAF patients. Reputable societies encourage decisions to be made based on patient characteristics and a risk/benefit analysis (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).
    - All TSOACs have demonstrated non-inferiority to conventional therapy for acute VTE. The ACCP guidelines recommend the TSOACs over warfarin for the first 3 months of therapy for non-cancer associated VTE. Warfarin is recommended over LMWH for long-term VTE therapy; however LMWH is preferred in patients with cancer (*Guyatt et al, 2012; Kearon et al, 2016*).

- For patients with recurrent VTE and currently administered anticoagulants, the ACCP guidelines recommend patients be switched to LMWH, at least temporarily, in lieu of warfarin and TSOACs. If a recurrent VTE occurs while a patient is taking long-term LMWH, then a dose increase of 1/4 or 1/3 is recommended (*Guyatt et al, 2012; Kearon et al, 2016*).
- For VTE prophylaxis in patients undergoing TKR or THR surgery, the AAOS does not recommend a specific medication (*AAOS, 2011*). The ACCP does favor LMWH over ARIXTRA, ELIQUIS, XARELTO, or UFH (*Guyatt et al, 2012*). If a TSOAC is prescribed, the treatment duration of ELIQUIS and XARELTO is a minimum of 10 to 14 days for a TKR (prescribing information recommends 12 days) and 35 days for a THR which is in agreement with the prescribing information.

## SAFETY SUMMARY

- Contraindications:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
  - BEVYXXA, COUMADIN, ELIQUIS, JANTOVEN, PRADAXA and XARELTO also have contraindications in patients with a severe hypersensitivity to any component of the products.
  - PRADAXA has an additional contraindication in patients with mechanical prosthetic heart valves; additionally, the indication for BEVYXXA has a limitation of use in patients with prosthetic heart valves as this population has not been studied.
  - COUMADIN and JANTOVEN are contraindicated in patients with hemorrhagic tendencies or blood dyscrasias, recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces, threatened abortion, eclampsia, preeclampsia, unsupervised patients with conditions associated with potential high level of non-compliance, spinal puncture, other diagnostic or therapeutic procedures with the potential for uncontrollable bleeding, major regional or lumbar block anesthesia, malignant hypertension, or bleeding tendencies associated with active ulceration, overt bleeding of the GI, genitourinary, or respiratory tract, CNS hemorrhage, cerebral aneurysms, dissecting aorta, bacterial endocarditis, pericarditis, or pericardial effusions.
- A boxed warning exists for:
  - PRADAXA, XARELTO, SAVAYSA, and ELIQUIS with regards to the increased risk of thrombotic events when prematurely discontinuing therapy without adequate continuous anticoagulation. BEVYXXA, or treatment with the aforementioned agents, increases the risk of epidural or spinal hematoma which may cause long-term or permanent paralysis in patients receiving neuraxial anesthesia or undergoing spinal puncture. The optimal timing between the administration of PRADAXA, SAVAYSA, or ELIQUIS and neuraxial procedures is not known.
  - SAVAYSA should not be used in NVAF patients with CrCL > 95 mL/min. In trials, these patients had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin.
  - COUMADIN and JANTOVEN may cause major or fatal bleeding. Drugs, dietary changes, and other factors affect INR levels achieved with COUMADIN or JANTOVEN therapy. Regular monitoring of INR in all patients is recommended.
- Warnings/Precautions:
  - Warnings and precautions for all agents within the oral anticoagulant class include an increased risk of serious or potentially fatal bleeding (including hemorrhage). Patients should be evaluated for signs and symptoms of blood loss or thrombotic events when treated with oral anticoagulants.
  - Additional warnings and precautions for the TSOACs (ELIQUIS, PRADAXA, SAVAYSA, and XARELTO) include a risk of thrombotic events (including stroke) after premature discontinuation, use is not recommended in patients with heart valves (ie, prosthetic, bioprosthetic, mechanical valves, or moderate to severe mitral stenosis), and an increased risk of long-term or permanent paralysis from an epidural or spinal hematoma when neuraxial anesthesia or spinal/epidural puncture is employed in patients treated with an antithrombotic agent.
  - ELIQUIS and XARELTO have a warning and precaution that use is not recommended acutely as an alternative to unfractionated heparin in patients with PE who present with hemodynamic instability or receive thrombolysis or pulmonary embolectomy.
  - COUMADIN, JANTOVEN, and XARELTO has a warning and precaution in pregnant women due to the potential for obstetric hemorrhage. XARELTO may also cause emergent delivery. COUMADIN and JANTOVEN are contraindicated during pregnancy; however, the benefits may outweigh the risks in pregnant patients with mechanical heart valves at high risk of thromboembolism.
  - BEVYXXA and XARELTO have a warning and precaution of use in renal impairment. XARELTO has a warning and precaution of use in hepatic impairment; additionally, BEVYXXA is not recommended for use in these patients.

- An additional warning and precaution for SAVAYSA is reduced efficacy in NVAF patients with CrCL > 95 mL/min.
- COUMADIN and JANTOVEN have a warning and precaution that fatal and serious calciphylaxis or calcium uremic arteriolopathy has been reported with use in patients with and without end stage renal disease. When calciphylaxis is diagnosed, warfarin should be discontinued and an alternate anticoagulant considered. Additional warnings and precautions include the potential for tissue necrosis or gangrene, systemic atheroemboli, cholesterol microemboli, possible limb ischemia, necrosis, and gangrene in patients with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Should any of these issues occur, COUMADIN or JANTOVEN should be discontinued. Should HIT or HITTS occur, treatment with COUMADIN or JANTOVEN may be considered after the platelet count has normalized.

- Adverse events:
  - The most common adverse reactions reported with these agents include bleeding (all agents), anemia (SAVAYSA), rash (SAVAYSA), abnormal liver function tests (SAVAYSA), and gastritis-like symptoms (PRADAXA).
- Drug interactions:
  - BEVYXXA and PRADAXA have a warning and precaution of concomitant use with P-gp inducers or inhibitors, and XARELTO has a warning and precaution of combined use with dual P-gp and strong CYP3A4 inhibitors or inducers. Generally use with these products should be avoided. Although not a warning and precaution, interactions between strong P-gp inhibitors or inducers, CYP3A4 inhibitors or inducers, and oral anticoagulants either in combination or when co-administered alone are noted within the ELIQUIS and SAVAYSA labeling.
  - Concomitant use with other drugs (ie, aspirin, platelet inhibitors, antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs [NSAIDs], selective serotonin reuptake inhibitors [SSRIs], and serotonin norepinephrine reuptake inhibitors [SNRIs]) that impair hemostasis increase the risk of bleeding.
  - Numerous drug and dietary interactions exist for warfarin.
- Additional safety considerations:
  - All oral anticoagulants in class are contraindicated in active pathological bleeding.
    - Two oral anticoagulants have reversal agents available for urgent situations. These include warfarin (COUMADIN and JANTOVEN) and dabigatran (PRADAXA). Vitamin K functions as a reversal agent for warfarin, and idarucizumab (PRAXBIND) is a specific reversal agent for PRADAXA.
    - A specific reversal agent for ELIQUIS, SAVAYSA, and XARELTO is not available. Hemodialysis does not significantly contribute to clearance. The use of prothrombin complex concentrates (PCC), or other procoagulant reversal agents such as activated prothrombin complex concentrate (APCC) or recombinant FVIIa may be considered but has not been evaluated in studies.
      - Andexanet alfa is a reversal agent under clinical development. In August 2016, a CRL was issued by the FDA questioning manufacturing and clinical data. In August 2017, Portola Pharmaceuticals re-submitted the BLA addressing deficiencies noted in the CRL (*Portola Pharmaceuticals press release, 2017*).

## DOSING AND ADMINISTRATION

- Table 3 outlines general dosing recommendations. Please refer to prescribing information for additional details regarding certain drug interactions, various special populations, converting to other anticoagulants, and guidance as it relates to surgical procedures.

**Table 3. Dosing and Administration**

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| BEVYXXA (betrixaban) | Capsule: 40 mg, 80 mg | Reduction in the risk of DVT and PE in hospitalized patients with acute medical illness with restricted mobility and other VTE risk factors: 160 mg as a single dose, followed by 80 mg once daily for 35 to 42 days; CrCL 15 to 29 mL/min or taking concomitant P-gp inhibitors: 80 mg as a single dose, followed by 40 mg once daily for 35 to 42 days | -- | Take with food. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| ELIQUIS (apixaban) | Tablet: 2.5 mg, 5 mg | Reduce the risk of stroke in NVAF: 5 mg twice daily<br><br>In NVAF patients with at least 2 of the following characteristics: (1) age ≥ 80 years, (2) Body weight ≤ 60 kg, or (3) serum creatinine ≥ 1.5mg/dL, the recommended dose is 2.5 mg twice daily.<br><br>Prophylaxis of DVT following hip or knee replacement surgery: Knee: 2.5 mg twice daily for 12 days; Hip: 2.5 mg twice daily for 35 days. Note: First dose should be taken 12 to 24 hrs after surgery.<br><br>Treatment of DVT and PE: 10 mg twice daily for 7 days, followed by 5 mg twice daily.<br><br>Reduction in the risk of DVT and PE recurrence: 2.5 mg twice daily after at least 6 months of treatment for DVT or PE. | -- | For patients unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tabs may be crushed and are stable in water, D5W, apple juice or applesauce. May deliver through a nasogastric tube after mixed in 60 mL of D5W or water. |
| PRADAXA (dabigatran) | Capsule: 75 mg, 110 mg, 150 mg | Reduce the risk of stroke in NVAF: CrCL > 30 mL/min: 150 mg twice daily; CrCL 15 to 30 mL/min: 75 mg twice daily; CrCL 30 to 50 mL/min with concomitant use of P-gp inhibitors (only dronedarone or ketoconazole): 75 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 30 mL/min.<br><br>Treatment of DVT and PE/Reduction in the risk of DVT and PE recurrence:* CrCL > 30 mL/min: 150 mg twice daily; Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min.<br><br>Prophylaxis of VTE following hip replacement surgery: CrCL > 30 mL/min: 110 mg on the first day, then 220 mg once daily for 28 to 35 days; Note: The initial dose should be taken 1 to 4 hrs after surgery. Avoid concomitant use of P-gp inhibitors in patients with CrCL < 50 mL/min. | -- | Take with or without food. |
| SAVAYSA (edoxaban) | Capsule: 15 mg, 30 mg, 60 mg | Reduce the risk of stroke in NVAF: CrCL 95 to 51 mL/min: 60 mg once daily; for CrCL 15 to 50 mL/min: 30 mg once daily; Do not use for CrCL > 95 mL/min<br><br>Treatment of DVT and PE: 60 mg once daily following 5 to 10 days of initial parenteral | -- | Take with or without food. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | anticoagulant; CrCL 15 to 50 mL/min, weight ≤ 60 kg, or taking concomitant P-gp inhibitors: 30 mg once daily | | |
| XARELTO (rivaroxaban) | Tablet: 10 mg, 15 mg, 20 mg<br><br>Starter pack (tablet): 15 and 20 mg | Prophylaxis of DVT following hip or knee replacement surgery: Knee: 10 mg once daily for 12 days<br>Hip: 10 mg once daily for 35 days<br>Note: The initial dose should be taken 6 to 10 hrs after surgery.<br><br>Reduce the risk of stroke in NVAF:<br>CrCL > 50 mL/min: 20 mg once daily with the evening meal<br>CrCL 15 to 50 mL/min: 15 mg once daily with the evening meal<br><br>Treatment of DVT and PE: 15 mg twice daily with food, for first 21 days. Then after 21 days, 20 mg once daily with food for remaining treatment<br><br>Reduction in the risk of recurrence of DVT and of PE: 20 mg once daily with food | -- | The 10 mg, 15 mg and 20 mg tablets may be crushed and are stable in water or applesauce for up to 4 hours. |
| COUMADIN; JANTOVEN (warfarin) | Tablet: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg | Prophylaxis and treatment of the thromboembolic complications associated with AF and/or cardiac valve replacement:<br>Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 for most bioprosthetic and mechanical heart valves and an INR of 2.5 to 3.5 for tilting disk valves, bileaflet mechanical valves in the mitral position, or caged ball or caged disk valves<br><br>Prophylaxis and treatment of venous thrombosis and its extension, PE:<br>Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; maintain an INR of 2 to 3 and treat for a minimum of 3 months and reassess the risk-benefit ratio of long-term treatment.<br><br>Reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI:<br>Initial, 2 to 5 mg/day; Maintenance, 2 to 10 mg/day; for high risk patients with MI, maintain an INR of 2 to 3 (moderate intensity) plus low-dose aspirin ≤ 100 mg/day for at least 3 months after MI | An INR > 4 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding<br><br>Dosing may be modified in patients with certain identified genotypes. | |

## CONCLUSION

- Four TSOACs, PRADAXA, XARLETO, SAVAYSA, and ELIQUIS, are all indicated for the reduction of stroke and systemic embolism in NVAF and for the treatment of DVT and PE, otherwise known as events caused by a VTE. PRADAXA, XARELTO, and ELIQUIS are indicated for the reduction in the risk of recurrence of DVT and PE; and DVT and PE prophylaxis in patients undergoing THR. XARELTO and ELIQUIS are indicated for DVT and PE prophylaxis in patients undergoing TKR surgery. 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 to reduce the risk of death, recurrent MI and thromboembolic events such as stroke or systemic embolization after MI. BEVYXXA is the only agent in class indicated for patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- Warfarin has long-term efficacy and safety data and is generically available. Trial evidence and recommendations from current clinical guidelines support the use of warfarin for all FDA-approved indications.
- Therapy with warfarin is associated with challenges including a slow on- and offset of action, unpredictable variability in response, a narrow therapeutic window, frequent monitoring, and numerous food and drug interactions. In addition, maintenance of a therapeutic level of anticoagulation may be difficult for patients and requires a good understanding of the pharmacokinetic and pharmacodynamic properties of warfarin.
- The major advancement with the TSOACs is that they do not require routine laboratory monitoring; however, this may make it difficult for physicians to objectively assess adherence to therapy. In addition, their propensity for drug and dietary interactions is less than warfarin. There is uncertainty regarding how to manage bleeding or perioperative management in patients treated with TSOACs. There are no FDA-approved assays or calibration reagents to measure the effect of the TSOACs. However, partial thromboplastin time (PTT) and thrombin time (TT) can be useful for measuring the effects of PRADAXA (*Raval et al, 2017*).
- PRADAXA is the first TSOAC with an available antidote, idarucizumab (*PRAXBIND prescribing information, 2015*). There are no specific antidotes for BEVYXXA, ELIQUIS, SAVAYSA, or XARELTO; however, antidotes, ciraparantag and andexanet alfa, are in the pipeline (*Perosphere press release, 2017; Portola Pharmaceuticals press release, 2017*).
- Warfarin, BEVYXXA, SAVAYSA, and XARELTO are approved for once-daily dosing, while ELIQUIS is administered twice-daily. Based on the indication, PRADAXA may be administered once or twice-daily. BEVYXXA, ELIQUIS, PRADAXA, SAVAYSA, and XARELTO require a dose adjustment in patients with renal impairment and are only available as branded products.
- No head-to-head studies have been conducted comparing the TSOACs. Also, there is a lack of long-term efficacy and safety data and limited real-world experience with the TSOACs.
- In terms of current available evidence, the following has been demonstrated:
  - For those TSOACs FDA-approved for the prevention of stroke and systemic embolism in patients with NVAF, all TSOACs have been found to be superior or non-inferior to warfarin within pivotal trials; however, clinical differences have not been clearly defined (*Connolly et al, 2009; Connolly et al, 2014; Giugliano et al, 2013; Granger et al, 2011; Patel et al, 2011*).
  - ELIQUIS, PRADAXA, SAVAYSA, and XARELTO have demonstrated non-inferiority to conventional therapy for acute VTE. XARELTO (EINSTEIN-PE only) and ELIQUIS have also demonstrated significant reductions in major bleeds; however, PRADAXA and SAVAYSA have similar rates of major bleeding compared to that observed with conventional therapy. Due to the design of the trials, SAVAYSA and PRADAXA also require 5 to 10 days of parenteral anticoagulation prior to initiating treatment (*Agnelli et al [a], 2013; Bauersachs et al, 2010; Büller et al, 2013; Büller et al, 2012; Prins et al, 2013; Schulman et al, 2009; Schulman et al, 2014*).
  - For the reduction of risk recurrence of VTE as demonstrated in extended VTE trials, PRADAXA, ELIQUIS, and XARELTO have demonstrated superiority to placebo for recurrent VTE; however, bleeding rates were comparable. PRADAXA has demonstrated non-inferiority to warfarin with less risk of major or clinically relevant bleeding and had lower major bleeding rates than those rates observed in the RE-COVER trials (*Agnelli et al [b], 2013; Bauersachs et al, 2010; Schulman et al, 2013*).
  - For VTE prophylaxis in patients undergoing TKR or THR surgery, XARELTO has demonstrated superiority to enoxaparin doses in both THR and TKR studies. ELIQUIS was found to be superior for THR and when compared to enoxaparin 40 mg once daily for TKR; however, ELIQUIS was found to be inferior to the US enoxaparin recommended dose of 30 mg twice daily (*Eriksson et al, 2008; Kakkar et al, 2008; Lassen et al, 2009; Lassen et al, 2010 [b]; Turpie et al, 2009*). The FDA has approved PRADAXA for VTE prophylaxis associated with THR surgery

after non-inferiority was demonstrated compared to enoxaparin 40 mg once daily and bleeding rates were similar (*Eriksson et al, 2007 [a]; Eriksson et al, 2007 [b]; Eriksson et al, 2011*).

- In hospitalized patients with restricted mobility from acute illness and other VTE risk factors, the use of oral anticoagulants has demonstrated a likelihood to reduce VTE when administered prophylactically. Studies have been conducted with BEVYXXA, ELIQUIS, and XARELTO; however, only BEVYXXA is specifically FDA-approved for this indication. ELIQUIS and XARELTO have demonstrated non-inferiority or were similar to enoxaparin, but were also associated with an increased bleeding risk. BEVYXXA was associated with numerically fewer events of asymptomatic or symptomatic proximal DVT, non-fatal PE, or VTE-related death compared to enoxaparin, but no increased incidence of major bleeding (*Cohen et al, 2013; Cohen et al, 2016; Gibson et al, 2017; Goldhaber et al, 2011*).
- Reputable societies encourage decisions to be made based on indication, patient characteristics, and a risk/benefit analysis (*Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Doherty et al, 2017; Furie et al, 2012; Guyatt et al, 2012; January et al, 2014; Kearon et al, 2016; Kernan et al, 2014; Nishimura et al, 2017; Otto et al, 2017; Ravel et al, 2017; Smith et al, 2017*).

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## Benlysta

**Initial Prior Authorization Criteria**:

- Recipient has a diagnosis of systemic lupus erythematosus (SLE), and
- The drug is prescribed by or in consultation with a rheumatologist, and
- Documentation confirms that the recipient is positive for anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA), and
- Recipient is currently receiving at least one standard of care treatment for SLE that includes one or more of the following agents (unless all agents are contraindicated): corticosteroids, glucocorticoids (e.g., prednisone), antimalarial (e.g., azathioprine, methotrexate, mycophenolate, or immunosuprressants), and
- Recipient must not have active CNS lupus.

**Other suggestions to possibly include:**

- Recipient must be 18 years of age or older,
- SLE active by Selena Sledai score,
- SLE remains active while on corticosteroids, antimalarials, corticosteroids, or immunosuppressants),
- Recipient is not currently receiving treatment for a chronic infection,
- Must not have a history of anaphylaxis with Benlysta,
- Must not have evidence of severe renal disease.

**Continuing Therapy Criteria**:

- Documentation of positive clinical response to Benlysta®.

**Other suggestions to possibly include:**

- Recipient must not have a history of anaphylaxis with Benlysta,
- Must not have evidence of severe renal disease, and
- Recipient must not have active CNS lupus.

**Approval Duration**:

- Initial authorization duration for 6 months.
- Initial authorization was also suggested for 12 months.
- Continued authorization for 12 months.

# Benlysta (belimumab)

DRUG.00044

| Override(s) | Approval Duration |
|---|---|
| Prior Authorization<br>Quantity Limit | 1 year |

| Medications | Comments | Quantity Limit |
|---|---|---|
| Benlysta (belimumab) 120mg Intravenous Solution<br><br>Benlysta (belimumab) 400mg Intravenous Solution | For Medicaid, applicable to AGP, VA MCD ONLY | N/A |
| Benlysta (belimumab) 200mg/ml Prefilled autoinjector/syringe | For Medicaid, applicable to all MCD | 4 injections per 28 days |

**APPROVAL CRITERIA**

Requests for Benlysta (belimumab) may be approved for individuals age 18 or older when **ALL** the following criteria are met prior to initiating therapy:

I. Clinical diagnosis of SLE per the American College of Rheumatology (ACR) criteria; **AND**
II. Unequivocally positive ANA (anti-nuclear antibody) titer greater than or equal to 1:80 or anti-dsDNA (double stranded DNA antibody) greater than or equal to 30 IU/mL; **AND**
III. SLE is active as documented by a SELENA-SLEDAI score greater than or equal to 6 while on current treatment regimen; **AND**
IV. There is no evidence of severe renal disease (proteinuria greater than 6 gm/day, serum creatinine greater than 2.5 mg/dl, or requiring renal dialysis); **AND**
V. There is no evidence of active central nervous system lupus (for example, psychosis or seizures); **AND**
VI. SLE remains active while on corticosteroids, antimalarials, or immunosuppressants (alone or as combination therapy) for at least the last 30 days.

Continuing therapy with Benlysta (belimumab) for treatment of SLE may be approved for individuals age 18 or older when **ALL** the following criteria are met:

I. Clinical diagnosis of SLE per the ACR criteria; **AND**
II. There is documentation of previous improvement in disease activity following treatment with belimumab indicating a therapeutic response; **AND**
III. There is no evidence of severe renal disease (proteinuria greater than 6 gm/day, serum creatinine greater than 2.5 mg/dl, or requiring renal dialysis); **AND**

IV. There is no evidence of active central nervous system lupus (for example, psychosis or seizures).

**May <u>NOT</u> be approved:**

Benlysta (belimumab) **<u>may not</u>** be approved for active SLE when all of the criteria specified above are not met, or when any of the following contraindications are present:

- Individuals treated with rituximab or any other B cell targeted therapy within the past year.
- Individuals treated with IV cyclophosphamide within the past 180 days.
- Individuals treated with intravenous immunoglobulin (Ig) within the past 90 days.
- Individuals that have required prednisone at doses greater than 100 mg/day (or equivalent dose of another steroid) within the past 90 days.
- Individuals that have required treatment for an acute or chronic infection within the past 60 days.
- Individuals with human immunodeficiency virus (HIV) infection, hepatitis B virus infection, or hepatitis C virus infection.

Benlysta (belimumab) **<u>may not</u>** be approved for all other indications.

| State Specific Mandates | | |
|---|---|---|
| State name<br>N/A | Date effective<br>N/A | Mandate details (including specific bill if applicable)<br>N/A |

**<u>Key References</u>**:

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DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.

DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated periodically.

Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2016; Updated periodically.

# Nevada Medicaid
## Benlysta (belimumab)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Benlysta | belimumab |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Systemic Lupus Erythematosus (SLE)** Indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. Limitations of Use: The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Benlysta has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of Benlysta is not recommended in these situations.

### Approval Criteria

**1.** Diagnosis of active systemic lupus erythematosus (SLE)
**AND**
**2.** Autoantibody positive (i.e., anti-nuclear antibody [ANA] titer greater than or equal to 1:80 or anti-dsDNA level greater than or equal to 30 IU/mL) [2, 3]
**AND**
**3.** Currently receiving at least one standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials [e.g., Plaquenil (hydroxychloroquine)], corticosteroids [e.g., prednisone], or immunosuppressants [e.g., methotrexate, Imuran (azathioprine)]) [2, 3]
**AND**
**4.** Prescribed by or in consultation with a rheumatologist

**Approval length:** 6 months

### Reauthorization Criteria

1. Documentation of positive clinical response to Benlysta (belimumab) therapy

**Approval length:** 6 months

# BENLYSTA® (belimumab)

**Protocol:** PHA023
**Effective Date:** September 1, 2016

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***INSTRUCTIONS FOR USE***

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

## COMMERCIAL, MEDICARE AND MEDICAID COVERAGE RATIONALE

Benlysta (belimumab) is **medically necessary** for the treatment of:

**Systemic Lupus Erythematosus** (SLE) when **both** of the following criteria are met:

1. Autoantibody positive [e.g., anti-nuclear antibody (ANA) titer ≥ 1:80 or anti-double-stranded DNA (anti-dsDNA) level ≥ 30 IU/mL]
   AND
2. Currently receiving at least one standard of care treatment for active systemic lupus erythematosus (e.g., antimalarials, corticosteroids, or immunosuppressants)

Benlysta is **not medically necessary** for:

1. Severe active lupus nephritis
2. Severe active central nervous system (CNS) lupus

3. Use in combination with other biologics or intravenous cyclophosphamide
4. Waldenström macroglobulinemia
5. Sjögren's syndrome
6. Rheumatoid arthritis

**Centers for Medicare and Medicaid Services (CMS):**
Medicare does not have a National Coverage Determination (NCD) for BENLYSTA® (belimumab). Local Coverage Determinations (LCDs) for Nevada do not exist at this time. However, HCPC Code J0490 used for BENLYSTA (belimumab) is addressed in the Articles for Approved Drugs and Biologicals: Includes Cancer Chemotherapeutic Agents.

Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf. Accessed July 2016.

**For Medicare and Medicaid Determinations Related to States Outside of Nevada:**
Please review Local Coverage Determinations that apply to other states outside of Nevada.
http://www.cms.hhs.gov/mcd/search

**Important Note:** Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services' Website.

## BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met.

## CLINICAL EVIDENCE

**Medically Necessary Uses**
**Systemic Lupus Erythematosus**
Belimumab is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

Ginzler et al evaluated the efficacy/safety of belimumab plus standard therapy in patients (n=449) with active systemic lupus erythematosus (SLE) treated up to 7 years (n=177 currently ongoing). Patients (n = 345) who completed a double-blind, placebo-controlled, 52-week study of belimumab 1, 4, or 10

mg/kg and 24-week extension of belimumab (placebo switched to 10 mg/kg; belimumab same dose or switched to 10 mg/kg) could receive belimumab 10 mg/kg in an open-label continuation study (n = 296). Disease activity was analyzed in patients with active SLE at baseline of the initial study. Efficacy endpoints measured included percentage change in the Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), frequency of 1 new British Isles Lupus Assessment Group (BILAG) A or 2 new B scores, frequencies of mild-moderate and severe flares as defined by SELENA-SLEDAI Flair Index (SFI), and change in corticosteroid use. Total belimumab exposure over 7 years (double-blind5 and open-label periods) was 1746 patient-years. SLE Responder Index (SRI) response rates reported at Week 52 in autoantibody-positive patients was placebo, 29%; belimumab, 46% ($p<0.05$). Researchers reported the following in the continuation study: 57% of auto-antibody-positive patients had an SRI response by Year 2 and 65% by Year 7; severe flares occurred in 19% with placebo and 17% with belimumab during the first year, with the annual rate declining to 2%-9% during years 2-7. Anti-dsDNA autoantibodies in patients positive for them at baseline had a progressive decline of 40%-60% from baseline over 2-7 years with belimumab. Corticosteroid use decreased over time with ≥ 50-55% reduction in median dose during years 5-7. Serious and overall annual AE rates, including infections, were generally stable or decreased during 7-year treatment. Researchers concluded that the data showed that belimumab administered over the long term with standard therapy was generally well tolerated, and sustained disease control was maintained for up to 7 years in patients with active SLE at baseline.

In a post hoc, pooled analysis of the BLISS-52 and BLISS-76 studies, Strand et al assessed the effects of belimumab treatment on health-related quality of life (HRQOL) in patients with active, autoantibody-positive systemic lupus erythematosus (SLE). The authors analyzed data from the major secondary endpoints of the two studies, which were the mean change in SF-36v2 Health Survey Physical Component Summary (PCS) scores at week 24. Additional pre-specified secondary endpoints included mean changes from baseline in Short Form-36 (SF-36) PCS, Mental Component Summary (MCS), and domains, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) V.4, and EuroQol-5D (EQ-5D) scores at weeks 12, 24, 52 and 76 (BLISS-76 only). The SF-36, FACIT-Fatigue, and EQ-5D were administered at baseline, and weeks 4, 8, 12, 24 and 52 in both trials, and additionally at weeks 20, 32, 40, 48, 68 and 76 in BLISS-76 and week 36 in BLISS-52. Baseline SF-36 scores were 1.5 standard deviations (SDs) below age-/sex-matched US norms with similar improvement at week 24 across treatment groups. Mean changes from baseline in PCS scores were significantly ($p<0.05$) greater with belimumab 1 mg/kg (4.20) and 10 mg/kg (4.18) versus placebo (2.96) in BLISS-52, week 52. In BLISS-76, significantly ( $p<0.05$) greater improvements were seen with belimumab 1 mg/kg in PCS (belimumab 1 mg/kg=4.37, 10 mg/kg=3.41 vs placebo=2.85) and Mental Component Summary (MCS) scores (belimumab 1 mg/kg=3.14, 10 mg/kg=2.70 vs placebo=1.40) at week 52, and in MCS score at week 76 (belimumab 1 mg/kg=3.05, 10 mg/kg=2.28 vs placebo=1.36), however, mean changes in PCS and MCS scores with belimumab 10mg/kg were not significantly different (week 52: PCS=3.41, MCS=2.70, and MCS week 76=2.28). In pooled analysis, there were significantly greater improvements in PCS scores with both belimumab doses versus placebo ($p<0.05$), and MCS scores with 1mg/kg ($p<0.01$). FACIT-Fatigue scores were not significantly different at week 24, however at week 52, scores improved significantly ($p<0.05$) with belimumab 1 and 10mg/kg vs. placebo in BLISS-52, and with 1mg/kg at weeks 52 and 76 in BLISS-76. In pooled analysis, FACIT-Fatigue scores were significantly improved ($p<0.05$) with both dosages at week 52, as well as weeks 8 and 12. EQ-5D utility index and VAS scores were not significantly different between treatment groups in BLISS-52. In BLISS-76, the EQ-5D VAS score was only

significantly improved with belimumab 1mg/kg at week 52. The authors concluded that patients receiving belimumab reported clinically meaningful improvements in HRQOL and fatigue versus placebo, in both individual BLISS studies and by pooled analyses, that are consistent with the reductions in disease activity observed in the trials.

**Not Medically Necessary**

Efficacy of belimumab has not been established in patients with severe active lupus nephritis or severe active CNS lupus, and belimumab has not been studied in combination with other biologic agents or IV cyclophosphamide. Therefore, use of belimumab in these situations is **not medically necessary**. The use of belimumab is also being investigated for treatment of other conditions, such as, Waldenström macroglobulinemia, Sjögren's syndrome, and rheumatoid arthritis. Use of belimumab is considered **not medically necessary** for these indications due to a lack of large, controlled clinical trials and published evidence demonstrating improved health outcomes.

**Professional Societies**

**The European League Against Rheumatism (EULAR)**

In 2008, EULAR published their recommendations for the treatment of systemic lupus erythematosus (SLE). Their recommendations are as follows.

**A. GENERAL MANAGEMENT**

**1. Treatment**

In the treatment of SLE without major organ manifestations antimalarials and/or glucocorticoids are of benefit and may be used. NSAIDs may be used judiciously for limited periods of time at patients at low risk for their complications. In non-responsive patients or patients not being able to reduce steroids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate should also be considered.

**2. Adjunct therapy**

Photo-protection may be beneficial in patients with skin manifestations and should be considered. Lifestyle modifications (smoking cessation, weight control, exercise) are likely to be beneficial for patient outcomes and should be encouraged. Depending on the individual medication and the clinical situation, other agents (low-dose aspirin, calcium/vitamin D, biphosphonates, statins, anti-hypertensives (including angiotensin converting enzyme inhibitors)) should be considered. Estrogens (oral contraceptives, hormonal replacement therapy) may be used but accompanying risks should be assessed.

**B. NEUROPSYCHIATRIC LUPUS**

More expansive EULAR guidelines for neuropsychiatric lupus were published in 2010. Treatment guidelines from 2008 are below:

**1. Treatment**

SLE patients with major neuropsychiatric manifestations considered to be of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressive therapy.

## C. PREGNANCY IN LUPUS

Pregnancy affects mothers with SLE and their off-springs in several ways.

### 1. Mother

There is no significant difference in fertility in lupus patients. Pregnancy may increase lupus disease activity but these flares are usually mild. Patients with lupus nephritis and anti-phospholipid antibodies are more at risk of developing pre-eclampsia and should be monitored more closely.

### 2. Fetus

SLE may affect the fetus in several ways, especially if the mother has a history of lupus nephritis, antiphospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with an increase of the risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction and fetal heart block. Prednisolone, azathioprine, hydroxychloroquine, and low dose aspirin may be used in lupus pregnancies. At present evidence suggests that mycophenolate mofetil, cyclophosphamide and methotrexate must be avoided.

## D. ANTI-PHOSPHOLIPID SYNDROME

In patients with SLE and anti-phospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss. Other risk factors for thrombosis should also be assessed. Estrogen-containing drugs increase the risk for thrombosis. In non-pregnant patients with SLE and APS–associated thrombosis, long-term anticoagulation with oral anticoagulants is effective for secondary prevention of thrombosis. In pregnant patients with SLE and anti-phospholipid syndrome combined unfractionated or LMW heparin and aspirin reduce pregnancy loss and thrombosis and should be considered.

## E. LUPUS NEPHRITIS

More expansive EULAR guidelines for lupus nephritis were published in 2012.
Treatment guidelines from 2008 are below:

### 1. Treatment

In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however, associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared to pulse cyclophosphamide and a more favorable toxicity profile: failure to respond by 6 months should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

### 2. End-stage renal disease

Dialysis and transplantation in SLE have comparable rates for long-term patient and graft-survival as those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

## U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Benlysta is a B-lymphocyte stimulator (BLyS)-specific inhibitor FDA-labeled for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy.

Limitations of Use:

- The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.
- Benlysta has not been studied in combination with other biologics or intravenous cyclophosphamide.

Use of Benlysta is **not recommended** in these situations.

Progressive Multifocal Leukoencephalopathy (PML):
Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including Benlysta. Risk factors for PML include:

- Testing positive for anti-JC virus (JCV) antibodies
- Longer duration of treatment with immunosuppressant therapies, including Benlysta
- Impairment of immune function.

The risks and benefits of continuing treatment with Benlysta should be carefully considered in those patients who are found to be anti-JCV antibody positive and have one or more of these risk factors for PML.

Consider the diagnosis of PML in any patient presenting with new-onset or deteriorating neurological signs and symptoms and consult with a neurologist or other appropriate specialist as clinically indicated. In patients with confirmed PML, consider stopping immunosuppressant therapy, including Benlysta.

A patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated, and has been ordered by a healthcare professional. The Stratify JCV® DxSelect™ Antibody ELISA test was cleared by FDA on January 20, 2012.

The safety and efficacy of Benlysta has not been established in children.

In phase 3 trials, response rates for the primary endpoint were lower for African-American subjects in the Benlysta group relative to African-American subjects in the placebo group. Therefore, Benlysta should be used with caution in African-American patients.

Benlysta should be administered by healthcare providers prepared to manage anaphylaxis.

## APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non- covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

| HCPCS Codes | Description |
|---|---|
| J0490 | Injection, belimumab, 10 mg |

**ICD-10 Codes (Effective 10/1/15)**
ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures) must be used to report diagnoses for services provided on or after October 1, 2015.
***ICD-10 codes will not be accepted for services provided prior to October 1, 2015.***

| ICD-10 Diagnosis Code | Description |
|---|---|
| M32.0 | Drug-induced systemic lupus erythematosus |
| M32.10 | Systemic lupus erythematosus, organ or system involvement unspecified |
| M32.11 | Endocarditis in systemic lupus erythematosus |
| M32.12 | Pericarditis in systemic lupus erythematosus |
| M32.13 | Lung involvement in systemic lupus erythematosus |
| M32.14 | Glomerular disease in systemic lupus erythematosus |
| M32.15 | Tubulo-interstitial nephropathy in systemic lupus erythematosus |
| M32.19 | Other organ or system involvement in systemic lupus erythematosus |
| M32.8 | Other forms of systemic lupus erythematosus |
| M32.9 | Systemic lupus erythematosus, unspecified |

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## PROTOCOL HISTORY/REVISION INFORMATION

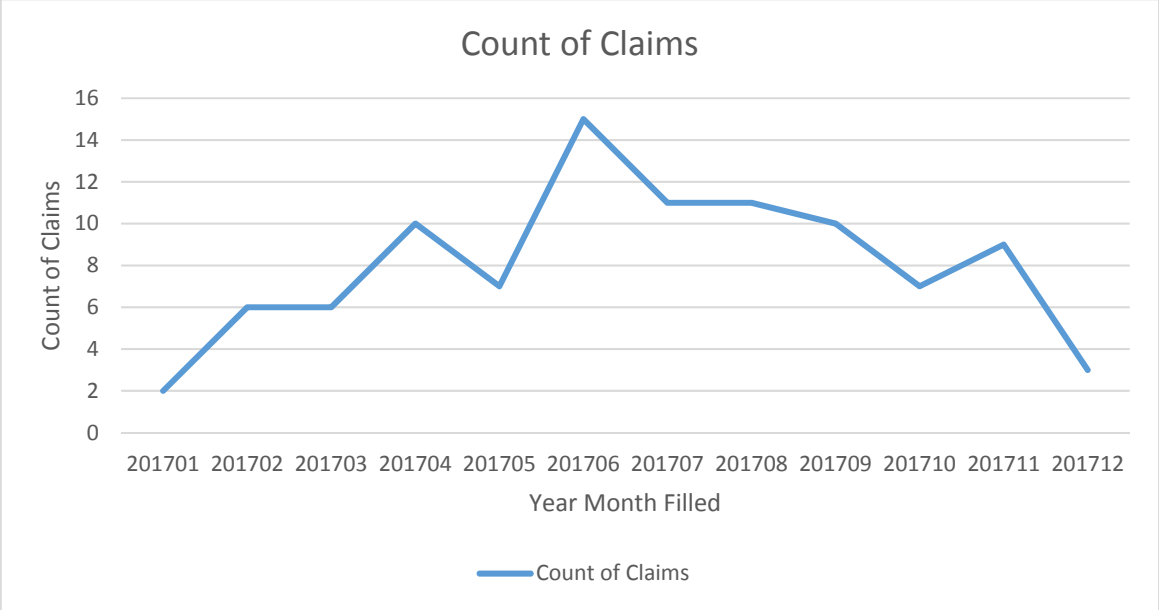
| Date | Action/Description |
|---|---|
| 07/28/2016<br>10/29/2015<br>07/23/2015<br>07/24/2014<br>07/25/2013<br>05/23/2013 | Corporate Medical Affairs Committee |

The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.

**Benlysta Utilization**

Jan 1, 2017 - Dec 31, 2017

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201701 | BENLYSTA | 1 | 2 | 2 | 3 | $ 2,725.75 |
| 201702 | BENLYSTA | 4 | 6 | 6 | 8.667 | $ 9,184.18 |
| 201703 | BENLYSTA | 4 | 6 | 6 | 8.667 | $ 9,184.18 |
| 201704 | BENLYSTA | 6 | 10 | 10 | 16.667 | $ 10,495.39 |
| 201705 | BENLYSTA | 5 | 7 | 7 | 11.333 | $ 10,459.60 |
| 201706 | BENLYSTA | 8 | 15 | 15 | 23.667 | $ 24,525.74 |
| 201707 | BENLYSTA | 7 | 11 | 11 | 15.834 | $ 15,521.64 |
| 201708 | BENLYSTA | 6 | 11 | 11 | 16.667 | $ 16,792.91 |
| 201709 | BENLYSTA | 6 | 10 | 10 | 15.667 | $ 15,458.64 |
| 201710 | BENLYSTA | 5 | 7 | 34 | 12.667 | $ 10,451.92 |
| 201711 | BENLYSTA | 5 | 9 | 36 | 15.667 | $ 13,213.67 |
| 201712 | BENLYSTA | 3 | 3 | 30 | 6 | $ 5,735.36 |



Health Plan of Nevada

# Benlysta Utilization

October 1, 2016 - September 30, 2017

| Year/Month Filled/Paid | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 2017/05 | BENLYSTA (Medical) | 1 | 2 | | 80 | $ 2,398.00 |
| 2017/07 | BENLYSTA (Medical) | 1 | 3 | | 64 | $ 1,926.25 |

## INTRODUCTION

- Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease that can affect virtually every organ system. Symptoms can range from mild to severe, and vary from patient to patient. The disease course of SLE is characterized by remissions and relapses (*Gladman 2017*).
- Approximately 170,000 to 200,000 adults are estimated to have SLE in the United States. It is typically diagnosed between the ages of 14 and 50 years, and is more common in female and non-white populations (*Benlysta dossier 2017*). SLE is associated with organ damage, morbidity, increased mortality, and decreased quality of life (*Navarra et al 2011, Thong et al 2017*).
- Clinical manifestations of SLE in adults may include the following (*Gladman 2017*):
  - constitutional symptoms (fatigue, fever, myalgia, weight loss)
  - arthritis and arthralgias
  - skin and mucous membrane involvement (facial eruption [“butterfly rash”], discoid lesions, photosensitivity, oral/nasal ulcers, alopecia)
  - vascular abnormalities (Raynaud phenomenon, vasculitis, thromboembolic disease)
  - renal involvement (nephritis)
  - gastrointestinal involvement (esophagitis, intestinal pseudo-obstruction, protein-losing enteropathy, hepatitis, pancreatitis, mesenteric vasculitis or ischemia, peritonitis)
  - pulmonary involvement (pleuritis, pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, alveolar hemorrhage)
  - cardiac disease (pericarditis is the most common; may also involve the myocardium, valves, conduction system, and coronary arteries)
  - hematologic abnormalities (anemia of chronic disease, autoimmune hemolytic anemia, leukopenia, thrombocytopenia
  - lymphadenopathy and splenomegaly
  - ophthalmic involvement
  - neuropsychiatric involvement
- SLE in children has similar manifestations as in adults, although the frequency of specific manifestations varies, and the disease may be worse in children if the diagnosis is delayed (*Lehman et al 2016*).
- Several disease activity indices have been developed for SLE (See Appendix). These indices, which are used for research purposes, use a combination of history, physical examination, and laboratory data (*Wallace 2016*).
  - Examples of scoring systems include the SLE Disease Activity Index (SLEDAI), the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI (SELENA-SLEDAI), and the British Isles Lupus Assessment Group (BILAG) index, among others.
  - Clinical trials are also using combinations of indices as composite measures. An example is the SLE responder index (SRI).
- Although there is no consensus on what constitutes an SLE disease flare, most clinicians agree that that a moderate or severe flare refers to a measureable disease activity increase that is significant enough to result in a change in therapy (*Wallace 2016*).
- Effective management of SLE varies based on the patient’s disease manifestations, disease severity, and comorbidities. Patients are generally managed by a rheumatologist, but may require multidisciplinary care. The overall goals of treatment are to achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, ensure long-term survival, and improve quality of life (*Wallace et al 2016*).
- Medications used in the treatment of SLE include (*Thong et al 2017, Wallace et al 2016*):
  - Antimalarials: hydroxychloroquine, chloroquine
    - Used routinely in most SLE patients; have broad benefits on many SLE manifestations and may reduce disease flares, organ damage, and mortality
  - Corticosteroids: prednisone, methylprednisolone

    - Used orally in patients with active manifestations, and intravenously (IV) in acute situations (eg, onset of nephritis, cerebritis, or myocarditis)
  - Immunosuppressants: azathioprine, mycophenolate mofetil, cyclophosphamide
    - Used in lupus nephritis and other significant organ involvement
  - Biologics: rituximab (off-label), belimumab
    - Used in selected patients with active disease
- Many of the treatments in use have not been specifically Food and Drug Administration (FDA)-approved to treat SLE (*Clinical Pharmacology 2017*).
- The role of rituximab in SLE is uncertain. Most of the data supporting its efficacy for reducing disease activity is observational, and significant benefit has not been conclusively shown in randomized trials (*Cobo-Ibáñez 2014, Wallace 2016*). Efficacy in lupus nephritis has also not been conclusively demonstrated; however, it is supported by consensus opinion for use in selected patients failing to benefit from established therapies (*Hahn et al 2012, Thong et al 2017*).
- Benlysta (belimumab) is the only biologic FDA-approved to treat SLE. It is a monoclonal antibody that acts as a specific inhibitor of B lymphocyte stimulator protein (BLyS), a survival cytokine for B lymphocytes that is overexpressed in patients with SLE and other autoimmune diseases.
- Benlysta was initially approved by the FDA in 2011 as an IV formulation. A new subcutaneous (SC) formulation was FDA approved in July 2017.
- Medispan class: SLE Agents; BLyS-Specific Inhibitors

## INDICATIONS

- Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy (*Benlysta prescribing information 2017*).
  - Limitations of use: The efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system (CNS) lupus. Belimumab has not been studied in combination with other biologics or IV cyclophosphamide. Use of belimumab is not recommended in these situations.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Two Phase 3, double-blind (DB), randomized trials, BLISS-52 (N = 865) and BLISS-76 (N = 819), compared IV belimumab to placebo in adults meeting the American College of Rheumatology (ACR) criteria for SLE (*Furie et al 2011, Navarra et al 2011*). Enrolled patients had active disease and a baseline score of ≥ 6 on the SELENA-SLEDAI. Patients were also required to have a positive antinuclear antibody (ANA) or double-stranded deoxyribonucleic acid (dsDNA) antibody, and to be on a stable regimen of SLE medications (prednisone, nonsteroidal anti-inflammatory drug [NSAID], antimalarial, and/or immunosuppressive agent). Patients with severe active lupus nephritis or CNS lupus were excluded.
  - The primary endpoint for both studies was the response rate at week 52 assessed with the SRI, a composite index for disease activity and response.
    - In BLISS-52, this endpoint was reached by 58% and 44% of patients in the belimumab 10 mg/kg and placebo groups, respectively (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.30 to 2.59; p = 0.0006).
    - In BLISS-76, this endpoint was reached by 43.2% and 33.5%, respectively (OR not reported; p = 0.017).
  - Some (but not all) key secondary endpoints were met in these studies at their primary assessments (week 24, 52, or 76). Notably:
    - In BLISS-52, components of the SRI measuring disease activity (SELENA-SLEDAI) and the physician's global assessment (PGA) demonstrated superiority of belimumab 10 mg/kg vs placebo. However, a quality of life measure was not improved, and reductions in prednisone dose did not reach statistical significance.
    - In BLISS-76, a higher percentage of patients achieved a clinically meaningful reduction on the SELENA-SLEDAI, but most other secondary endpoints, such as the PGA, quality of life, and reduction in prednisone dose, were not significantly improved.
- More recently, a Phase 3, DB, randomized trial, BLISS-SC, compared belimumab 200 mg SC once weekly to placebo in 836 patients with SLE (*Stohl et al 2017*). Inclusion and exclusion criteria were similar to the BLISS-52 and BLISS-76 trials, but patients were required to have a slightly more severe baseline disease activity (score ≥ 8 on the SELENA-SLEDAI, described as moderate to severe).

- The primary endpoint, the SRI at week 52, was achieved by 61.4% and 48.4% of patients in the belimumab and placebo groups, respectively (OR, 1.68; 95% CI, 1.25 to 2.25; p = 0.0006).
  - In a subgroup analysis, patients with SELENA-SLEDAI scores ≥ 10 had significant treatment responses with belimumab, whereas those with less severe disease (scores ≤ 9) did not.
- Notable results for secondary endpoints were as follows:
  - Belimumab-treated patients were less likely to experience a severe flare compared to placebo-treated patients.
  - Patients treated with belimumab had a greater reduction in fatigue than those in the placebo group.
  - In patients with baseline proteinuria, fewer patients had a renal flare in the belimumab group compared to the placebo group.
  - Differences between groups were not significant for corticosteroid dose reduction or reduction in renal flare in the overall population.

- In the belimumab IV trials, the SRI response rate was lower for black patients receiving belimumab relative to black patients receiving placebo (both with concomitant standard therapy). In the SC trial, the SRI response was slightly higher for black patients receiving belimumab relative to black patients receiving placebo (both with concomitant standard therapy), but the treatment difference was not as large as that observed in the overall population. No definitive conclusion can be drawn from this subgroup analysis. Caution should be used when considering treatment with belimumab in black/African-American patients.

## CLINICAL GUIDELINES

- Clinical guidelines from the ACR and the European League Against Rheumatism (EULAR) provide background information and general guidance of management of patients with SLE. However, in most cases the guidelines do not provide specific recommendations or algorithms for drug selection and dosing. Neither guideline has been updated to include the place in therapy for belimumab.

- **American College of Rheumatology**. Guidelines for referral and management of SLE in adults (*ACR 1999*).
  - These guidelines were developed to improve the quality of care for SLE patients by primary care physicians. Recommendations were evidence-based when possible; where evidence is unavailable, the guidelines were based on recommendations of SLE specialists.
  - Referral to a rheumatologist and/or other appropriate specialist is recommended for the following:
    - Establishment of the diagnosis
    - Assessment of disease activity and severity
    - Establishment of a disease management plan
    - Management of uncontrolled disease
    - Management of disease with major organ damage
    - Management/prevention of complications of therapies
    - Management of special clinical situations (eg, antiphospholipid antibody syndrome, pregnancy, surgery)
  - Lifelong monitoring is required for most patients with SLE in order to detect flares of disease early and institute appropriate therapy. This monitoring should consist of targeted history-taking, physical examination, and laboratory tests.
  - Particular care should be taken to assure the safe use of medications in SLE.
  - Treatment of mild SLE may appropriately incorporate the following:
    - Topical sunscreens
    - Topical glucocorticoid preparations
    - NSAIDs
    - Antimalarial agents (eg, hydroxychloroquine)
      - Antimalarial agents are useful for skin and joint involvement, constitutional symptoms, and preventing flares. Additionally, they may reduce fatigue and decrease low-density lipoprotein levels.
    - Oral glucocorticoids
      - Systemic glucocorticoids are not usually needed for mild SLE. Patients should be referred to a specialist for initiation of therapy.
  - Considerations in the treatment of serious, life-threatening, or organ-threatening SLE:
    - Organ involvement may lead to irreversible damage.
    - High-dose glucocorticoids are used for refractory SLE manifestations and severe organ-threatening disease.

- Immunosuppressive/cytotoxic agents that have been used to treat SLE include azathioprine, cyclophosphamide, methotrexate, chlorambucil, cyclosporine, and nitrogen mustard. Choice of therapy depends on the nature and severity of the condition (eg, methotrexate for severe arthritis, azathioprine or cyclophosphamide for nephritis).

- **European League Against Rheumatism**. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (*Bertsias et al 2008*).
  - Guideline development used an evidence-based approach followed by expert consensus.
  - In the treatment of SLE without major organ manifestations, antimalarials and/or glucocorticoids are of benefit and may be used.
  - NSAIDs may be used judiciously for limited periods of time in patients at low risk for their complications.
  - In non-responsive patients or patients not able to reduce corticosteroids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine, mycophenolate mofetil and methotrexate should be considered.
  - SLE patients with major neuropsychiatric manifestations considered to be of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressive therapy.
  - In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens; however, these are associated with considerable adverse effects (AEs). In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favorable toxicity profile. Small, non-controlled trials suggest that up to 50% of patients refractory to cyclophosphamide may have a clinically significant response to rituximab. Flares following remission are not uncommon and require careful follow-up.

## SAFETY SUMMARY

- **Contraindications**
  - Prior anaphylaxis with belimumab
- **Key warnings/precautions**
  - Mortality: There were more deaths reported with belimumab than with placebo during the controlled period of clinical trials with IV belimumab.
    - Out of 2133 patients in 3 clinical trials of IV belimumab, a total of 14 deaths occurred during the DB, placebo-controlled treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) in the groups receiving placebo and belimumab 1 mg/kg, 4 mg/kg, and 10 mg/kg, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease, and suicide.
    - In the controlled trial of SC belimumab (N = 836), a total of 5 deaths occurred during the DB, placebo-controlled treatment period: 2/280 (0.7%) and 3/556 (0.5%) in the placebo and belimumab groups, respectively. Infection was the most common cause of death.
  - Serious infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including belimumab. Belimumab should be used cautiously in patients with severe or chronic infections. Interruption of therapy should be considered if patients develop a new infection during belimumab treatment.
    - In the controlled clinical trials of IV belimumab, the overall incidence of infections was 71% in patients treated with belimumab and 67% of patients treated with placebo, and the incidence of serious infections was 6.0% and 5.2%, respectively.
    - In the controlled trial of SC belimumab, the overall incidence of infections was 55% in patients treated with belimumab and 57% in patients treated with placebo, and the incidence of serious infections was 4.1% and 5.4%, respectively.
  - Progressive multifocal leukoencephalopathy (PML): Cases of PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including belimumab. Patients presenting with new-onset or deteriorating neurological signs and symptoms should be evaluated for PML by an appropriate specialist. If PML is confirmed, discontinuation of immunosuppressant therapy, including belimumab, should be considered.
  - Hypersensitivity reactions, including anaphylaxis: Serious and fatal reactions have been reported.

- In the controlled clinical trials of IV belimumab, hypersensitivity reactions occurring on the same day as the infusion were reported in 191/1458 (13%) of patients receiving belimumab and 76/675 (11%) of patients receiving placebo, and anaphylaxis was observed in 0.6% and 0.4% of patients, respectively. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. IV belimumab should be administered by healthcare providers prepared to manage anaphylaxis.
- In the controlled trials of SC belimumab, systemic hypersensitivity reactions were similar to those observed in the IV clinical trials.

- Depression: Depression and suicidality have been reported in trials with belimumab. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.
  - In the controlled clinical trials of IV belimumab, psychiatric events were reported more frequently with belimumab than placebo (16% and 12%, respectively). These were primarily related to depression-related events (6.3% vs 4.7%), insomnia (6.0% vs 5.3%), and anxiety (3.9% vs 2.8%). Serious psychiatric events were reported in 0.8% of patients receiving belimumab (0.6% and 1.2% with 1 mg/kg and 10 mg/kg, respectively) and 0.4% of patients receiving placebo. Serious depression was reported in 0.4% and 0.1% of patients receiving belimumab and placebo, respectively, and 2 suicides (0.1%) were reported in patients receiving belimumab.
  - In the controlled trial of SC belimumab, psychiatric events were reported in 6% and 11% of patients receiving belimumab and placebo, respectively, and depression-related events were reported in 2.7% and 3.6%, respectively. Serious psychiatric events were reported in 0.2% of patients receiving belimumab and in no patients receiving placebo. There were no serious depression-related events or suicides in either group.

- **Adverse effects**
  - Common AEs (≥ 5%) with IV belimumab were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. The safety profile observed for SC belimumab was consistent with the safety profile of IV belimumab, with the addition of local injection site reactions.
- **Drug Interactions**
  - Formal drug interaction studies have not been performed with belimumab.
  - Live vaccines should not be given for 30 days before or concurrently with belimumab because clinical safety has not been established. Additionally, because of its mechanism of action, belimumab may interfere with the response to immunizations.
  - Belimumab has not been studied in combination with other biologic therapies or IV cyclophosphamide, and concomitant use with these agents is not recommended.

## DOSING AND ADMINISTRATION

**Table 1. Dosing and Administration**

| Drug | Available Formulations | Usual Recommended Frequency | Comments |
|---|---|---|---|
| Benlysta (belimumab) | Injection for IV use | Every 2 weeks for 3 doses, then every 4 weeks | • Should be administered by healthcare providers prepared to manage anaphylaxis |
| | Injection for SC use | Once weekly | • The first dose should be administered under supervision of a healthcare professional; thereafter, a patient or caregiver may administer when deemed appropriate |

See the current prescribing information for full details

## CONCLUSION

- Belimumab is a unique agent in that it is the only biological agent FDA-approved to treat SLE. Clinical trials have demonstrated efficacy, but effects on key endpoints have been somewhat limited. Across the Phase 3, placebo-controlled trials with IV and SC belimumab, the percentage of patients classified as responders ranged from approximately 43% to 61% for FDA-approved doses of belimumab and 34% to 48% for placebo, and belimumab has not conclusively shown improvements in quality of life or reductions in the need for corticosteroids. Belimumab is well-

tolerated in most patients; however, warnings/precautions note potential risks of infections, PML, hypersensitivity, depression/suicidality, and increased mortality (which was observed with the IV formulation).
  - Belimumab may have a role in patients with moderate to severe SLE who have failed to respond adequately to more well-established therapies.
  - The SC formulation provides a more convenient administration route compared to the IV formulation, and allows for the option of self-administration. Safety and efficacy appear to be comparable for the 2 formulations, but they have not been directly compared to each other.

## APPENDIX

### Study Endpoint Descriptions

- **British Isles Lupus Assessment Group (BILAG) and BILAG-2004** (*Lam et al 2005, Mikdashi et al 2015*)
  - The BILAG index provides disease activity scores across 8 organ systems on an ordinal scale (A to E).
    - Organ systems assessed include general, mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculitis, renal, and hematological.
  - Disease activity occurring over the past 4 weeks is recorded. Questions within each system are answered as 0 (not present), 1 (improving), 2 (same), 3 (worse), or 4 (new). Based on these items, each system is given a score of A (most active), B (moderate activity), C (minor activity), D (stable), or E (never present).
  - In an updated version (BILAG-2004), the original system of vasculitis was removed and 2 systems, ophthalmic and abdominal, were added. In this version, the total number of items is increased from 86 to 97.
- **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)** (*Kosinski et al 2013, Strand et al 2014*)
  - A health-related quality of life questionnaire measuring fatigue in patients with chronic illness.
  - Contains 13 items that measure an individual's level of fatigue during the past week on a 5-point scale (4 = not at all fatigued to 0 = very much fatigued).
  - Scores range from 0 to 52, with lower scores representing more severe disease.
  - An improvement of ≥ 4 is considered clinically important.
- **Physician's Global Assessment (PGA)** (*Benlysta dossier 2017, Furie et al 2011*)
  - The PGA used in the BLISS trials used a visual analog scale, with markings of 0 (none), 1 (mild), 2 (moderate), and 3 (severe).
- **Renal Flare Measurement** (*Stohl et al 2017*)
  - In the BLISS-SC trial, a renal flare was defined as confirmed development of ≥ 1 of the following 3 features:
    - Increase in 24-hour urinary protein to > 1000 mg if baseline was < 200 mg, or to > 2000 mg if baseline was 200 mg to 1000 mg, or to more than twice a baseline value of > 1000 mg
    - Decrease in the glomerular filtration rate of > 20%, accompanied by proteinuria (> 1000 mg/24 hours), hematuria (≥ 4 red blood cells per high-power field), and/or cellular (red blood cell or white blood cell) casts
    - New hematuria (≥ 11 to 20 red blood cells per high-power field) or a 2-grade increase in hematuria compared with baseline, associated with > 25% dysmorphic red blood cells, glomerular in origin, and accompanied by an 800 mg increase in 24 hour urinary protein level or new red blood cell casts
- **Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)** (*Benlysta dossier 2017, Bombardier et al 1992, Castrejón et al 2014, Petri et al 2005*)
  - SELENA-SLEDAI is a measure of global improvement in SLE.
  - This index assesses disease activity by scoring 24 weighted disease activity descriptors of SLE as present or absent in the preceding 10 days. Items include: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.
  - Scores range from 0 to 105, with higher numbers indicating increased disease activity. In practice, few patients have scores > 45.
  - Although interpretation of scores varies slightly among publications, activity categories can be generalized to the following approximate ranges: mild (1 to 5), moderate (6 to 10), high (11 to 19), and very high (≥ 20).

- A reduction in the SELENA-SLEDAI score of 2 to 3 is considered clinically meaningful; however, a higher threshold of a ≥ 4-point reduction from baseline may be important to demonstrate a desired treatment effect over and above another therapy.

- **SELENA-SLEDAI Flare Index (or SLE Flare Index)** (*Petri 1999, Petri 2005*)
  - An index used to measure SLE flare activity and identify the severity of flares.
  - A mild/moderate flare is defined as the presence of 1 or more of the following:
    - A change in SELENA-SLEDAI score of ≥ 3 (but not to more than 12)
    - New or worsened:
      - skin manifestations (discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus)
      - nasopharyngeal ulcers
      - pleuritis
      - pericarditis
      - arthritis
      - fever (SLE)
    - Increase in prednisone, but not to > 0.5 mg/kg/day
    - Added NSAID or hydroxychloroquine for SLE activity
    - ≥ 1.0 increase in PGA score, but not to > 2.5
  - A severe flare is defined as:
    - Change in SELENA-SLEDAI score to > 12
    - New or worsened of the following, requiring doubling of the prednisone dose, prednisone increase to > 0.5 mg/kg/day, or hospitalization:
      - CNS SLE
      - vasculitis
      - nephritis
      - myositis
      - platelets < 60,000
      - hemolytic anemia (hemoglobin < 70 g/L or decrease in hemoglobin > 30 g/L)
    - Increase in prednisone to > 0.5 mg/kg/day
    - New cyclophosphamide, azathioprine, or methotrexate for SLE activity
    - Hospitalization for SLE activity
    - Increase in PGA score to > 2.5
  - Note: In the *modified* SLE flare index, the criterion of increased SELENA-SLEDAI score to > 12 for identification of a severe flare is excluded.

- **36-item Short Form Health Survey (SF-36)** (*Strand et al 2014*)
  - The SF-36 is a set of generic (not disease-specific) quality of life measures. It includes a total of 36 questions across 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.
  - Two overall summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS), can be computed. For each summary score, the raw domain scores are converted to a 0 to 100 scale, with higher scores indicating better quality of life.
  - The minimum clinically important differences for the summary scores are +2.5 for improvement and -0.8 for deterioration.

- **SLE Responder Index (SRI)** (*Stohl et al 2017*)
  - A composite index requiring all of the following, compared to baseline:
    - A ≥ 4-point reduction in the SELENA-SLEDAI scale
    - No worsening (increase < 0.3 from baseline) in the PGA
    - No new BILAG A organ domain score
    - ≤ 1 new BILAG B organ domain scores

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## Vosevi

**Initial Prior Authorization Criteria**:

- Recipient must have a diagnosis of chronic hepatitis C virus (HCV) infection confirmed by submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 within the last 6 months, **OR**
- Submission of medical records (e.g., chart notes, laboratory values) documenting diagnosis of chronic hepatitis C genotype 1a or 3, and
- Prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious disease specialist, HIV specialist certified through the American Academy of HIV Medicine, and
- Recipient is a previous relapser to a sofosbuvir-based regimen without an NS5A inhibitor, and
- Is without decompensated liver disease, and
- Is not receiving Vosevi in combination with another HCV direct acting antiviral agent.

**Other suggestions to possibly include:**

- Recipient must be 18 years or older,
- Life expectancy ≥ 12 months with HCV treatment,
- Documented sobriety from alcohol and illicit IV drugs for ≥ 6 months prior to starting therapy, if applicable,
- Advanced liver disease defined as a or b:
  a. Advanced fibrosis indicated by i or ii:
  i. Liver biopsy showing a METAVIR score of F3 or equivalent (Knodell, Scheuer, Batts-Ludwig – F3; Ishak – F4/5),
  ii. One serologic test and one radiologic test showing an equivalent score to METAVIR F3 per Appendix C;
  b. Cirrhosis indicated by i, ii or iii:
  i. Hepatocellular carcinoma (HCC) - and the HCC is amenable to resection, ablation or transplant;
  ii. Liver biopsy showing a METAVIR score of F4 or equivalent (Knodell, Scheuer, Batts-Ludwig – F4; Ishak - F5/6);
  iii. Both of the following:
  a) One serologic test showing an equivalent score to METAVIR F4 per Appendix C;
  b) One radiologic test showing an equivalent score to METAVIR F4 per Appendix C or other radiologic test showing evidence of cirrhosis (e.g., portal hypertension);
- Prescribed regimen is consistent with an FDA or AASLD-IDSA recommended regimen (*see Section V Dosage and Administration for reference*);
- If cirrhosis is present, confirmation of Child-Pugh A status,
- Member meets one of the following (a or b):
  a. If HCV genotype 1, 2, 3, 4, 5 or 6, member has previously been treated with an HCV regimen containing one of the following NS5A inhibitors: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir;
  b. If HCV genotype is 1a or 3, member has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);
- Member has received ≥ 8 weeks of the prior direct-acting antiviral agent (DAA) regimen from 9a or 9b above, unless virologic failure was determined prior to 8 weeks of therapy,
- Member has a contraindication or intolerance to Mavyret and meets one of the following (a or b):

a. Member has genotype 1 without cirrhosis or with compensated cirrhosis (Child-Pugh A) and has previously been treated with an HCV regimen containing an NS5A inhibitor;
b. Member has genotype 1a or 3 and has previously been treated with an HCV regimen containing sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir);

- Member agrees to participate in a medication adherence program meeting both of the following components:

a. Medication adherence monitored by pharmacy claims data or member report;
b. Member's risk for non-adherence identified by adherence program or member/prescribing physician follow-up at least every 4 weeks;

- Member is hepatitis B virus (HBV) negative, or if positive, documentation that concurrent HBV infection is being treated (e.g., tenofovir alafenamide, adefovir, entecavir**)**, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix B*);
- Prescribed dose does not exceed one tablet (sofosbuvir 400 mg/velpatasvir 100mg/voxilaprevir 100 mg) daily.

**Continuing Therapy Criteria**:

- Documentation of positive clinical response to Vosevi® therapy (e.g., decreased HCV RNA level, no unacceptable toxicity).

**Other suggestion to possibly include:**

- Prescribed dose does not exceed one tablet (sofosbuvir 400 mg/velpatasvir 100mg/voxilaprevir 100 mg) daily.

**Approval Duration**:

- Authorization will be approved for up to a total of 12 weeks.
- Continued authorization will be approved for up to a total of 12 weeks.

**Nevada Medicaid**
Mavyret (glecaprevir/pibrentasvir)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Mavyret | glecaprevir/pibrentasvir |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Chronic Hepatitis C (CHC)** Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). Indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor (PI), but not both.

### Approval Criteria

Treatment-Naïve without Cirrhosis – 8 week authorization

1. Diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6
2. Patient is treatment-naïve
3. Patient is without cirrhosis
4. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

Treatment-Naïve with Compensated Cirrhosis – 12 week authorization

1. Diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6
2. Patient is treatment-naïve
3. Patient has compensated cirrhosis (Child-Pugh Class A)
4. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.

5. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

GT 1, Treatment-Experienced (prior failure to an NS3/4A Protease Inhibitor), without Decompensated Cirrhosis – 12 week authorization

1. Diagnosis of chronic hepatitis C genotype 1
2. Patient has experienced failure with a previous treatment regimen that included a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)]
3. Patient has had no previous treatment experience with a treatment regimen that included an NS5A inhibitor (e.g., Daklinza [daclatasvir])
4. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

GT 1, Treatment-Experienced (Prior failure to an NS5A Inhibitor), without decompensated Cirrhosis – 16 week authorization

1. Diagnosis of chronic hepatitis C genotype 1
2. Patient has experienced failure with a previous treatment regimen that included an NS5A inhibitor (e.g., Daklinza [daclatasvir])
3. Patient has had no previous treatment experience with a treatment regimen that included a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)]
4. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

GT 3, Treatment-experienced (Interferon or Sovaldi-based regimen), without decompensated cirrhosis – 16 week authorization

1. Diagnosis of chronic hepatitis C genotype 3

2. Patient has experienced treatment failure with a previous treatment regimen that included interferon, peginterferon, ribavirin, and/or Sovaldi (sofosbuvir)
3. Patient has had no previous treatment experience with a treatment regimen that included a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (e.g., Daklinza [daclatasvir]
4. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

GT 1, 2, 4, 5 or 6, Treatment-experienced (Interferon- or Sovaldi-based regimen), without cirrhosis – 8 week authorization

1. Diagnosis of chronic hepatitis C genotype 1, 2, 4, 5 or 6
2. Patient has experienced treatment failure with a previous treatment regimen that included interferon, peginterferon, ribavirin, and/or Sovaldi (sofosbuvir)
3. Patient has had no previous treatment experience with a treatment regimen that included a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (e.g., Daklinza [daclatasvir])
4. Patient is without cirrhosis
5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

GT 1, 2, 4, 5 or 6, Treatment-experienced (Interferon- or Sovaldi-based regimen), with compensated cirrhosis – 12 week authorization

1. Diagnosis of chronic hepatitis C genotype 1, 2, 4, 5 or 6
2. Patient has experienced treatment failure with a previous treatment regimen that included interferon, peginterferon, ribavirin, and/or Sovaldi (sofosbuvir)
3. Patient has had no previous treatment experience with a treatment regimen that included a HCV NS3/4A protease inhibitor [e.g., Incivek (telaprevir), Olysio (simeprevir), Victrelis (boceprevir)] or an NS5A inhibitor (e.g., Daklinza [daclatasvir])
4. Patient has compensated cirrhosis (e.g., Child-Pugh Class A)

5. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
6. The patient is not receiving Mavyret in combination with another HCV direct acting antiviral agent

# Nevada Medicaid

Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Vosevi | sofosbuvir/velpatasvir/voxilaprevir |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Chronic Hepatitis C (CHC)** Indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: • Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor. • Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. (Additional benefit of Vosevi over Epclusa [sofosbuvir/velpatasvir] was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.)

### Approval Criteria

GT 1, 2, 3, 4, 5, or 6 without decompensated cirrhosis, prior relapse to NS5A-Based regimen. – 12 week approval

1. Diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5 or 6
2. Patient is a previous relapser to an NS5A-based regimen (e.g., Daklinza [daclatasvir]; Epclusa [sofosbuvir/velpatasvir]; Harvoni [ledipasvir/sofosbuvir]; Technivie [ombitasvir/paritaprevir/ritonavir]; Viekira [ombitasvir/paritaprevir/ritonavir & dasabuvir]; Zepatier [elbasvir/grazoprevir])
3. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
4. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
5. Patient is not receiving Vosevi in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Zepatier (elbasvir/grazoprevir)]

**Nevada Medicaid**

Vosevi (sofosbuvir/velpatasvir/voxilaprevir)

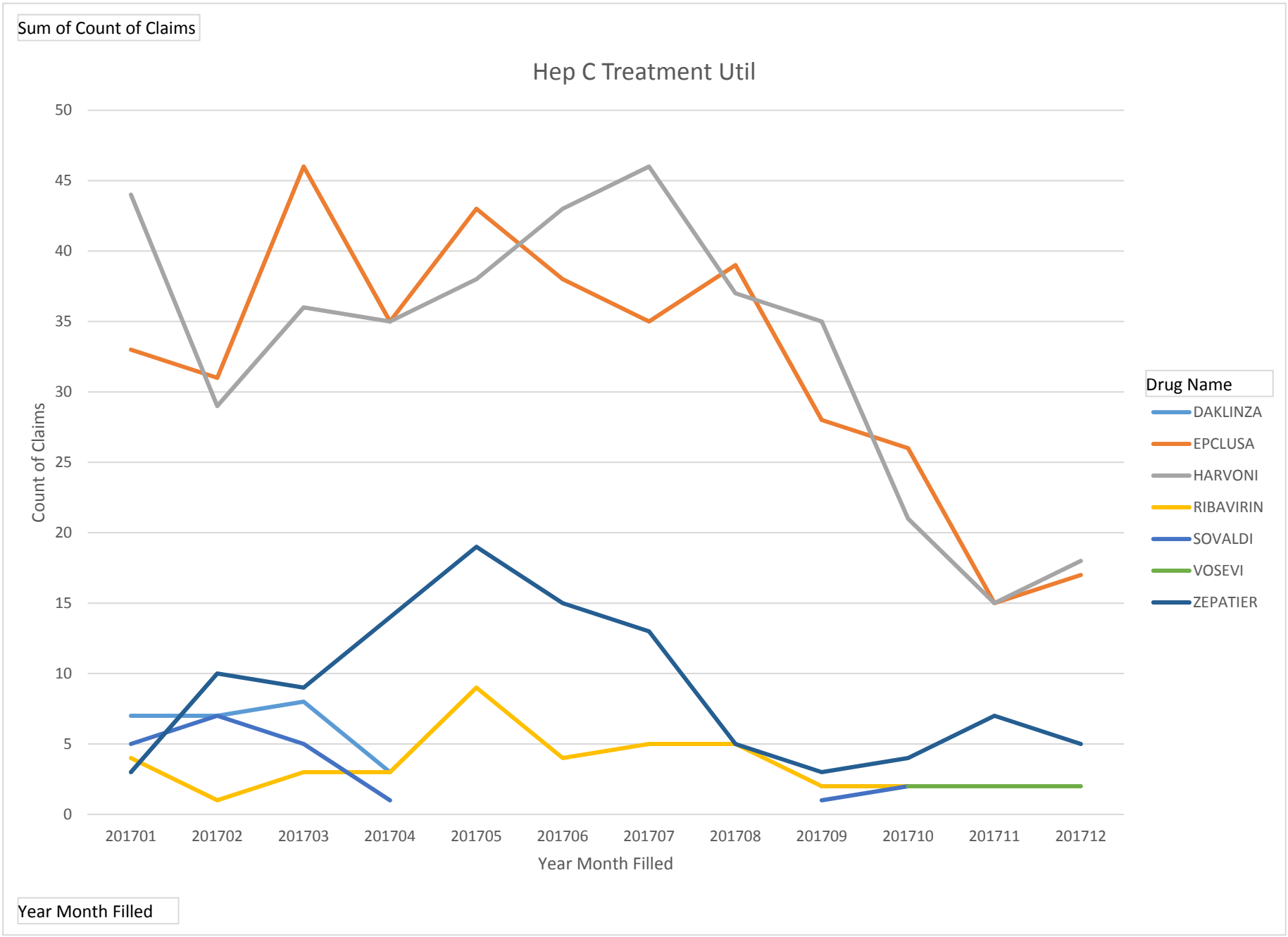
Pharmacy Coverage Guideline

GT 1a or 3, without decompensated cirrhosis, prior relapse to Sofosbuvir-based regimen without an NS5A inhibitor - 12 week approval

1. Diagnosis of chronic hepatitis C genotype 1a or 3
2. Patient is a previous relapser to a sofosbuvir-based regimen without an NS5A inhibitor
3. Patient is without decompensated liver disease (e.g., Child-Pugh Class B or C)
4. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, infectious disease specialist or HIV specialist certified through the American Academy of HIV Medicine.
5. Patient is not receiving Vosevi in combination with another HCV direct acting antiviral agent [e.g., Harvoni (ledipasvir/sofosbuvir), Zepatier (elbasvir/grazoprevir)]

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Pd |
|---|---|---|---|---|---|---|
| 201701 | DAKLINZA | 5 | 7 | 126 | 126 | $ 70,979.97 |
| 201702 | DAKLINZA | 4 | 7 | 126 | 126 | $ 91,247.94 |
| 201703 | DAKLINZA | 6 | 8 | 154 | 154 | $ 91,251.64 |
| 201704 | DAKLINZA | 3 | 3 | 42 | 42 | $ 30,422.76 |
| 201709 | DAKLINZA | 2 | 2 | 42 | 42 | $ 10,224.07 |
| 201710 | DAKLINZA | 1 | 2 | 42 | 42 | $ 30,650.94 |
| 201701 | EPCLUSA | 21 | 33 | 560 | 574 | $ 386,563.26 |
| 201702 | EPCLUSA | 22 | 31 | 518 | 518 | $ 409,383.25 |
| 201703 | EPCLUSA | 27 | 46 | 728 | 728 | $ 573,345.88 |
| 201704 | EPCLUSA | 23 | 35 | 602 | 602 | $ 490,674.54 |
| 201705 | EPCLUSA | 29 | 43 | 812 | 812 | $ 647,868.84 |
| 201706 | EPCLUSA | 26 | 38 | 753 | 756 | $ 623,845.06 |
| 201707 | EPCLUSA | 24 | 35 | 624 | 630 | $ 491,921.20 |
| 201708 | EPCLUSA | 23 | 39 | 694 | 686 | $ 587,892.52 |
| 201709 | EPCLUSA | 20 | 28 | 462 | 462 | $ 396,687.98 |
| 201710 | EPCLUSA | 18 | 26 | 518 | 518 | $ 422,446.82 |
| 201711 | EPCLUSA | 11 | 15 | 294 | 294 | $ 255,339.72 |
| 201712 | EPCLUSA | 12 | 17 | 392 | 392 | $ 316,359.76 |
| 201701 | HARVONI | 30 | 44 | 817 | 817 | $ 646,973.20 |
| 201702 | HARVONI | 21 | 29 | 501 | 501 | $ 485,487.69 |
| 201703 | HARVONI | 22 | 36 | 588 | 588 | $ 519,346.82 |
| 201704 | HARVONI | 22 | 35 | 520 | 520 | $ 536,801.66 |
| 201705 | HARVONI | 24 | 38 | 700 | 700 | $ 733,095.08 |
| 201706 | HARVONI | 27 | 43 | 742 | 742 | $ 778,940.65 |
| 201707 | HARVONI | 28 | 46 | 826 | 826 | $ 840,020.57 |
| 201708 | HARVONI | 24 | 37 | 658 | 658 | $ 626,968.46 |
| 201709 | HARVONI | 21 | 35 | 658 | 658 | $ 666,264.98 |
| 201710 | HARVONI | 13 | 21 | 364 | 364 | $ 398,958.63 |
| 201711 | HARVONI | 12 | 15 | 364 | 364 | $ 305,694.23 |
| 201712 | HARVONI | 12 | 18 | 350 | 350 | $ 322,610.00 |
| 201701 | RIBAVIRIN | 4 | 4 | 93 | 454 | $ 224.88 |
| 201702 | RIBAVIRIN | 1 | 1 | 30 | 90 | $ 70.96 |
| 201703 | RIBAVIRIN | 3 | 3 | 86 | 398 | $ 299.33 |
| 201704 | RIBAVIRIN | 3 | 3 | 84 | 448 | $ 322.66 |
| 201705 | RIBAVIRIN | 6 | 9 | 196 | 1008 | $ 1,391.11 |
| 201706 | RIBAVIRIN | 4 | 4 | 112 | 504 | $ 756.06 |
| 201707 | RIBAVIRIN | 4 | 5 | 121 | 586 | $ 790.69 |
| 201708 | RIBAVIRIN | 4 | 5 | 123 | 604 | $ 936.66 |
| 201709 | RIBAVIRIN | 2 | 2 | 58 | 288 | $ 442.71 |
| 201710 | RIBAVIRIN | 2 | 2 | 58 | 288 | $ 442.71 |
| 201701 | SOVALDI | 4 | 5 | 98 | 98 | $ 95,630.25 |
| 201702 | SOVALDI | 4 | 7 | 154 | 154 | $ 150,267.39 |
| 201703 | SOVALDI | 5 | 5 | 126 | 126 | $ 122,938.65 |
| 201704 | SOVALDI | 1 | 1 | 14 | 14 | $ 13,664.37 |
| 201709 | SOVALDI | 1 | 1 | 14 | 14 | $ 14,010.17 |

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Pd |
|---|---|---|---|---|---|---|
| 201710 | SOVALDI | 1 | 2 | 42 | 42 | $ 42,020.34 |
| 201710 | VOSEVI | 1 | 2 | 42 | 42 | $ 37,400.34 |
| 201711 | VOSEVI | 2 | 2 | 56 | 56 | $ 49,860.34 |
| 201712 | VOSEVI | 2 | 2 | 42 | 42 | $ 37,400.34 |
| 201701 | ZEPATIER | 2 | 3 | 56 | 56 | $ 36,430.51 |
| 201702 | ZEPATIER | 6 | 10 | 182 | 182 | $ 118,401.70 |
| 201703 | ZEPATIER | 9 | 9 | 182 | 182 | $ 118,391.53 |
| 201704 | ZEPATIER | 9 | 14 | 252 | 252 | $ 163,942.38 |
| 201705 | ZEPATIER | 12 | 19 | 364 | 364 | $ 218,586.76 |
| 201706 | ZEPATIER | 10 | 15 | 308 | 308 | $ 162,615.57 |
| 201707 | ZEPATIER | 9 | 13 | 218 | 238 | $ 97,785.42 |
| 201708 | ZEPATIER | 5 | 5 | 92 | 112 | $ 35,555.22 |
| 201709 | ZEPATIER | 3 | 3 | 84 | 84 | $ 17,776.22 |
| 201710 | ZEPATIER | 4 | 4 | 98 | 98 | $ 8,896.90 |
| 201711 | ZEPATIER | 5 | 7 | 140 | 140 | $ 53,334.22 |
| 201712 | ZEPATIER | 4 | 5 | 112 | 112 | $ 71,085.46 |


Sum of Count of Claims
Hep C Treatment Util
50
45
40
35
30
25
20
15
10
5
0
Count of Claims
201701
201702
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
Year Month Filled
Drug Name
DAKLINZA
EPCLUSA
HARVONI
RIBAVIRIN
SOVALDI
VOSEVI
ZEPATIER
Year Month Filled

UU. Hepatitis C direct-acting antivirals

Therapeutic Class: Hepatitis C direct acting antivirals
Last Reviewed by the DUR Board: July 28, 2016
Previously reviewed by the DUR Board: January 28, 2016

Hepatitis C direct-acting antivirals are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the 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:

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

   b. Recipients must meet all of the following criteria:

      1. The recipient has a diagnosis of chronic Hepatitis C Virus (HCV) infection; and

      2. The recipient is 18 years of age or older; and

      3. All of the following must be included with the PA request:

         a. Medical records and results of laboratory and diagnostic tests which support all of the following:

            1. The HCV genotype (and subtype, if applicable); and

            2. The baseline HCV RNA viral load and date drawn; and

            3. The hepatic fibrosis stage, including tests supporting liver disease staging (e.g., APRI, Fibroscan, Fibrosure, FIB-4). (Results of diagnostic tests or imaging studies that are inconclusive may require additional testing); and

         b. A complete treatment regimen; and

         c. The duration of treatment; and

         d. Any previous treatment experience and length of treatment, if any, including outcome (e.g. discontinued due to side effects, relapsed, non-responder, null-responder); and

      4. The prescriber must certify that the treatment will be discontinued if the viral load is detectable at week four of treatment and has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or

thereafter); and

5. Requests for recipients with decompensated cirrhosis (Child Turcotte Pugh (CTP) class B or C) and requests for recipients who have chronic hepatitis C infection status-post liver transplant will be evaluated on a case by case basis.

2. Harvoni® (ledipasvir/sofosbuvir) Initial Requests

a. The requested dose is one 90 mg/400 mg tablet once daily.

b. Genotype 1:

1. The recipient is treatment naïve and must meet one of the following:

a. No cirrhosis, pre-treatment HCV RNA < six million and the requested duration is eight weeks; or

b. No cirrhosis, pre-treatment HCV RNA ≥ six million and the requested duration is 12 weeks; or

c. Compensated Cirrhosis (CTP class A), requested duration is 12 weeks.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin) and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) will be treated with ribavirin and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), documentation is provided that the recipient is unable to take ribavirin and the requested duration is 24 weeks.

3. The recipient is treatment-experienced (failed peginterferon + ribavirin + an NS3 protease inhibitor) and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), documentation is provided that the recipient is unable to take ribavirin and the requested duration is 24 weeks.

4. The recipient is treatment-experienced (failed Sovaldi + ribavirin ± peginterferon) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 24 weeks.

c. Genotype 4:

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin) and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), documentation is provided the recipient is unable to take ribavirin and the requested duration is 24 weeks.

d. Genotype 5 and 6:

1. The recipient is treatment-naïve and the requested duration is 12 weeks; or

2. The recipient is treatment-experienced (failed peginterferon + ribavirin) and the requested duration is 12 weeks.

3. Viekira Pak® (dasabuvir-ombitasvir-paritaprevir-ritonavir) (Initial Requests)

a. The requested dose is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (25/150/100 mg) and one dasabuvir 250 mg tablet twice daily.

b. Genotype 1a:

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, recipient will be treated with ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

c. Genotype 1b:

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

2. The recipient is treatment experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

4. Technivie® (ombitasvir/paritaprevir/ritonavir) (Initial Requests)

a. The requested dose is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (25/150/100 mg).

b. Genotype 4:

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, the recipient will be treated with ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

2. The recipient is treatment-experienced (failed peginterferon and ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, the recipient will be treated with ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 12 weeks.

5. Daklinza® (daclatasvir) (Initial Requests)

a. The requested dose is one of the following:

1. 60 mg (one tablet) daily; or

2. 30 mg (one tablet) and the recipient is receiving a strong CYP3A inhibitor; or

3. 90 mg (one tablet) daily and the recipient is receiving a concomitant moderate CYP3A inducer.

b. Genotype 1

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi + ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks, documentation has been provided showing the recipient is unable to take ribavirin and

documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. Compensated cirrhosis (CTP class A) will be treated with Sovaldi, the requested duration is 24 weeks, documentation is provided showing that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

3. The recipient is treatment-experienced (failed peginterferon + ribavirin + NS3 protease inhibitor) and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks and documentation is provided showing that the recipient is unable to take ribavirin.

c. Genotype 2

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 16 weeks and documentation is provided showing the recipient is unable to take ribavirin.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy), documentation is provided showing the recipient is unable to take

ribavirin and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and the requested duration is 16 to 24 weeks.

3. The recipient is treatment-experienced (failed Sovaldi + ribavirin dual therapy), documentation has been provided showing the recipient is unable to take peginterferon and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

b. No cirrhosis, will be treated with Sovaldi, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take ribavirin; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take ribavirin.

d. Genotype 3

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks and documentation has been provided showing the recipient is unable to take ribavirin.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy), documentation is provided showing that the recipient is unable to receive peginterferon and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take peginterferon.

3. The recipient is treatment-experienced (failed Sovaldi + ribavirin therapy dual therapy), documentation is provided that the recipient is unable to receive peginterferon and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks.

6. Olysio® (simeprevir) (Initial Request)

a. The requested dose is 150 mg (one capsule) daily.

b. Genotype 1a

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and ribavirin and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. Compensated cirrhosis (CTP class A) will be treated with Sovaldi, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism, documentation is provided showing that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin, the requested duration is 24 weeks and the recipient is negative for the Q80K polymorphism; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism and documentation has been provided showing that the recipient is unable to take ribavirin.

c. Genotype 1b

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks and documentation has been provided showing that the recipient is unable to take ribavirin.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with Sovaldi and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Sovaldi and ribavirin and the requested duration is 24 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Sovaldi, the requested duration is 24 weeks and documentation has been provided showing that the recipient is unable to take ribavirin.

7. <u>Sovaldi® (sofosbuvir) (Initial Requests)</u>

a. The requested dose is 400 mg daily.

b. Genotype 1

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Olysio and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Daklinza + ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-

recommended regimen; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza, requested duration is 24 weeks, documentation is provided showing the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

e. Compensated cirrhosis (CTP class A), genotype 1a, will be treated with Olysio and ribavirin, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

f. Compensated cirrhosis (CTP class A), genotype 1a, will be treated with Olysio, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism, documentation is provided showing the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

g. Compensated cirrhosis (CTP class A), genotype 1b, will be treated with Olysio and ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

h. Compensated cirrhosis (CTP class A), genotype 1b, will be treated with Olysio, the requested duration is 24 weeks, documentation has been provided that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Olysio and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza, requested duration is 24 weeks, documentation is provided showing

that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

e. Compensated cirrhosis (CTP class A), genotype 1a, will be treated with Olysio and ribavirin, the requested duration is 24 weeks the recipient is negative for the Q80K polymorphism and documentation is provided why the recipient cannot use a guideline-recommended regimen; or

f. Compensated cirrhosis (CTP class A), genotype 1a, will be treated with Olysio, the requested duration is 24 weeks, the recipient is negative for the Q80K polymorphism, documentation is provided showing that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

g. Compensated cirrhosis (CTP class A), genotype 1b, will be treated with Olysio and ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

h. Compensated cirrhosis (CTP class A), genotype 1b, will be treated with Olysio, the requested duration is 24 weeks, documentation is provided showing that the recipient is unable to take ribavirin and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

3. The recipient is treatment-experienced (failed peginterferon + ribavirin + NS3 protease inhibitor) and must meet one of the following:

a. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin and the requested duration is 24 weeks; or

c. Compensated cirrhosis (CTP class A) will be treated with Daklinza, the requested duration is 24 weeks and documentation has been provided showing the recipient is unable to take ribavirin.

c. Genotype 2

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 16 weeks to 24 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza, the requested duration is 16 weeks and documentation has been provided showing that the recipient is unable to take ribavirin.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Daklinza, the requested duration is 12 weeks and documentation is provided showing the recipient is unable to take ribavirin.

c. Compensated cirrhosis (CTP class A), will be treated with ribavirin and the requested duration is 16 weeks to 24 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin and the requested duration is 16 weeks to 24 weeks, and documentation is provided showing the recipient is unable to take ribavirin; or

e. Compensated cirrhosis (CTP class A), will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

3. The recipient is treatment-experienced (failed Sovaldi + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation has been provided showing the recipient is unable to receive peginterferon; or

b. No cirrhosis, will be treated with Daklinza, the requested duration is 24 weeks and documentation has been provided showing that the recipient is unable to take ribavirin and documentation has been provided showing that the recipient is unable to receive peginterferon; or

c. No cirrhosis, will be treated with ribavirin and peginterferon and the requested duration is 12 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation has been provided showing that the recipient is unable to receive peginterferon; or

e. Compensated cirrhosis (CTP class A), will be treated with Daklinza, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take peginterferon and ribavirin.

f. Compensated cirrhosis (CTP class A), will be treated with ribavirin and peginterferon and the requested duration is 12 weeks.

d. Genotype 3

1. The recipient is treatment-naive and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and peginterferon and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin and peginterferon and the requested duration is 12 weeks; or

e. Compensated cirrhosis (CTP class A) will be treated with ribavirin, the requested duration is 24 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

f. Compensated cirrhosis (CTP class A) will be treated with Daklinza and ribavirin, the requested duration is 24 weeks; or

g. Compensated cirrhosis (CTP class A) will be treated with Daklinza, the requested duration is 24 weeks and documentation has been provided showing that the recipient is unable to take ribavirin.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with peginterferon and ribavirin and the

requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Daklinza and the requested duration is 12 weeks; or

c. Compensated cirrhosis (CTP class A), will be treated with peginterferon and ribavirin and the requested duration is 12 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take peginterferon.

3. The recipient is treatment-experienced (failed Sovaldi + ribavirin therapy dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with peginterferon and ribavirin and the requested duration is 12 weeks; or

b. No cirrhosis, will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take peginterferon; or

c. Compensated cirrhosis (CTP class A), will be treated with peginterferon and ribavirin and the requested duration is 12 weeks; or

d. Compensated cirrhosis (CTP class A), will be treated with Daklinza and ribavirin, the requested duration is 24 weeks and documentation is provided showing the recipient is unable to take peginterferon.

e. Genotype 4

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

b. Compensated cirrhosis (CTP class A) will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon alfa + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to

why the recipient cannot use a guideline-recommended regimen; or

b. Compensated cirrhosis (CTP class A) will be treated with ribavirin, the requested duration is 24 weeks, documentation is provided as to why the recipient cannot take peginerferon and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

f. Genotype 5, 6

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

b. Compensated cirrhosis (CTP class A) will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon alfa + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

b. Compensated cirrhosis (CTP class A) will be treated with ribavirin and peginterferon, the requested duration is 12 weeks and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

8. Zepatier® (elbasvir and grazoprevir)

a. The requested dose is one tablet (50/100 mg) daily.

b. Genotype 1a

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis, the requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. Compensated cirrhosis (CTP class A), requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis, the requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected and documentation is provided as to why the recipient cannot use a guideline-recommended regimen; or

c. Compensated cirrhosis (CTP class A), requested duration is 12 weeks, and there are no baseline NS5A RAVs for elbasvir detected; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected and documentation is provided as to why the recipient cannot use a guideline-recommended regimen.

3. The recipient is treatment-experienced (failed peginterferon + ribavirin + NS3 protease inhibitor) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin, the requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected; or

c. Compensated cirrhosis (CTP class A), will be treated with ribavirin, requested duration is 12 weeks, and there are no baseline NS5A RAVs for elbasvir detected; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected.

c. Genotype 1b

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual therapy) and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

3. The recipient is treatment-experienced (failed peginterferon + ribavirin + NS3 protease inhibitor) and must meet one of the following:

a. No cirrhosis, will be treated with ribavirin, the requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 16 weeks and baseline NS5A RAVs for elbasvir have been detected; or

c. Compensated cirrhosis (CTP class A), will be treated with ribavirin, requested duration is 12 weeks and there are no baseline NS5A RAVs for elbasvir detected; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 16 weeks, baseline NS5A RAVs for elbasvir have been detected.

d. Genotype 4

1. The recipient is treatment-naïve and must meet one of the following:

a. No cirrhosis and the requested duration is 12 weeks; or

b. Compensated cirrhosis (CTP class A) and the requested duration is 12 weeks.

2. The recipient is treatment-experienced (failed peginterferon + ribavirin dual

therapy) and must meet one of the following:

a. No cirrhosis, the requested duration is 12 weeks and documentation is provided showing the recipient experienced virologic relapse to peginterferon + ribavirin dual therapy; or

b. No cirrhosis, will be treated with ribavirin, the requested duration is 16 weeks and documentation has been provided showing the recipient experienced on-treatment virologic failure to peginterferon + ribavirin dual therapy; or

c. Compensated cirrhosis (CTP class A), the requested duration is 12 weeks and documentation is provided showing the recipient experienced virologic relapse to peginterferon + ribavirin dual therapy; or

d. Compensated cirrhosis (CTP class A), will be treated with ribavirin, the requested duration is 16 weeks and documentation has been provided showing the recipient experienced on-treatment virologic failure to peginterferon + ribavirin dual therapy.

9. Recipients who have received previous therapy with an NS5A inhibitor (e.g., daclatasvir, ledipasvir, ombitasvir) or combination therapy with sofosbuvir + simeprevir.

   a. The recipient must meet one of the following:

      1. The recipient has cirrhosis; or

      2. Documentation includes the clinical rationale for urgent retreatment.

   b. Testing for resistance-associated variants (RAVs) have been done and results have been provided.

   c. The requested regimen does not include agents in which RAVs have developed.

   d. The requested regimen includes ribavirin or documentation has been provided that ribavirin is contraindicated.

10. Epclusa® (sofosbuvir/velpatasvir)

   a. The requested dose is one tab daily; and

      1. The recipient is treatment-naïve, with or without cirrhosis and the requested duration is 12 weeks; or

      2. The recipient is treatment-experienced, with or without cirrhosis, the requested duration is 12 weeks and must meet one of the following:

a. Genotype 1a, peginterferon + ribavirin treatment experienced; or

b. Genotype 1b, peginterferon + ribavirin treatment experienced; or

c. Genotype 1, HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprivir) plus peginterferon + ribavirin treatment experienced; or

d. Genotype 2, peginterferon + ribavirin treatment experienced; or

e. Genotype 2, sofosbuvir + ribavirin treatment experienced; or

f. Genotype 3, peginterferon + ribavirin treatment experienced; or

g. Genotpe 3, sofosbuvir + ribavirin treatment experienced; or

h. Genotype 4, peginterferon + ribavirin treatment experienced; or

i. Genotype 5 or 6, peginterferon + ribavirin treatment experienced.

11. For requests for recertification (for treatment beyond 12 weeks), the recipient must meet all of the following:

    a. Laboratory results for HCV RNA viral load at week four and week six (if applicable) have been submitted with the PA request; and

    b. The recipient's HCV viral load must meet one of the following:

        1. Undetectable HCV RNA viral load week four; or

        2. Detectable HCV RNA viral load at treatment week four and HCV RNA increased by $\leq$ 10-fold ($\leq$1 $\log_{10}$ IU/mL) on repeat testing at treatment week six (or thereafter).

        3. And, the recipient is compliant on all drugs in the treatment regimen.

12. Prior Authorization Guidelines:

    a. Prior authorization approval will be for a maximum of 12 weeks (unless the requested regimen is less than 12 weeks long or the remaining duration of therapy is less than 12 weeks).

    b. The initial prescription will be limited to a 14-day supply; subsequent refills can be up to 34 days.

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

# Therapeutic Class Overview
Hepatitis C Direct-Acting Antivirals

## INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2016*).
  - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
  - The CDC estimates that 2.7 to 3.9 million persons in the U.S. have chronic hepatitis C (CHC).
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is the most common indication for liver transplant (*CDC 2016*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2014, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
  - Rapid virologic response (RVR): undetectable viral load at week 4
  - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
  - End-of-treatment response (ETR): undetectable viral load at the end of treatment
  - Sustained virologic response (SVR): undetectable viral load at the conclusion of therapy and 24 weeks after the conclusion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2015*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first direct-acting antiviral-containing regimens were single-ingredient direct-acting antivirals that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the direct-acting antivirals, including: Daklinza, Epclusa, Harvoni, Mavyret, Olysio, Sovaldi, Technivie, Viekira Pak, Viekira XR, Vosevi and Zepatier
- Medispan Class: Hepatitis C Agents

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| Daklinza (daclatasvir) | -- |
| Epclusa (sofosbuvir/velpatasvir) | -- |
| Harvoni (ledipasvir/sofosbuvir) | -- |

| Drug | Generic Availability |
|---|---|
| Mavyret (glecaprevir-pibrentasvir) | -- |
| Olysio (simeprevir) | -- |
| Sovaldi (sofosbuvir) | -- |
| Technivie (ombitasvir/paritaprevir/ritonavir) | -- |
| Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir) | -- |
| Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) | -- |
| Vosevi (sofosbuvir-velpatasvir-voxilaprevir) | -- |
| Zepatier (elbasvir/grazoprevir) | -- |

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | Daklinza (daclatasvir) | Epclusa (sofosbuvir-velpatasvir) | Harvoni* (ledipasvir/sofosbuvir) | Mavyret (glecaprevir-pibrentasvir) | Olysio (simeprevir) | Sovaldi* (sofosbuvir) | Technivie (ombitasvir/paritaprevir/ritonavir) | Viekira Pak, Viekira XR (ombitasvir/paritaprevir/ritonavir/dasabuvir) | Vosevi† (sofosbuvir-velpatasvir-voxilaprevir) | Zepatier (elbasvir/grazoprevir) |
|---|---|---|---|---|---|---|---|---|---|---|
| Genotype 1 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | ✔ | ✔ | ✔ |
| Genotype 2 | | ✔ | | ✔ | | ✔ | | | ✔ | |
| Genotype 3 | ✔ | ✔ | | ✔ | | ✔ | | | ✔ | |
| Genotype 4 | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | ✔ | ✔ |
| Genotype 5 | | ✔ | ✔ | ✔ | | | | | ✔ | |
| Genotype 6 | | ✔ | ✔ | ✔ | | | | | ✔ | |

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.
† Only approved in patients with prior failure to an NS5A inhibitor- or sofosbuvir-containing regimen.
(*Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2017, Olysio 2017, Sovaldi 2017, Technivie 2017, Viekira Pak 2017, Viekira XR 2017, Vosevi 2017, Zepatier 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in three pivotal phase 3 trials.
  - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (*Poordad et al 2016*).
  - ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir

therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
  - ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).
- The ALLY-3+ was an additional phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa
- The clinical safety and efficacy of Epclusa was evaluated in four pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled, MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
  - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
  - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, $p < 0.001$) (*Foster et al 2015*).
  - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).

Harvoni

*Adults*
- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 2 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).

- ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
- ION-4 was an OL, MC trial in patients (n = 335) evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
- SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
- Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
- ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gale et al 2015*).
- SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

*Pediatric*

- A phase 2, OL, MC study (N = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 4 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7% (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2017*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017, Mavyret prescribing information 2017*).
- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146) (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of sofosbuvir plus daclatasvir was -1.2% (95% CI, -5.6% to

3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2017*).
  - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2017, Wyles et al 2017*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up (*Mavyret prescribing information 2017*).
- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2017, Poordad et al 2017*).
  - In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).

Olysio

- The clinical safety and efficacy of simeprevir in combination with sofosbuvir were evaluated in two pivotal phase 3 trials (OPTIMIST-1 and OPTIMIST-2) and one phase 2 trial (COSMOS). Simeprevir is also indicated with PegIFN and RBV, however the results of these trials are not presented here since simeprevir triple therapy is no longer recommended by treatment guidelines for genotype 1 or 4 infection.
  - OPTIMIST-1 was an OL, MC, randomized study comparing a treatment regimen of 12 weeks (n = 155) or 8 weeks (n = 155) of simeprevir in combination with sofosbuvir in chronic HCV genotype 1 infected patients without cirrhosis. In the 12- and 8-week treatment arms, the overall SVR12 rate was 97% (95% CI, 93.7 to 99.9; superiority demonstrated vs historical control) and 83% (95% CI, 76.3 to 88.9; superiority was not demonstrated vs historical control) (*Kwo et al 2016*).
  - OPTIMIST-2 was an OL, MC study (n = 103) evaluating 12 weeks of simeprevir in combination with sofosbuvir in chronic HCV genotype 1 infected patients with cirrhosis. The SVR12 rate was 83% (95% CI, 75.8 to 91.1), demonstrating superiority over a historical control rate of 70%. SVR rates were numerically higher in treatment-naive vs treatment-experienced patients. SVR rates were numerically higher in patients with genotype 1a without the Q80K mutation vs with the Q80K mutation (*Lawitz et al 2016*).
  - COSMOS was an OL, randomized study comparing sofosbuvir plus simeprevir for 12 or 24 weeks, with or without RBV. Of the 167 patients in the overall intention-to-treat population, 92% achieved SVR12. The addition of RBV did not increase response rates in comparison with simeprevir in combination with sofosbuvir alone. Response rates were also similar regardless of treatment duration, though sample sizes were small (*Lawitz et al 2014*).

Sovaldi

*Adults*

- The clinical safety and efficacy of sofosbuvir were evaluated in six pivotal phase 3 trials.
  - NEUTRINO was a single-arm, OL study of sofosbuvir in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
  - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with sofosbuvir plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz et al 2013*).
  - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with sofosbuvir and RBV or matching placebos. Rates

of SVR at 12 weeks were significantly higher in the sofosbuvir treatment group compared to placebo (78 vs 0%, respectively; p < 0.001) (*Jacobson et al 2013*).
- In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with sofosbuvir and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
- The VALENCE trial evaluated sofosbuvir in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
- PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of sofosbuvir in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

*Pediatric*
- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).

Technivie
- The efficacy of Technivie was evaluated in a single, phase 2b, OL, MC, randomized pivotal trial (PEARL-I). The trial evaluated genotype 1b (*Lawitz et al 2015*) and genotype 4 (*Hézode et al 2015*) patients; however Technivie is only FDA approved for genotype 4. Genotype 4 patients received Technivie with or without RBV, for 12 weeks. Genotype 1b patients received Technivie for 12 or 24 weeks, without RBV.
  - In genotype 4 treatment-naive patients, SVR12 rates were 100% (42/42, 95% CI, 91.6 to 100) in the RBV-containing regimen and 90.9% (40/44, 95% CI, 78.3 to 97.5) in the RBV-free regimen; there was no statistical difference in SVR12 rates between these 2 treatment groups after adjusting for IL28B genotype (p = 0.086). All treatment-experienced patients received Technivie with RBV and the SVR12 rate was 100% (49/49).
  - In genotype 1b patients, SVR12 was achieved in 95.2% (40/42, 95% CI, 83.8 to 99.4) of treatment-naïve and 90.0% (36/40, 95% CI, 76.3 to 97.2) of treatment-experienced patients without cirrhosis. Among patients with cirrhosis, SVR12 was achieved in 97.9% (46/47, 95% CI, 88.7 to 99.9) of treatment-naïve and 96.2% (50/52, 95% CI, 86.8 to 99.5) of treatment-experienced patients.

Vosevi
- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 7 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
  - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, double-blind, placebo controlled trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.
- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Viekira XR

- The approval of Viekira XR was based on comparability of bioavailability for each of the components in Viekira XR compared to that of the previously approved formulations in Viekira Pak. A clinical trial to evaluate the efficacy and safety of Viekira XR was not required.

Zepatier

- The safety and efficacy of Zepatier were evaluated in 6 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a double-blind, placebo-controlled, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2016*).
  - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
  - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).

## CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2017*).
  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless

of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

## SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Technivie, Viekira Pak, and Viekira XR are contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8 (Viekira Pak and Viekira XR only)
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:
  - Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
  - Technivie, Viekira Pak, and Viekira XR carry a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.
- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Daklinza in combination with Sovaldi: headache and fatigue
    - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea
    - Epclusa: headache and fatigue
    - Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
    - Harvoni: fatigue, headache, and asthenia
    - Mavyret: headache and fatigue
    - Olysio with Sovaldi during 12 or 24 weeks of treatment: fatigue, headache, and nausea
    - Olysio with PegIFN and RBV during the first 12 weeks of treatment: rash (including photosensitivity), pruritus, and nausea
    - Sovaldi in combination with RBV: fatigue and headache; Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
    - Technivie in combination with RBV: asthenia, fatigue, nausea, and insomnia
    - Viekira Pak and Viekira XR: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
    - Viekira Pak or Viekira XR without RBV: nausea, pruritus, and insomnia
    - Vosevi: headache, fatigue, diarrhea, and nausea
    - Zepatier: fatigue, headache, and nausea.

- Zepatier with RBV: anemia and headache

- On October 4, 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. The new *Boxed Warning* is based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with direct-acting antivirals. In a few cases, HBV reactivation in patients treated with direct-acting antivirals resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|
| Daklinza (daclatasvir) | Oral | One tablet once daily (60 mg dose); must be used in combination with Sovaldi | *Recommended dosage modification with CYP3A inhibitors and inducers*:<br>• Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily<br>• Moderate CYP3A inducers and nevirapine: 90 mg once daily<br><br>*Duration of therapy:*<br>• 12 to 24 weeks (when used in combination with Sovaldi) |
| Epclusa (sofosbuvir/velpatasvir) | Oral | One tablet once daily | • No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD).<br><br>*Duration of therapy:*<br>• 12 weeks |
| Harvoni (ledipasvir/sofosbuvir) | Oral | One tablet once daily | • No dosage recommendation can be given for patients with severe renal impairment or ESRD. |
| Mavyret (glecaprevir/pibrentasvir) | Oral | Three tablets daily | • Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B).<br><br>*Duration of therapy:*<br>• 8 to 16 weeks |
| Olysio (simeprevir) | Oral | One capsule once daily; must be used with PegIFN/RBV or Sovaldi | • In HCV genotype 1a-infected patients with compensated cirrhosis, screening for the |

| Drug | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|
| | | | presence of virus with the NS3 Q80K polymorphism may be considered prior to initiation of treatment with Olysio with Sovaldi.<br>• Prior to initiation of treatment with Olysio in combination with PegIFN/RBV, screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism is strongly recommended.<br>• Not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher simeprevir exposures.<br><br>*Duration of therapy:*<br>• 12 to 24 weeks (when used in combination with Sovaldi) |
| Sovaldi (sofosbuvir) | Oral | One tablet once daily; must be used in combination with RBV ± PegIFN, Sovaldi, or Daklinza | • Safety and efficacy have not been established in patients with severe renal impairment.<br><br>*Duration of therapy:*<br>• 12 to 24 weeks (when used in combination with Daklinza or Olysio) |
| Technivie (ombitasvir/paritaprevir/ritonavir) | Oral | Two tablets once daily | • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C).<br><br>*Duration of therapy:*<br>• 12 weeks |
| Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir) | Oral | Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) | • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C).<br><br>*Duration of therapy:*<br>• 12 to 24 weeks |
| Viekira XR (ombitasvir/paritaprevir/ ritonavir/dasabuvir) | Oral | Three tablets once daily | • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C).<br>*Duration of therapy:*<br>• 12 to 24 weeks |

| Drug | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|
| Vosevi (sofosbuvir/velpatasvir/voxilaprevir) | Oral | One tablet once daily | • No dosage recommendation can be given for patients with severe renal impairment or ESRD.<br>• Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C).<br><br>*Duration of therapy:*<br>• 12 weeks |
| Zepatier (elbasvir/grazoprevir) | Oral | One tablet once daily | • Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration.<br>• Contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure.<br><br>*Duration of therapy:*<br>• 12 to 16 weeks |

See the current prescribing information for full details

## CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2017*).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2017*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2017*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2017*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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Publication Date: October 11, 2017

## Kevzara

**Initial Prior Authorization Criteria**:

- Recipient has a diagnosis of moderate to severe rheumatoid arthritis (RA), and
- Must be 18 years of age or older, and
- Prescribed by or in consultation with a rheumatologist, and
- Recipient has had a trial and failure of, contraindication, or intolerance to one or more nonbiologic disease modifying anti-rheumatic drugs (DMARD), and
- Recipient is not receiving Kevzara in combination with a biologic DMARD (e.g., Enbrel, Humira, Cimzia).

**Other suggestions to possibly include:**

- Member meets one of the following; failure of methotrexate (MTX) for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effect is experienced, or if intolerance or contraindication to MTX: sulfasalaline, leflunomide, or hydroxychloroquine for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced,
- Failure of etanercept (Enbrel is preferred) and adalimumab (Humira is preferred), each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced,
- TB test within the past 12 months is negative, or if positive, active TB has been ruled out and the patient has received treatment for latent TB infection,
- The dose does not exceed 200 mg (1 syringe) once every 2 weeks.

**Continuing Therapy Criteria**:

- Documentation of positive clinical response to Kevzara® therapy (e.g., reduction in joint pain/swelling/tenderness, improvement in erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) levels, activities of daily living), and
- Recipient is not receiving Kevzara in combination with a biologic DMARD.

**Other suggestion to possibly include:**

- If request is for a dose increase, new dose does not exceed 200 mg (1 syringe) once every 2 weeks.

**Approval Duration**:

- Initial authorization duration for 12 months.
- Initial authorization was also suggested for 6 months.
- Continued authorization for 12 months.

| Market Applicability/Effective Date | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Market** | **FL & FHK** | **FL MMA** | **FL LTC** | **GA** | **KS** | **KY** | **LA** | **MD** | **NJ** | **NV** | **NY** | **TN** | **TX** | **WA** |
| **Applicable** | X | NA | NA | X | NA | X | X | X | X | X | X | NA | NA | X |

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# Kevzara (sarilumab)

DRUG.00101

| Override(s) | Approval Duration |
|---|---|
| Prior Authorization<br>Quantity Limit | 1 year |

| Medications | Quantity Limit |
|---|---|
| Kevzara (sarilumab) | May be subject to quantity limit |

## APPROVAL CRITERIA

I. Kevzara (sarilumab) may be approved for the treatment of an individual with moderately to severely active Rheumatoid Arthritis (RA) when **ALL** of the following criteria are met:
   A. Individual is 18 years of age or older; **AND**
   B. Agent is used for any of the following reasons:
      1. To reduce signs or symptoms; **OR**
      2. To induce or maintain clinical response; **OR**
      3. To inhibit the progression of structural damage; **OR**
      4. To improve physical function;

   **AND**
   C. Individual has had an inadequate response to a trial (medication samples/coupons/discount cards are excluded from consideration as a trial) of 1 or more disease modifying anti-rheumatic drugs (DMARDs) (for example, methotrexate [MTX]) or a tumor necrosis factor [TNF] antagonist drug; **AND**
   D. May be used alone or in combination with MTX **or** with other nonbiologic DMARDs; **AND**
   E. Individual has had a trial (medication samples/coupons/discount cards are excluded from consideration as a trial) and inadequate response to TWO (2) preferred biologic agents [Current preferred biologics include – Enbrel (etanercept), Humira (adalimumab] unless the following criteria are met:
      1. The preferred agents are not acceptable due to concomitant clinical conditions, such as but not limited to any of the following:
         a. Known hypersensitivity to any active or inactive component which is not also associated with the Kevzara (sarilumab); **OR**
         b. Individuals age; **OR**
         c. Pregnant or planning on becoming pregnant; **OR**

| Market Applicability/Effective Date | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Market** | **FL & FHK** | **FL MMA** | **FL LTC** | **GA** | **KS** | **KY** | **LA** | **MD** | **NJ** | **NV** | **NY** | **TN** | **TX** | **WA** |
| **Applicable** | X | NA | NA | X | NA | X | X | X | X | X | X | NA | NA | X |

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d. Serious infections or concurrent sepsis;

**OR**

2. The individual has either concomitant clinical condition:
    a. Demyelinating disease; **OR**
    b. Heart failure with documented left ventricular dysfunction;

Kevzara (sarilumab) may **NOT** be approved for an individual with **any** of the following:

A. In combination with other biologic DMARDs such as anti-CD20 monoclonal antibodies, IL-1R antagonists, Janus kinas inhibitors (for example, tofacitinib citrate), selective co-stimulation modulators, or TNF antagonists; **or**
B. At initiation of therapy, absolute neutrophil count (ANC) less than 2000/$mm^3$, platelet count less than 100,000/$mm^3$, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 1.5 times the upper limit of normal (ULN); **or**
C. Tuberculosis, invasive fungal infection, or other active serious infections or a history of recurrent infections; **or**
D. Individual has not had a tuberculin skin test (TST) or Centers for Disease Control and Prevention (CDC)-recommended equivalent to evaluate for latent tuberculosis prior to initiating Kevzara (sarilumab).

Kevzara (sarilumab) is considered **investigational and may NOT be approved** when the criteria above are not met and for all other indications, including but not limited to the treatment of:

A. adult onset Still's disease (AOSD)
B. ankylosing spondylitis (AS)
C. Crohn's disease (CD)
D. Takayasu's arteritis
E. systemic lupus erythematosus (SLE)
F. tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
G. unicentric Castleman disease

**Note:**
Kevzara (sarilumab) has a black box warning for risk of serious infections. Individuals treated with Kevzara are at increased risk for developing serious infections that may lead to hospitalization or death. Opportunistic infections have also been reported in patients receiving sarilumab. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Avoid use of Kevzara

| Market Applicability/Effective Date | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Market** | **FL & FHK** | **FL MMA** | **FL LTC** | **GA** | **KS** | **KY** | **LA** | **MD** | **NJ** | **NV** | **NY** | **TN** | **TX** | **WA** |
| **Applicable** | X | NA | NA | X | NA | X | X | X | X | X | X | NA | NA | X |

*FHK- Florida Healthy Kids

(sarilumab) in patients with an active infection. Reported infections include: Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before sarilumab use and during therapy. Treatment for latent infection should be initiated prior to sarilumab use; Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease; Bacterial, viral and other infections due to opportunistic pathogens. Closely monitor patients for signs and symptoms of infection during treatment with sarilumab. If a serious infection develops, interrupt sarilumab until the infection is controlled. Consider the risks and benefits of treatment with sarilumab prior to initiating therapy in patients with chronic or recurrent infection.

| State Specific Mandates | | |
|---|---|---|
| State name<br>N/A | Date effective<br>N/A | Mandate details (including specific bill if applicable)<br>N/A |

**Key References**:


1. Centers for Disease Control (CDC) and Prevention. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection - United States, 2010; 59(No. RR 5):1-28. Available at: http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf. Accessed on May 25, 2017.
2. Kevzara [Product Information], sanofi-aventis U.S., Bridgewater, NJ and Regeneron Pharmaceuticals, Inc., Tarrytown, NY; May 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf. Accessed on May 25, 2017.
3. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016; 68(1):1-26.
4. U.S. National Institutes of Health (NIH). ClinicalTrials.gov. Search: sarilumab. Available at: https://clinicaltrials.gov/ct2/results?term=sarilumab&Search=Search. Accessed on May 25, 2017.

**Nevada Medicaid**
Kevzara (sarilumab)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Kevzara | sarilumab |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Rheumatoid arthritis** Indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). **Approval Criteria**

Initial Approval Criteria

1. The recipient has had a negative tuberculin test and
2. The recipient does not have an active infection or a history of recurring infections and
3. The approval will not be given for the use of more than one biologic at a time (combination therapy) and
4. The recipient has a diagnosis of moderately to severly active RA and
5. The recipient is 18 years of age or older and
6. The recipient has had a rheumatology consultation, including the date of the visit, and one of the following:
    a. The recipient has had RA for ≤ six months (early RA) and has high disease activity; and an inadequate or adverse reaction to a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine) OR
    b. The recipient has had RA for ≥ six months (intermediate or long-term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine) OR
    c. The recipient has had RA for ≥ six months (intermediate or long-term disease duration) and has high disease activity.

Approval – 12 Months

**Nevada Medicaid**
Kevzara (sarilumab)
Pharmacy Coverage Guideline

Reauthorization:

1. Documentation of positive clinical response to Kevzara therapy
2. The patient is not receiving Kevzara in combination with a biologic DMARD

Approval – 12 Months

**Immunomodulator Utilization**

Jan 1, 2017 - Dec 31, 2017

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201701 | ACTEMRA | 1 | 1 | 28 | 3.6 | $ 3,347.24 |
| 201702 | ACTEMRA | 1 | 1 | 28 | 3.6 | $ 3,603.41 |
| 201703 | ACTEMRA | 2 | 3 | 30 | 33.6 | $ 5,151.91 |
| 201704 | ACTEMRA | 2 | 3 | 30 | 27.6 | $ 4,849.66 |
| 201705 | ACTEMRA | 4 | 7 | 88 | 64.8 | $ 10,007.07 |
| 201706 | ACTEMRA | 3 | 4 | 58 | 37.2 | $ 8,760.82 |
| 201707 | ACTEMRA | 4 | 5 | 86 | 40.8 | $ 8,868.58 |
| 201708 | ACTEMRA | 4 | 5 | 140 | 18 | $ 14,629.16 |
| 201709 | ACTEMRA | 5 | 8 | 116 | 74.4 | $ 14,046.87 |
| 201710 | ACTEMRA | 5 | 10 | 118 | 72.4 | $ 18,950.64 |
| 201711 | ACTEMRA | 5 | 7 | 88 | 54.8 | $ 11,103.04 |
| 201712 | ACTEMRA | 3 | 4 | 58 | 21.2 | $ 8,706.57 |
| 201701 | CIMZIA | 1 | 1 | 30 | 1 | $ 3,592.15 |
| 201702 | CIMZIA | 3 | 4 | 114 | 4 | $ 14,466.49 |
| 201703 | CIMZIA | 3 | 3 | 86 | 3 | $ 7,130.74 |
| 201704 | CIMZIA | 5 | 6 | 170 | 6 | $ 17,947.82 |
| 201705 | CIMZIA | 3 | 3 | 86 | 3 | $ 10,690.56 |
| 201706 | CIMZIA | 5 | 6 | 167 | 6 | $ 21,381.12 |
| 201707 | CIMZIA | 6 | 7 | 198 | 7 | $ 25,803.69 |
| 201708 | CIMZIA | 6 | 6 | 172 | 6 | $ 22,378.47 |
| 201709 | CIMZIA | 5 | 5 | 140 | 5 | $ 18,509.10 |
| 201710 | CIMZIA | 6 | 6 | 143 | 6 | $ 22,200.75 |
| 201711 | CIMZIA | 8 | 8 | 201 | 8 | $ 29,794.79 |
| 201712 | CIMZIA | 8 | 11 | 260 | 12 | $ 45,035.54 |
| 201704 | CIMZIA STARTER KIT | 1 | 1 | 30 | 3 | $ 11,049.78 |
| 201706 | CIMZIA STARTER KIT | 2 | 2 | 70 | 6 | $ 22,099.56 |
| 201709 | CIMZIA STARTER KIT | 1 | 1 | 30 | 3 | $ 11,583.57 |
| 201703 | COSENTYX | 1 | 2 | 2 | 2 | $ 50.00 |
| 201704 | COSENTYX | 1 | 3 | 3 | 4 | $ 100.00 |
| 201707 | COSENTYX | 1 | 1 | 1 | 1 | $ 25.00 |
| 201709 | COSENTYX | 1 | 1 | 56 | 4 | $ 8,859.71 |
| 201712 | COSENTYX | 3 | 3 | 86 | 17 | $ 39,853.44 |
| 201701 | COSENTYX SENSOREADY PEN | 2 | 2 | 56 | 4 | $ 8,149.48 |
| 201702 | COSENTYX SENSOREADY PEN | 2 | 3 | 84 | 6 | $ 12,224.22 |
| 201703 | COSENTYX SENSOREADY PEN | 2 | 3 | 84 | 6 | $ 12,711.96 |
| 201704 | COSENTYX SENSOREADY PEN | 2 | 2 | 56 | 6 | $ 12,945.66 |
| 201705 | COSENTYX SENSOREADY PEN | 4 | 6 | 168 | 16 | $ 38,836.98 |
| 201706 | COSENTYX SENSOREADY PEN | 4 | 4 | 112 | 7 | $ 17,274.44 |
| 201707 | COSENTYX SENSOREADY PEN | 3 | 4 | 112 | 7 | $ 17,199.53 |
| 201708 | COSENTYX SENSOREADY PEN | 5 | 5 | 140 | 15 | $ 33,965.37 |
| 201709 | COSENTYX SENSOREADY PEN | 5 | 5 | 140 | 15 | $ 52,512.24 |
| 201710 | COSENTYX SENSOREADY PEN | 5 | 6 | 170 | 12 | $ 43,884.82 |
| 201711 | COSENTYX SENSOREADY PEN | 5 | 7 | 198 | 19 | $ 42,411.35 |
| 201712 | COSENTYX SENSOREADY PEN | 5 | 5 | 198 | 10 | $ 30,388.39 |

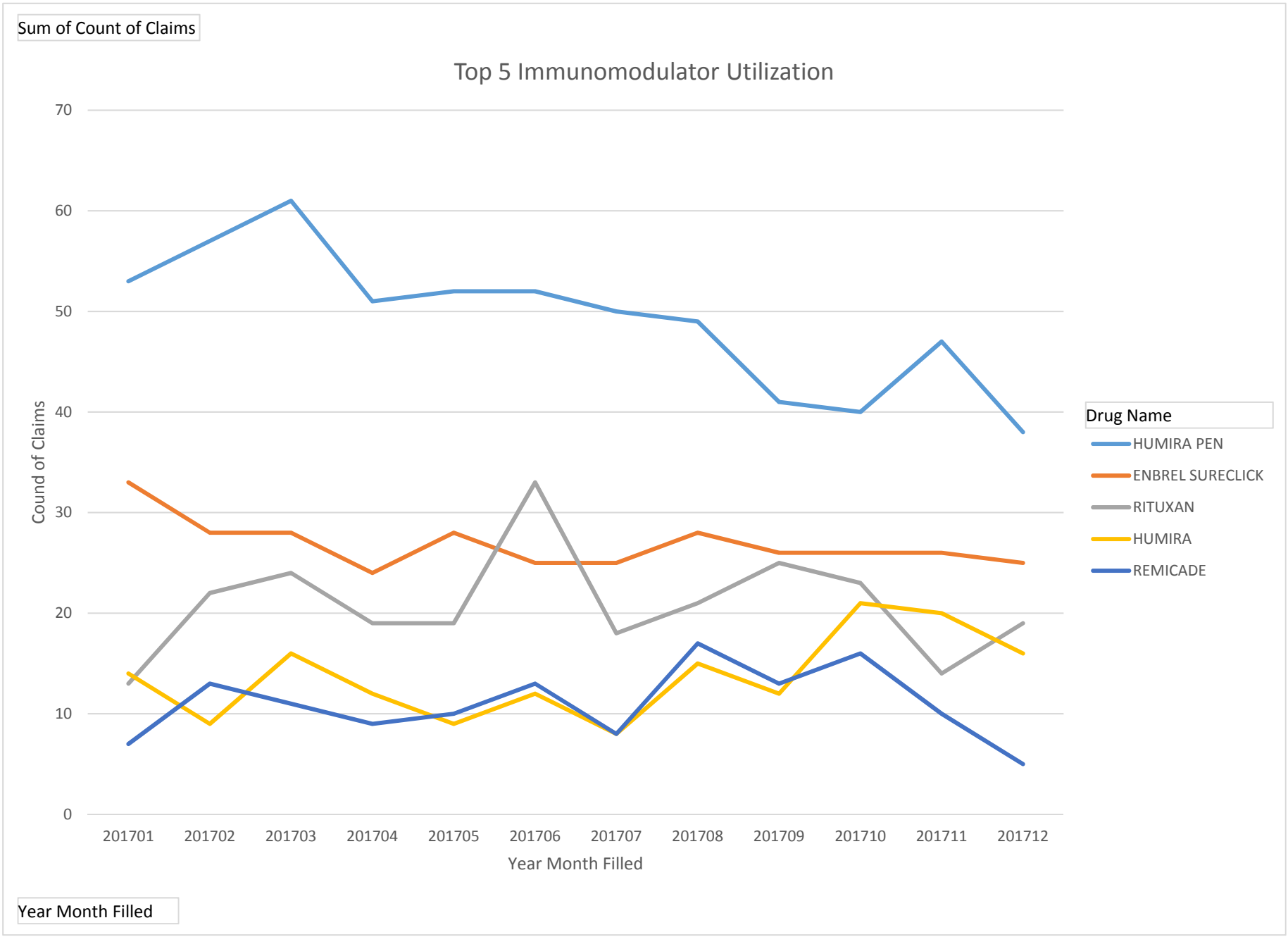
| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201701 | ENBREL | 7 | 7 | 200 | 31.76 | $ 22,288.27 |
| 201702 | ENBREL | 8 | 8 | 228 | 35.68 | $ 19,610.12 |
| 201703 | ENBREL | 7 | 7 | 254 | 37.56 | $ 30,302.10 |
| 201704 | ENBREL | 5 | 5 | 142 | 21.8 | $ 19,403.90 |
| 201705 | ENBREL | 8 | 10 | 340 | 49.56 | $ 36,758.49 |
| 201706 | ENBREL | 5 | 5 | 144 | 21.88 | $ 17,312.18 |
| 201707 | ENBREL | 8 | 8 | 392 | 57.32 | $ 51,792.14 |
| 201708 | ENBREL | 6 | 6 | 224 | 33.56 | $ 28,034.73 |
| 201709 | ENBREL | 7 | 7 | 198 | 25.64 | $ 25,896.76 |
| 201710 | ENBREL | 4 | 4 | 112 | 13.8 | $ 15,111.96 |
| 201711 | ENBREL | 7 | 7 | 198 | 25.64 | $ 21,610.39 |
| 201712 | ENBREL | 7 | 7 | 198 | 25.64 | $ 21,636.04 |
| 201701 | ENBREL SURECLICK | 31 | 33 | 931 | 141.12 | $ 121,870.14 |
| 201702 | ENBREL SURECLICK | 27 | 28 | 847 | 125.44 | $ 113,124.41 |
| 201703 | ENBREL SURECLICK | 25 | 28 | 788 | 121.52 | $ 130,507.80 |
| 201704 | ENBREL SURECLICK | 23 | 24 | 676 | 109.76 | $ 108,734.69 |
| 201705 | ENBREL SURECLICK | 27 | 28 | 877 | 121.52 | $ 124,923.95 |
| 201706 | ENBREL SURECLICK | 24 | 25 | 705 | 101.92 | $ 112,041.19 |
| 201707 | ENBREL SURECLICK | 23 | 25 | 795 | 109.76 | $ 120,886.67 |
| 201708 | ENBREL SURECLICK | 24 | 28 | 791 | 113.68 | $ 125,225.47 |
| 201709 | ENBREL SURECLICK | 24 | 26 | 788 | 113.68 | $ 125,205.14 |
| 201710 | ENBREL SURECLICK | 23 | 26 | 786 | 113.68 | $ 125,205.14 |
| 201711 | ENBREL SURECLICK | 24 | 26 | 730 | 105.84 | $ 116,588.53 |
| 201712 | ENBREL SURECLICK | 24 | 25 | 700 | 101.92 | $ 112,270.06 |
| 201702 | ENTYVIO | 2 | 2 | 2 | 2 | $ 10,424.46 |
| 201704 | ENTYVIO | 3 | 3 | 3 | 3 | $ 16,262.16 |
| 201706 | ENTYVIO | 4 | 4 | 31 | 5 | $ 27,113.77 |
| 201707 | ENTYVIO | 1 | 1 | 56 | 1 | $ 5,430.89 |
| 201708 | ENTYVIO | 4 | 4 | 4 | 4 | $ 16,387.26 |
| 201709 | ENTYVIO | 1 | 1 | 56 | 1 | $ 5,430.89 |
| 201710 | ENTYVIO | 2 | 2 | 2 | 2 | $ 5,762.65 |
| 201711 | ENTYVIO | 1 | 1 | 1 | 1 | $ 129.00 |
| 201701 | HUMIRA | 12 | 14 | 392 | 28 | $ 52,179.29 |
| 201702 | HUMIRA | 9 | 9 | 252 | 22 | $ 42,927.64 |
| 201703 | HUMIRA | 14 | 16 | 448 | 36 | $ 73,157.31 |
| 201704 | HUMIRA | 10 | 12 | 394 | 30 | $ 64,534.75 |
| 201705 | HUMIRA | 9 | 9 | 252 | 20 | $ 43,033.33 |
| 201706 | HUMIRA | 12 | 12 | 336 | 30 | $ 64,534.74 |
| 201707 | HUMIRA | 8 | 8 | 252 | 20 | $ 43,023.17 |
| 201708 | HUMIRA | 14 | 15 | 406 | 36 | $ 77,447.79 |
| 201709 | HUMIRA | 12 | 12 | 338 | 26 | $ 55,946.38 |
| 201710 | HUMIRA | 19 | 21 | 563 | 50 | $ 107,543.78 |
| 201711 | HUMIRA | 18 | 20 | 620 | 50 | $ 107,471.14 |
| 201712 | HUMIRA | 14 | 16 | 534 | 40 | $ 85,976.91 |
| 201701 | HUMIRA PEN | 48 | 53 | 1450 | 110 | $ 198,081.16 |
| 201702 | HUMIRA PEN | 53 | 57 | 1570 | 124 | $ 224,498.10 |
| 201703 | HUMIRA PEN | 55 | 61 | 1749 | 136.5 | $ 246,653.61 |

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201704 | HUMIRA PEN | 47 | 51 | 1392 | 146 | $ 214,844.20 |
| 201705 | HUMIRA PEN | 49 | 52 | 1418 | 112.5 | $ 214,924.52 |
| 201706 | HUMIRA PEN | 46 | 52 | 1486 | 162.5 | $ 244,959.38 |
| 201707 | HUMIRA PEN | 47 | 50 | 1360 | 184 | $ 215,157.55 |
| 201708 | HUMIRA PEN | 46 | 49 | 1409 | 112.5 | $ 223,524.90 |
| 201709 | HUMIRA PEN | 40 | 41 | 1234 | 102.5 | $ 206,298.19 |
| 201710 | HUMIRA PEN | 36 | 40 | 1114 | 132 | $ 193,572.41 |
| 201711 | HUMIRA PEN | 39 | 47 | 1425 | 122 | $ 258,563.64 |
| 201712 | HUMIRA PEN | 35 | 38 | 1238 | 98 | $ 211,482.95 |
| 201701 | HUMIRA PEN-CROHNS DISEASE | 1 | 1 | 28 | 6 | $ 11,957.50 |
| 201702 | HUMIRA PEN-CROHNS DISEASE | 2 | 2 | 56 | 12 | $ 12,964.77 |
| 201703 | HUMIRA PEN-CROHNS DISEASE | 1 | 1 | 28 | 6 | $ 12,961.07 |
| 201704 | HUMIRA PEN-CROHNS DISEASE | 2 | 2 | 109 | 12 | $ 12,964.77 |
| 201706 | HUMIRA PEN-CROHNS DISEASE | 1 | 1 | 84 | 6 | $ 12,961.07 |
| 201708 | HUMIRA PEN-CROHNS DISEASE | 1 | 1 | 30 | 6 | $ 12,961.07 |
| 201710 | HUMIRA PEN-CROHNS DISEASE | 2 | 2 | 35 | 12 | $ 25,922.14 |
| 201711 | HUMIRA PEN-CROHNS DISEASE | 2 | 2 | 56 | 12 | $ 25,922.14 |
| 201712 | HUMIRA PEN-CROHNS DISEASE | 2 | 2 | 56 | 12 | $ 25,922.14 |
| 201702 | HUMIRA PEN-PSORIASIS STAR | 1 | 1 | 28 | 4 | $ 8,644.26 |
| 201703 | HUMIRA PEN-PSORIASIS STAR | 2 | 2 | 56 | 8 | $ 17,288.52 |
| 201704 | HUMIRA PEN-PSORIASIS STAR | 1 | 1 | 57 | 4 | $ 8,644.26 |
| 201706 | HUMIRA PEN-PSORIASIS STAR | 1 | 1 | 28 | 4 | $ 3.70 |
| 201707 | HUMIRA PEN-PSORIASIS STAR | 3 | 3 | 69 | 12 | $ 25,932.78 |
| 201708 | HUMIRA PEN-PSORIASIS STAR | 4 | 4 | 140 | 16 | $ 34,577.04 |
| 201710 | HUMIRA PEN-PSORIASIS STAR | 2 | 2 | 63 | 8 | $ 17,288.52 |
| 201711 | HUMIRA PEN-PSORIASIS STAR | 1 | 1 | 56 | 4 | $ 8,644.26 |
| 201704 | INFLECTRA | 2 | 2 | 2 | 60 | $ 16,221.00 |
| 201707 | INFLECTRA | 1 | 1 | 1 | 32 | $ 15,785.00 |
| 201708 | INFLECTRA | 1 | 1 | 1 | 4 | $ 1,262.80 |
| 201710 | INFLECTRA | 1 | 1 | 1 | 3 | $ 2,838.84 |
| 201712 | INFLECTRA | 1 | 1 | 1 | 3 | $ 2,838.84 |
| 201701 | KINERET | 1 | 1 | 28 | 37.52 | $ 7,402.65 |
| 201702 | KINERET | 1 | 1 | 28 | 37.52 | $ 7,402.65 |
| 201703 | KINERET | 1 | 1 | 28 | 37.52 | $ 7,402.65 |
| 201704 | KINERET | 1 | 1 | 28 | 37.52 | $ 7,402.65 |
| 201706 | KINERET | 2 | 3 | 84 | 93.8 | $ 18,511.71 |
| 201707 | KINERET | 2 | 2 | 56 | 56.28 | $ 11,109.06 |
| 201708 | KINERET | 2 | 2 | 56 | 56.28 | $ 11,109.06 |
| 201709 | KINERET | 1 | 1 | 28 | 18.76 | $ 3,706.41 |
| 201710 | KINERET | 1 | 1 | 28 | 37.52 | $ 7,402.65 |
| 201711 | KINERET | 2 | 2 | 56 | 56.28 | $ 11,109.06 |
| 201712 | KINERET | 2 | 2 | 56 | 56.28 | $ 11,109.06 |
| 201701 | ORENCIA | 8 | 8 | 62 | 28 | $ 17,514.30 |
| 201702 | ORENCIA | 6 | 6 | 33 | 20 | $ 12,901.89 |
| 201703 | ORENCIA | 8 | 10 | 37 | 32 | $ 16,619.60 |
| 201704 | ORENCIA | 8 | 8 | 62 | 27 | $ 16,843.24 |
| 201705 | ORENCIA | 8 | 8 | 62 | 26 | $ 18,523.00 |

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201706 | ORENCIA | 7 | 7 | 63 | 24 | $ 13,916.32 |
| 201707 | ORENCIA | 9 | 9 | 65 | 28 | $ 17,864.44 |
| 201708 | ORENCIA | 10 | 10 | 64 | 31 | $ 20,702.53 |
| 201709 | ORENCIA | 11 | 12 | 66 | 36 | $ 21,655.87 |
| 201710 | ORENCIA | 7 | 8 | 62 | 28 | $ 17,779.18 |
| 201711 | ORENCIA | 10 | 11 | 119 | 39 | $ 26,125.18 |
| 201712 | ORENCIA | 5 | 5 | 59 | 15 | $ 11,319.09 |
| 201703 | ORENCIA CLICKJECT | 1 | 1 | 28 | 4 | $ 3,838.74 |
| 201704 | ORENCIA CLICKJECT | 1 | 1 | 28 | 4 | $ 3,838.74 |
| 201706 | ORENCIA CLICKJECT | 1 | 1 | 28 | 4 | $ 3,838.74 |
| 201710 | ORENCIA CLICKJECT | 1 | 1 | 28 | 4 | $ 3,838.74 |
| 201711 | ORENCIA CLICKJECT | 1 | 1 | 28 | 4 | $ 3,838.74 |
| 201701 | OTEZLA | 4 | 5 | 150 | 300 | $ 7,832.15 |
| 201702 | OTEZLA | 5 | 5 | 150 | 300 | $ 8,011.64 |
| 201703 | OTEZLA | 5 | 5 | 150 | 300 | $ 7,969.34 |
| 201704 | OTEZLA | 6 | 6 | 178 | 355 | $ 14,139.20 |
| 201705 | OTEZLA | 5 | 6 | 180 | 360 | $ 14,192.30 |
| 201706 | OTEZLA | 6 | 6 | 180 | 360 | $ 14,192.30 |
| 201707 | OTEZLA | 6 | 6 | 180 | 360 | $ 14,192.30 |
| 201708 | OTEZLA | 4 | 4 | 120 | 240 | $ 8,516.86 |
| 201709 | OTEZLA | 4 | 4 | 120 | 240 | $ 8,516.86 |
| 201710 | OTEZLA | 4 | 4 | 120 | 240 | $ 8,784.60 |
| 201711 | OTEZLA | 5 | 6 | 180 | 360 | $ 11,923.39 |
| 201712 | OTEZLA | 4 | 4 | 116 | 230 | $ 12,226.86 |
| 201701 | REMICADE | 7 | 7 | 7 | 33 | $ 29,670.32 |
| 201702 | REMICADE | 13 | 13 | 40 | 57 | $ 49,250.39 |
| 201703 | REMICADE | 11 | 11 | 85 | 49 | $ 40,844.95 |
| 201704 | REMICADE | 9 | 9 | 36 | 36 | $ 30,799.35 |
| 201705 | REMICADE | 10 | 10 | 78 | 42 | $ 38,564.74 |
| 201706 | REMICADE | 13 | 13 | 54 | 54 | $ 50,703.69 |
| 201707 | REMICADE | 8 | 8 | 8 | 25.5 | $ 25,283.05 |
| 201708 | REMICADE | 16 | 17 | 17 | 59 | $ 52,474.95 |
| 201709 | REMICADE | 12 | 13 | 13 | 44.55 | $ 38,632.03 |
| 201710 | REMICADE | 14 | 16 | 16 | 61 | $ 58,310.79 |
| 201711 | REMICADE | 10 | 10 | 10 | 44 | $ 43,352.83 |
| 201712 | REMICADE | 5 | 5 | 5 | 18 | $ 16,088.55 |
| 201701 | RITUXAN | 11 | 13 | 13 | 540 | $ 35,771.89 |
| 201702 | RITUXAN | 15 | 22 | 62 | 1150 | $ 85,083.24 |
| 201703 | RITUXAN | 17 | 24 | 24 | 1200 | $ 86,487.40 |
| 201704 | RITUXAN | 15 | 19 | 19 | 1440 | $ 95,545.28 |
| 201705 | RITUXAN | 15 | 19 | 19 | 1210 | $ 87,332.12 |
| 201706 | RITUXAN | 21 | 33 | 66 | 2100 | $ 140,440.57 |
| 201707 | RITUXAN | 13 | 18 | 51 | 1260 | $ 72,190.96 |
| 201708 | RITUXAN | 12 | 21 | 59 | 1180 | $ 102,539.02 |
| 201709 | RITUXAN | 12 | 25 | 64 | 1260 | $ 106,540.99 |
| 201710 | RITUXAN | 11 | 23 | 112 | 1160 | $ 93,731.69 |
| 201711 | RITUXAN | 8 | 14 | 27 | 850 | $ 60,921.11 |

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201712 | RITUXAN | 7 | 19 | 46 | 940 | $ 49,368.49 |
| 201701 | SIMPONI | 2 | 2 | 58 | 1 | $ 3,696.73 |
| 201702 | SIMPONI | 2 | 2 | 58 | 1 | $ 4,024.83 |
| 201703 | SIMPONI | 2 | 2 | 58 | 1 | $ 8,049.66 |
| 201704 | SIMPONI | 2 | 3 | 88 | 1.5 | $ 12,074.49 |
| 201705 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 3,984.37 |
| 201706 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 3,995.70 |
| 201707 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 3,995.70 |
| 201708 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 3,995.70 |
| 201709 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 4,017.48 |
| 201710 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 4,017.48 |
| 201711 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 4,017.48 |
| 201712 | SIMPONI | 1 | 1 | 28 | 0.5 | $ 4,017.48 |
| 201703 | SIMPONI ARIA | 1 | 1 | 56 | 12 | $ 4,786.44 |
| 201705 | SIMPONI ARIA | 1 | 1 | 1 | 1000 | $ 17,322.50 |
| 201701 | STELARA | 2 | 2 | 31 | 1.5 | $ 20,286.78 |
| 201702 | STELARA | 1 | 1 | 28 | 1 | $ 17,690.61 |
| 201703 | STELARA | 2 | 2 | 84 | 2 | $ 36,582.18 |
| 201704 | STELARA | 3 | 3 | 146 | 2.5 | $ 45,637.42 |
| 201705 | STELARA | 3 | 3 | 112 | 2.5 | $ 45,637.42 |
| 201706 | STELARA | 3 | 3 | 148 | 2 | $ 36,514.57 |
| 201707 | STELARA | 1 | 1 | 30 | 1 | $ 18,291.09 |
| 201708 | STELARA | 3 | 3 | 230 | 2.5 | $ 45,693.92 |
| 201709 | STELARA | 1 | 1 | 56 | 1 | $ 18,291.09 |
| 201710 | STELARA | 2 | 2 | 140 | 2 | $ 36,582.18 |
| 201711 | STELARA | 1 | 1 | 90 | 0.5 | $ 9,220.54 |
| 201712 | STELARA | 1 | 1 | 56 | 1 | $ 18,384.27 |
| 201701 | TALTZ | 1 | 2 | 29 | 4 | $ 8,988.17 |
| 201702 | TALTZ | 1 | 1 | 28 | 2 | $ 8,948.17 |
| 201706 | TALTZ | 1 | 1 | 1 | 2 | $ 40.00 |
| 201707 | TALTZ | 2 | 2 | 56 | 6 | $ 28,684.44 |
| 201708 | TALTZ | 2 | 2 | 56 | 4 | $ 19,129.74 |
| 201709 | TALTZ | 1 | 1 | 28 | 2 | $ 9,564.87 |
| 201710 | TALTZ | 2 | 2 | 56 | 3 | $ 14,352.39 |
| 201711 | TALTZ | 1 | 1 | 28 | 1 | $ 4,787.52 |
| 201712 | TALTZ | 1 | 1 | 28 | 1 | $ 4,787.52 |
| 201707 | TREMFYA | 1 | 1 | 1 | 1 | $ 20.00 |
| 201708 | TREMFYA | 1 | 2 | 57 | 2 | $ 9,714.17 |
| 201710 | TREMFYA | 1 | 2 | 57 | 2 | $ 9,714.17 |
| 201712 | TREMFYA | 1 | 2 | 57 | 2 | $ 9,714.17 |
| 201701 | XELJANZ | 5 | 5 | 150 | 300 | $ 18,495.00 |
| 201702 | XELJANZ | 4 | 4 | 120 | 240 | $ 14,753.11 |
| 201703 | XELJANZ | 4 | 4 | 120 | 240 | $ 14,624.44 |
| 201704 | XELJANZ | 6 | 6 | 180 | 360 | $ 21,936.66 |
| 201705 | XELJANZ | 6 | 7 | 210 | 360 | $ 19,293.37 |
| 201706 | XELJANZ | 4 | 4 | 120 | 240 | $ 14,624.44 |
| 201707 | XELJANZ | 5 | 5 | 150 | 300 | $ 18,280.55 |

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201708 | XELJANZ | 4 | 4 | 120 | 240 | $ 14,624.44 |
| 201709 | XELJANZ | 3 | 3 | 90 | 180 | $ 10,968.33 |
| 201710 | XELJANZ | 3 | 3 | 90 | 180 | $ 11,002.94 |
| 201711 | XELJANZ | 2 | 3 | 90 | 180 | $ 11,072.16 |
| 201712 | XELJANZ | 3 | 3 | 90 | 180 | $ 11,072.16 |
| 201701 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 3,652.50 |
| 201703 | XELJANZ XR | 1 | 1 | 30 | 30 | $ 3,686.61 |
| 201704 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 3,690.31 |
| 201705 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 3,653.68 |
| 201706 | XELJANZ XR | 4 | 5 | 150 | 150 | $ 14,603.62 |
| 201707 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 3,653.68 |
| 201708 | XELJANZ XR | 4 | 5 | 150 | 150 | $ 14,684.50 |
| 201709 | XELJANZ XR | 5 | 5 | 150 | 150 | $ 14,673.41 |
| 201710 | XELJANZ XR | 3 | 3 | 90 | 90 | $ 10,977.33 |
| 201711 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 3,662.81 |
| 201712 | XELJANZ XR | 2 | 2 | 60 | 60 | $ 7,318.22 |


Sum of Count of Claims
Top 5 Immunomodulator Utilization
70
60
50
40
30
20
10
0
Cound of Claims
201701
201702
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
Year Month Filled
Drug Name
HUMIRA PEN
ENBREL SURECLICK
RITUXAN
HUMIRA
REMICADE
Year Month Filled

Health Plan of Nevada

# Kevzara Utilization

October 1, 2016 - September 30, 2017

| Year/Month Filled/Paid | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 2017/06 | KEVZARA INJ 200/1.14 | 1 | 1 | 28 | 2.28 | $ 1,657.89 |
| 2017/07 | KEVZARA INJ 200/1.14 | 1 | 1 | 28 | 2.28 | $ 3,097.45 |
| 2017/08 | KEVZARA INJ 200/1.14 | 1 | 1 | 28 | 2.28 | $ 3,097.45 |
| 2017/09 | KEVZARA INJ 200/1.14 | 1 | 1 | 28 | 2.28 | $ 3,150.00 |

L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators
Last Reviewed by the DUR Board: November 5, 2015

| | | |
|---|---|---|
| Actemra® (tocilizumab) | Ilaris ® (canakinumab) | Xeljanz® (tofacitinib) |
| Amevive® (alefacept) | Kineret® (ankinra) | |
| Arcalyst ® (rilonacept) | Orencia® (abatacept) | |
| Cimzia® (certolizumab pegol) | Remicade® (infliximab) | |
| Consentyx® (secukinumab) | Siliq ® (brodalumab) | |
| Enbrel® (etanercept) | Simponi® (golimumab) | |
| Entyvio® (vedolizumab) | Simponi® ARIA™ (golimumab) | |
| Humira® (adalimumab) | Stelara® (ustekinumab) | |

Immunomodulator Drugs are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the 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. For all recipients:

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

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

3. The approval will not be given for the use of more than one biologic at a time (combination therapy); and

4. Each request meets the appropriate diagnosis-specific criteria (b-j).

b. Rheumatoid Arthritis (RA):

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

2. The recipient is 18 years of age or older; and

3. The recipient has had a rheumatology consultation, including the date of the visit; and one of the following:

a. The recipient has had RA for ≤ six months (early RA) and has high disease activity; and an inadequate or adverse reaction to a disease modifying antirheumatic drug (DMARD) (methotrexate,

hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or

b. The recipient has had RA for ≥ six months (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

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

c. Psoriatic Arthritis:

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

2. The recipient is 18 years of age or older; and

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

4. 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).

d. Ankylosing Spondylitis:

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

2. The recipient is 18 years or older; and

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

4. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalzine, leflunomide, minocycline).

e. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis:

1. The recipient has a diagnosis of moderately or severely active juvenile RA or juvenile idiopathic arthritis; and

2. The recipient is at an appropriate age, based on the requested agent, and:

a. Abatacept: Six years of age or older.

b. Adalimumab, canakinumab, etanercept, tocilizumab: Two years of age or older.

3. And 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.

f. Plaque Psoriasis:

1. The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis; and

2. The recipient is 18 years of age of older; and

3. The agent is prescribed by a dermatologist; and

4. The recipient has failed to adequately respond to a topical agent; and

5. The recipient has failed to adequately respond to at least one oral treatment.

g. Crohn's Disease:

1. The recipient has a diagnosis of moderate to severe Crohn's Disease; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Adalimumab, infliximab: Six years of age or older.

b. All others: 18 years of age or older.

3. And the recipient has failed to adequately respond to conventional therapy (e.g. sulfasalzine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide); or

4. The recipient has fistulizing Crohn's Disease.

h. Ulcerative Colitis:

1. The recipient has a diagnosis of moderate to severe ulcerative colitis; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Infiximab: Six years of age or older.

b. All others: 18 years of age or older.

3. And 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.

i. Cryopyrin-Associated Periodic Syndromes (CAPS): Familial Cold Autoinflamatory Syndromes (FCAS) or Muckle-Wells Syndrome (MWS):

1. The recipient has a diagnosis of FCAS or MWS; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Canakinumab: Four years of age or older.

b. Rilonacept: 12 years of age or older.

j. Cryopyrin-Associated Periodic Syndromes (CAPS): Neonatal-Onset Multisystem Inflammatory Disease (NOMID):

1. The recipient has a diagnosis of NOMID.

2. 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.

## INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (Choy et al, 2001). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved five originator TNF inhibitors: CIMZIA® (certolizumab), ENBREL® (etanercept), HUMIRA® (adalimumab), REMICADE® (infliximab), and SIMPONI®/SIMPONI® ARIA™ (golimumab), as well as five biosimilar TNF inhibitors: AMJEVITA (adalimumab-atto), ERELZI (etanercept-szzs), INFLECTRA (infliximab-dyyb), RENFLEXIS (infliximab-abda), and CYLTEZO (adalimumab-adbm). Other agents targeting different cells and cytokines are also FDA approved for RA treatment. These include ORENCIA® (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; RITUXAN® (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; ACTEMRA® (tocilizumab) and KEVZARA® (sarilumab), which have activity directed against the IL-6 receptor; and KINERET® (anakinra), which targets the IL-1 receptor. An oral agent on the market, XELJANZ® and XELJANZ® XR (tofacitinib), targets Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include ILARIS® (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and ENTYVIO™ (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. OTEZLA® (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and STELARA (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; STELARA is additionally indicated for the treatment of CD. COSENTYX™ (secukinumab) and TALTZ® (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO; COSENTYX is additionally indicated to treat PsA and AS. A related agent, SILIQ™ (brodalumab), is an IL-17 receptor antagonist, and TREMFYA (guselkumab), an IL-23 antagonist, are indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - ILARIS for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - KINERET for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
    - ACTEMRA for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
- RITUXAN is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). These indications will not be discussed in this review.
- TYSABRI® (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (TYSABRI prescribing information, 2017). ARCALYST (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (ARCALYST prescribing information, 2016).
- Although FDA approved, the launch plans for AMJEVITA (adalimumab-atto), ERELZI (etanercept-szzs), and CYLTEZO (adalimumab-adbm) are pending and may be delayed; thus, information on AMJEVITA, ERELZI, and CYLTEZO is not currently included in this review.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

**Table 1. Medications Included Within Class Review**

| Drug | Manufacturer | FDA Approval Date | Biosimilar or Generic Availability | Type of Agent |
|---|---|---|---|---|
| ACTEMRA (tocilizumab) | Genentech | 01/08/2010 | - | Human monoclonal antibody targeting the IL-6 receptor |
| CIMZIA (certolizumab) | UCB | 04/22/2008 | - | TNFα inhibitor |
| COSENTYX (secukinumab) | Novartis | 01/21/2015 | - | Human monoclonal antibody to IL-17A |
| ENBREL (etanercept) | Amgen | 11/02/1998 | -* | sTNFR fusion protein, TNFα inhibitor |
| ENTYVIO (vedolizumab) | Takeda Pharmaceuticals America, Inc. | 05/20/2014 | - | Human monoclonal antibody binds to the α4β7 integrin |
| HUMIRA (adalimumab) | Abbott | 12/31/2002 | -* | TNFα inhibitor |
| ILARIS (canakinumab) | Novartis | 06/17/2009 | - | Human monoclonal antibody that binds to IL-1ß |
| INFLECTRA (infliximab-dyyb) | Celltrion/ Hospira/Pfizer | 04/05/2016 | N/A† | TNFα inhibitor |
| KEVZARA (sarilumab) | Sanofi Genzyme Regeneron | 05/22/2017 | - | Human monoclonal antibody targeting IL-6 receptor |
| KINERET (anakinra) | Swedish Orphan Biovitrum | 11/14/2001 | - | IL-1 receptor antagonist |
| ORENCIA (abatacept) | Bristol Myers Squibb | 12/23/2005 | - | sCTLA-4-Ig recombinant fusion protein |
| OTEZLA (apremilast) | Celgene Corporation | 03/21/2014 | - | Small-molecule phosphodiesterase 4 inhibitor |
| REMICADE (infliximab) | Janssen Biotech | 8/24/1998 | -† | TNFα inhibitor |
| RENFLEXIS (infliximab-abda) | Merck | 04/21/2017 | N/A† | TNFα inhibitor |
| RITUXAN (rituximab) | Genentech | 11/26/1997 | - | Anti-CD20 monoclonal antibody |
| SILIQ (brodalumab) | Valeant | 02/15/2017 | - | Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA) |
| SIMPONI/ SIMPONI ARIA (golimumab) | Janssen Biotech | 04/24/2009 and 07/18/2013 | - | TNFα inhibitor |
| STELARA (ustekinumab) | Janssen Biotech | 09/25/2009 | - | Human monoclonal antibody targeting the IL-12 and IL-23 cytokines |
| TALTZ (ixekizumab) | Eli Lilly | 03/22/2016 | - | Human monoclonal antibody to IL-17A |
| TREMFYA (guselkumab) | Janssen Biotech | 07/13/2017 | - | Human monoclonal antibody to IL-23 cytokine |
| XELJANZ / XELJANZ XR (tofacitinib) | Pfizer | 11/06/2012 and 02/23/2016 | - | Small molecule Janus kinase (JAK) inhibitor |

*ERELZI (etanercept-szzs), AMJEVITA (adalimumab-atto), and CYLTEZO (adalimumab-adbm) have been FDA approved as biosimilars to ENBREL (etanercept) and HUMIRA (adalimumab), respectively. The specific launch dates for these products are pending and may be delayed. Further information on ERELZI, AMJEVITA, and CYLTEZO will be included in this review closer to the time of launch.

†INFLECTRA (infliximab-dyyb) and RENFLEXIS (infliximab-abda) have been FDA approved as biosimilar agents to REMICADE (infliximab). They are not interchangeable biologics.

(Drugs@FDA, 2017; Prescribing information: ACTEMRA, 2017; CIMZIA, 2017; COSENTYX, 2016; ENBREL, 2017; ENTYVIO, 2014; HUMIRA, 2017; ILARIS, 2016; INFLECTRA, 2016; KEVZARA, 2017; KINERET, 2016; ORENCIA, 2017; OTEZLA, 2017; REMICADE, 2015; RENFLEXIS, 2017; RITUXAN, 2014; SILIQ, 2017; SIMPONI, 2017; SIMPONI ARIA, 2017; STELARA, 2016; TALTZ, 2017; TREMFYA, 2017; XELJANZ/XELJANZ XR, 2017)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications** (see footnotes for less common indications: CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPS)

| Drug | Rheumatoid Arthritis (RA) | Crohn's Disease (CD) | Systemic Juvenile Idiopathic Arthritis (SJIA) | Polyarticular Juvenile Idiopathic Arthritis (PJIA) | Plaque Psoriasis (PsO) | Psoriatic Arthritis (PsA) | Ankylosing Spondylitis (AS) | Ulcerative Colitis (UC) | Hidradenitis Suppurativa (HS) | Uveitis (UV) |
|---|---|---|---|---|---|---|---|---|---|---|
| ACTEMRA[ɣ] (tocilizumab) | ✔ * | | ✔ ** | ✔ ** | | | | | | |
| CIMZIA (certolizumab) | ✔ | ✔ | | | | ✔ | ✔ | | | |
| COSENTYX (secukinumab) | | | | | ✔ ‡ | ✔ | ✔ | | | |
| ENBREL (etanercept) | ✔ † | | | ✔ ** | ✔ ‡ | ✔ † | ✔ | | | |
| ENTYVIO (vedolizumab) | | ✔ | | | | | | ✔ | | |
| HUMIRA (adalimumab) | ✔ ‡‡ | ✔ ⌐ | | ✔ ∫ | ✔ ‡ | ✔ ∫∫ | ✔ | ✔ | ✔ | ✔ ▼ |
| ILARIS" (canakinumab) | | | ✔ ** | | | | | | | |

| Drug | Rheumatoid Arthritis (RA) | Crohn's Disease (CD) | Systemic Juvenile Idiopathic Arthritis (SJIA) | Polyarticular Juvenile Idiopathic Arthritis (PJIA) | Plaque Psoriasis (PsO) | Psoriatic Arthritis (PsA) | Ankylosing Spondylitis (AS) | Ulcerative Colitis (UC) | Hidradenitis Suppurativa (HS) | Uveitis (UV) |
|---|---|---|---|---|---|---|---|---|---|---|
| INFLECTRA (infliximab-dyyb) | ✔ ⊥ | ✔ ⌐⌐ | | | ✔ ‡‡‡ | ✔ | ✔ | ✔ ⊥⊥ | | |
| KEVZARA (sarilumab) | ✔ * | | | | | | | | | |
| KINERET▼▼ (anakinra) | ✔ ∞ | | | | | | | | | |
| ORENCIA (abatacept) | ✔ ∞∞ | | | ✔ ⌂ | | ✔ | | | | |
| OTEZLA (apremilast) | | | | | ✔ ‡ | ✔ | | | | |
| REMICADE (infliximab) | ✔ ⊥ | ✔ ⌐⌐ | | | ✔ ‡‡‡ | ✔ | ✔ | ✔ ⊥⊥ | | |
| RENFLEXIS (infliximab-abda) | ✔ ⊥ | ✔ ⌐⌐ | | | ✔ ‡‡‡ | ✔ | ✔ | ✔ ⊥⊥ | | |

| Drug | Rheumatoid Arthritis (RA) | Crohn's Disease (CD) | Systemic Juvenile Idiopathic Arthritis (SJIA) | Polyarticular Juvenile Idiopathic Arthritis (PJIA) | Plaque Psoriasis (PsO) | Psoriatic Arthritis (PsA) | Ankylosing Spondylitis (AS) | Ulcerative Colitis (UC) | Hidradenitis Suppurativa (HS) | Uveitis (UV) |
|---|---|---|---|---|---|---|---|---|---|---|
| RITUXAN‘‘‘ (rituximab) | ✔ǂ | | | | | | | | | |
| SILIQ (brodalumab) | | | | | ✔ǂǂ | | | | | |
| SIMPONI (golimumab) | ✔┤ | | | | | ✔┤┤ | ✔ | ✔˜ | | |
| SIMPONI ARIA (golimumab) | ✔┤ | | | | | | | | | |
| STELARA (ustekinumab) | | ✔⌐⌐⌐ | | | ✔‡ | ✔ | | | | |
| TALTZ (ixekizumab) | | | | | ✔‡ | | | | | |
| TREMFYA (guselkumab) | | | | | ✔‡ | | | | | |

| Drug | Rheumatoid Arthritis (RA) | Crohn's Disease (CD) | Systemic Juvenile Idiopathic Arthritis (SJIA) | Polyarticular Juvenile Idiopathic Arthritis (PJIA) | Plaque Psoriasis (PsO) | Psoriatic Arthritis (PsA) | Ankylosing Spondylitis (AS) | Ulcerative Colitis (UC) | Hidradenitis Suppurativa (HS) | Uveitis (UV) |
|---|---|---|---|---|---|---|---|---|---|---|
| XELJANZ / XELJANZ XR (tofacitinib) | ✓╪ | | | | | | | | | |

ϒACTEMRA is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.

*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [KEVZARA]) to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

**Patients 2 years and older.

†In combination with methotrexate (MTX) or used alone.

‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of ENBREL, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy.

‡‡Indicated for 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 RA. Can be used alone or in combination with MTX or other DMARDs.

‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.

∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.

▼Treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

▼▼KINERET is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).

"ILARIS also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.

∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.

∞∞Indicated for 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 RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.

⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.

⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.

⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with one or more TNF blockers

┴In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.

┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (REMICADE only). The biosimilars INFLECTRA and RENFLEXIS did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).

'"RITUXAN also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA).

╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to one or more TNF antagonist therapies.

Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for:  inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

## CLINICAL EFFICACY SUMMARY

**Rheumatoid arthritis (RA)**

- The approval of the subcutaneous (SQ) formulation of ORENCIA (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (Genovese et al, 2011).
- ORENCIA (abatacept), REMICADE (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (N=431). Enrolled patients had had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after six months of treatment, some differences in favor of abatacept were evident after one year of treatment. After one year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (Schiff et al, 2008).
- Treatment with ORENCIA (abatacept) was directly compared to treatment with HUMIRA (adalimumab), both added to MTX, in a multicenter, investigator-blind, randomized controlled trial (N=646) of RA patients with inadequate response to MTX. After two years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the two groups after two years of treatment. Rates of AEs were similar between treatment groups (Schiff et al, 2014).
- The RAPID-1 and RAPID-2 studies compared CIMZIA (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (Keystone et al, 2008; Smolen et al, 2009a). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks zero, two, and four then 200 or 400 mg every two weeks attained greater ACR 20, ACR 50 and ACR 70 responses over patients on placebo and MTX, respectively, after 24 weeks (P≤0.01). The response rates were sustained with active treatment over 52 weeks (Keystone et al, 2008). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (Keystone et al, 2008; Smolen et al, 2009a). A trial evaluated CIMZIA (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least one prior DMARD. 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 (Fleischmann et al, 2009).
- More CIMZIA (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, P≤0.05) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least six months (Smolen et al, 2015a).
- A randomized, double-blind, placebo-controlled trial (N=316) conducted in Japan compared CIMZIA (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (Atsumi et al, 2016). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; P<0.001). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; p<0.001) (Atsumi et al, 2017).
- The FDA approval of SIMPONI (golimumab) for RA was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients greater than or equal to18 years of age 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 vs patients treated with MTX alone (Emery et al, 2009; Keystone et al, 2009; Smolen et al, 2009b). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI)

(Keystone et al, 2009; Smolen et al, 2009b). Response with golimumab + MTX was sustained for up to five years (Keystone et al, 2013a; Smolen et al, 2015b).

- SIMPONI ARIA (golimumab) was studied in patients with RA. In one trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; P<0.001) (Kremer et al, 2010). In the GO-FURTHER trial (N=592), golimumab 2 mg/kg IV or placebo was given at weeks zero, four and then every eight weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [P<0.001]) (Weinblatt et al, 2013). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (Bingham et al, 2015). In the GO-MORE trial, investigators treated patients with golimumab SQ for six months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ+IV group and the SQ golimumab group (Combe et al, 2014).
- The efficacy and safety of ACTEMRA (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients ages 18 years and older with active RA. Patients were diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was given 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 tumor necrosis factor (TNF) antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (Emery et al, 2008; Genovese et al, 2008; Jones et al, 2010; Kremer et al, 2011; Smolen et al, 2008).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA 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 when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al, 2010).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had three times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at six months as compared to MTX (33% vs 4%), and these rates continued to increase over time to one year (47% vs 8%) (Kremer et al, 2011). These benefits were maintained or improved at two years with no increased side effects (Fleishmann et al, 2013).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV 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 less than 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (P<0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (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) (Smolen et al, 2008).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active RA. 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 than 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) (Genovese et al, 2008).

- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists was randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA 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 HUMIRA (adalimumab) and REMICADE (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al, 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (Gabay et al, 2013).

- More recently, results of a randomized, double-blind trial evaluating ACTEMRA (tocilizumab) in early RA were published (Bijlsma et al, 2016). Patients (N=317) had been diagnosed with RA within one year, were DMARD-naïve, and had a DAS28 score of ≥2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 <2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P<0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (P=0.06 for tocilizumab plus MTX vs MTX; P=0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the subcutaneous formulation of ACTEMRA (tocilizumab) was based on one multicenter, double-blind, randomized, controlled trial in patients (N=1,262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every four weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (Burmester et al, 2014a). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (Burmester et al, 2016). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ ACTEMRA administered every other week (Kivitz et al, 2014).
- A phase 3 trial (MONARCH) evaluating the efficacy of KEVZARA (sarilumab) monotherapy vs HUMIRA (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p<0.0001) (Burmester et al, 2017). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (Genovese et al, 2015; Fleischmann et al, 2016). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (Bae et al, 2017).
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the XELJANZ (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant

decreases in fatigue and pain (Fleishmann et al, 2012). In another Phase 3 study, XELJANZ (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to HUMIRA (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (van Vollenhoven et al, 2012). The ORAL Scan trial showed the ACR 20 response rates at month six for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo (P<0.0001 for both comparisons) (van der Heijde et al, 2013). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; P<0.001) (Lee et al, 2014). No radiographic progression was defined as a change from baseline in the modified total Sharp score of <0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to one or more TNF inhibitors were randomized to XELJANZ (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (Burmester et al, 2013a; Strand et al, 2015a). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; P=0.0024) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; P<0.0001) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; P<0.0001) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; P<0.0001) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- INFLECTRA (infliximab-dyyb) was evaluated and compared to REMICADE (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the REMICADE and INFLECTRA groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the two products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (N=302) through 102 weeks, all patients received INFLECTRA. Response rates were maintained, with no differences between the INFLECTRA maintenance group and the group who switched from REMICADE to INFLECTRA.
- RENFLEXIS (infliximab-abda) was evaluated and compared to REMICADE (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (Choe et al, 2017). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the RENFLEXIS and REMICADE groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the two products.
    - Secondary endpoints were also very similar between the 2 groups.
    - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking REMICADE were re-randomized to continue REMICADE or switch to RENFLEXIS; patients initially taking RENFLEXIS continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (RENFLEXIS FDA clinical review, 2017).
- Two studies, one double-blind and one open-label, evaluated RITUXAN (rituximab) in patients who had failed treatment with a TNF blocker (Cohen et al, 2006, Haraoui et al, 2011). All patients continued to receive MTX. Both studies showed greater than 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (Lopez-Olivo et al, 2015) examined RITUXAN (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.
- In the open-label ORBIT study (N=295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either RITUXAN (rituximab) (n=144) or a TNF inhibitor (physician/patient choice of ENBREL [etanercept] or HUMIRA [adalimumab]; n=151) (Porter et al, 2016). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.

  - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (Gottenberg et al, 2016). Patients (N=300) were randomized to receive a second TNF inhibitor (n=150) or a non-TNF-targeted biologic (n=150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included HUMIRA (adalimumab), ENBREL (etanercept), CIMZIA (certolizumab), and REMICADE (infliximab), and the non-TNF biologics included ACTEMRA (tocilizumab), RITUXAN (rituximab), and ORENCIA (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of >1.2 points resulting in a score of ≤3.2.
  - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (P=0.003 or P=0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (P=0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (Manders et al, 2015) evaluated the use of ORENCIA (abatacept) (n=43), RITUXAN (rituximab) (n=46), or a different TNF inhibitor (n=50) in patients (N=139) with active RA despite previous TNF inhibitor treatment. ACTEMRA (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined ORENCIA (abatacept) for the treatment of RA. 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 (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (Maxwell et al, 2009).
- The safety and efficacy of HUMIRA (adalimumab) for the treatment of RA were 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 (Navarro-Sarabia et al, 2005). In another study, patients received adalimumab 20 mg or 40 mg every other week for one year, and then could receive 40 mg every other week for an additional nine years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (Keystone et al, 2013b).
- A Phase 3, open-label study evaluated the long-term efficacy of HUMIRA (adalimumab) for RA. Patients receiving adalimumab in one of four early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (Furst et al, 2015).
- A Cochrane review was performed to compare KINERET (anakinra) to placebo in adult patients with RA. Significant improvements 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 AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (Mertens et al, 2009).

- In another Cochrane review, ENBREL (etanercept) was compared to MTX or placebo in adult patients with RA and found that at six months 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (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, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (Blumenauer et al, 2003). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (O'Dell et al, 2013).
- A more recent Cochrane review (Singh et al, 2016a) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included XELJANZ (tofacitinib) and 9 biologics (ORENCIA [abatacept], HUMIRA [adalimumab], KINERET [anakinra], CIMZIA [certolizumab], ENBREL [etanercept], SIMPONI [golimumab], REMICADE [infliximab], RITUXAN [rituximab], and ACTEMRA [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS <1.6 or DAS28 <2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
    - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or XELJANZ (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (Singh et al, 2016b). A total of 41 randomized trials (N=14,049) provided data for this review. Key results are as follows:
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
    - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or XELJANZ (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (Singh et al, 2017[a]). The review included 12 randomized trials (N=3,364). Key results are as follows:
    - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
    - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
    - There were no published data for tofacitinib monotherapy vs placebo.
    - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for XELJANZ (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (ORENCIA [abatacept], HUMIRA [adalimumab], KINERET [anakinra], CIMZIA [certolizumab], ENBREL [etanercept], SIMPONI [golimumab], REMICADE [infliximab], ACTEMRA [tocilizumab]) at 24

weeks (Bergrath et al, 2017). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).

- Another recent Cochrane review (Hazlewood et al, 2016) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or XELJANZ (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effects was small.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (Singh et al, 2017[b]). Agents included in the review were HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab), REMICADE (infliximab), ORENCIA (abatacept), and RITUXAN (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of REMICADE (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) (Wiens et al, 2009).
- Another meta-analysis of randomized controlled trials included HUMIRA (adalimumab), KINERET (anakinra), ENBREL (etanercept), and REMICADE (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, 1.7 (95% CI, 0.9 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) and with etanercept 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 3.5; P<0.05) (Nixon et al, 2007).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (Donahue et al, 2012). They concluded that there is limited head to head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of two biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of six trials (N=1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (Galvao et al, 2016). The biologics in the identified trials were TNF inhibitors, most commonly ENBREL (etanercept) or HUMIRA (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

**Ankylosing spondylitis (AS)**

- The FDA-approval of HUMIRA (adalimumab) for the treatment of AS was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; P<0.001). A greater than 50% improvement 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 (P<0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (P<0.001) (van der Heijde et al, 2006).

- In two double-blind, randomized, placebo-controlled trials, the efficacy of ENBREL (etanercept) was evaluated in patients with AS (Calin et al, 2004; Gorman et al, 2002). Etanercept had a significantly greater response to treatment compared to placebo (P<0.001)(Gorman et al, 2002). More patients achieved an ASAS 20 response compared to placebo (P<0.001)(Calin et al, 2004). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 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 (Davis et al, 2008). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 (P<0.0001). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (P<0.0001 for both) (Braun et al, 2011).
- The FDA-approval of SIMPONI (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 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 (Inman et al, 2008). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to five years in an open-label extension trial (Deodhar et al, 2015). Safety profile through five years was consistent with other TNF inhibitors.
- The efficacy of REMICADE (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (P<0.0001)(Braun et al, 2002), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group (P<0.001)(van der Heijde et al, 2005).
- INFLECTRA (infliximab-dyyb) was evaluated alongside REMICADE (infliximab; European Union formulation) for the treatment of AS in PLANETAS (N=250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between INFLECTRA and REMICADE. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the REMICADE and INFLECTRA groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (N=174) through 102 weeks, all patients received INFLECTRA. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of CIMZIA (certolizumab) for the treatment of AS was established in 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 (Landewe et at, 2014). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (Sieper et al, 2015a). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (Sieper et al, 2015b).
- The efficacy and safety of COSENTYX (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (Baeten et al, 2015). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, P<0.001 for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group (P<0.001 for secukinumab 150 mg vs placebo; P=0.10 for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20

response rates were 71.5% with both doses at week 104 (Braun et al, 2017; Marzo-Ortega et al, 2017). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (Baraliakos et al, 2017).

- In two systematic reviews of TNF blockers for the treatment of AS, patients taking SIMPONI (golimumab), ENBREL (etanercept), REMICADE (infliximab), and HUMIRA (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (Machado et al, 2013). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (Maxwell et al, 2015). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, COSENTYX (secukinumab), and ACTEMRA (tocilizumab; not FDA approved for AS) (Chen et al, 2016). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

**Crohn's disease (CD)**

- In a trial evaluating REMICADE (infliximab) for induction of remission, significantly more patients achieved remission at four weeks with infliximab compared to placebo (P<0.005)(Targan et al, 1997). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo (P=0.002 and P=0.02, respectively)(Present et al, 1999). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (Hyams et al, 2007).
- The safety and efficacy of ENTYVIO (vedolizumab) was demonstrated in two trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In one trial, a higher percentage of ENTYVIO-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, ENTYVIO did not achieve a statistically significant clinical response or clinical remission over placebo at week six (Sandborn et al, 2013; Sands et al, 2014).
- A meta-analysis evaluating CIMZIA (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; P=0.004) and remission (RR, 1.95; P<0.0001) over placebo. However, risk of infection was higher with certolizumab use (Shao et al, 2009).
- Additionally, HUMIRA (adalimumab), CIMZIA (certolizumab) and REMICADE (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; P<0.00001; RR, 1.74; P<0.0001 and RR, 1.66; P=0.0046, respectively) and maintain clinical remission (RR, 1.68; P=0.000072 with certolizumab and RR, 2.5; P=0.000019 with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (Behm et al, 2008). Other systematic reviews have further demonstrated the efficacy of these agents in CD (Singh et al, 2014).
- In a systematic review of patients with CD who had failed a trial with REMICADE (infliximab), the administration of HUMIRA (adalimumab) was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in zero to 19% of patients in up to four years of treatment (Ma et al, 2009).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or ENTYVIO (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (Chandar et al, 2015). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; $I^2$=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the two active treatments (P=0.95). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab (P=0.007). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.
- The use of STELARA (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (Feagan et al, 2016). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (N=741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to one or more TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of <150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P=0.002 for 130 mg dose vs placebo; P=0.003 for weight-based dose vs placebo).

Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI <150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
  - UNITI-2 (N=628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (P<0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
  - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SC every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (P=0.005 for every 8 week regimen vs placebo; P=0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

**Hidradenitis suppurativa (HS)**

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated HUMIRA (adalimumab) for the treatment of HS (Kimball et al, 2016). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of two treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week zero, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (P=0.003) and 58.9% vs 27.6% in PIONEER II (P<0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

**Juvenile idiopathic arthritis (JIA)**

- In a trial of pediatric patients (six to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with ORENCIA (abatacept) (P=0.0003). The time to flare was significantly different favoring abatacept (P=0.0002) (Ruperto et al, 2008).
- HUMIRA (adalimumab) was studied in a group of patients (four to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to 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 method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% 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 (Lovell et al, 2008).
- A double-blind, multicenter, randomized controlled trial compared HUMIRA (adalimumab) and placebo in 46 children ages six to 18 years with enthesitis-related arthritis (Burgos-Vargas et al, 2015). Patients were TNF inhibitor naïve. At

week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, P=0.039). A total of seven patients (three placebo; four adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; P=0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.

- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, ENBREL (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; P=0.003) (Lovell et al, 2000). Ninety-four percent of patients who remained in an open-label four year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious AEs related to etanercept therapy after four years (Lovell et al, 2006).
- The approval of ACTEMRA (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active SJIA 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)(De Benedetti et al, 2012). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (Brunner et al, 2015). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; P<0.0024).
- In two trials in patients with SJIA, ILARIS (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (Ruperto et al, 2012).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; one each for KINERET (anakinra), ILARIS (canakinumab), and ACTEMRA (tocilizumab), and 2 for rilonacept (not FDA approved for JIA and not included in this review) (Tarp et al, 2016). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

**Plaque psoriasis (PsO)**

- In a randomized, double-blind, double-dummy trial, HUMIRA (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (P<0.001) and placebo (P<0.001) groups, respectively (Saurat et al, 2008).
- More than 2,200 patients were enrolled in two published, pivotal, phase III trials that served as the primary basis for the FDA approval of STELARA (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter (Leonardi et al, 2008; Papp et al, 2008; Langley et al, 2015). In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (at least PASI 75 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) (Leonardi et al, 2008). 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 compared 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 such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (Papp et al, 2008). A total of 70% (849 of 1,212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (Langley et al, 2015).
- In a study comparing ENBREL (etanercept) and STELARA (ustekinumab), a greater proportion of PsO 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) (Griffiths et al, 2010).

- Approval of OTEZLA (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; P<0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; P<0.0001) at 16 weeks (Papp et al, 2015; Paul et al, 2015a).
    - Additional analyses of the ESTEEM trials have been published. In one (Thaçi et al, 2016), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al, 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- COSENTYX (secukinumab) was evaluated in two large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (N=738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
    - In FIXTURE (N=1,306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, ENBREL (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (Langley et al, 2014).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated COSENTYX (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (N=177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (Blauvelt et al, 2015).
    - In JUNCTURE (N=182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (Paul et al, 2015b).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of COSENTYX (secukinumab) (Blauvelt et al, 2015; Langley et al, 2014; Paul et al, 2015b).
- In the CLEAR study, COSENTYX (secukinumab) 300 mg SQ every four weeks and STELARA (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; P<0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- A meta-analysis of seven Phase 3 clinical trials demonstrated the efficacy of COSENTYX (secukinumab) vs placebo and vs ENBREL (etanercept) in patients with PsO (Ryoo et al, 2016). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the one-year trials.

- The use of TALTZ (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (N=1,296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (Gordon et al, 2016; Taltz product dossier, 2016). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively (P<0.001 for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively (P<0.001 for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (N=1,224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (Griffiths et al, 2015). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (N=1,346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (Griffiths et al, 2015). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (P<0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (Gordon et al, 2016). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-S study (N = 676) was a head-to-head study that compared TALTZ (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to STELARA (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (Reich et al, 2017[b]). The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted $p < 0.05$).
- The use of SILIQ (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (N=661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks zero, one, and two, followed by every two weeks to week 12 (Papp et al, 2016). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥2 and those initially receiving placebo received brodalumab 210 mg every two weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints

were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (P<0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (N=1,831) and AMAGINE-3 (N=1,881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, STELARA (ustekinumab), and placebo (Lebwohl et al, 2015). Brodalumab was given at weeks zero, one, and two, followed by every two weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every two weeks or 140 mg every two, four, or eight weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every two weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.08 for brodalumab 140 mg vs ustekinumab).
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (P<0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (P<0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; P=0.007 for brodalumab 140 mg vs ustekinumab).
  - In both studies, the two brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every two weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of TREMFYA (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, and NAVIGATE trials. All were phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or HUMIRA (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (N=837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 (p<0.001), and a higher percentage of patients achieved

PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; p<0.001) (Blauvelt et al, 2017). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs. 61.7%), and week 48 (80.5% vs 55.4%; p<0.001). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; p<0.001).
        - In VOYAGE 2 (N=992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) (p<0.001 for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) (p<0.001). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
    - In NAVIGATE (N=871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (Langley et al, 2017). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; p<0.001). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; p=0.001); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group (p≤0.001).
- For most immunomodulators that are FDA approved for the treatment of PsO, the indication is limited to adults. In 2016, ENBREL (etanercept) received FDA approval for treatment of PsO in pediatric patients aged four years and older. Limited information from published trials is also available on the use of STELARA (ustekinumab) in adolescent patients (age 12 to 17 years).
    - A 48-week, double-blind, placebo-controlled trial (N=211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (Paller et al, 2008). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (P<0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including three infections) occurred in three patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (N=182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (Paller et al, 2016).
    - A 52-week, double-blind, placebo-controlled trial (N=110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (Landells et al, 2015). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (P<0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively (P<0.001 for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.
- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (Feldman, 2015). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with ENBREL (etanercept) plus MTX may be beneficial for therapy-resistant patients (Busard et al, 2014; Gottlieb et al, 2012).

- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, HUMIRA (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (P<0.00001) while ENBREL (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 REMICADE (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 (Schmitt et al, 2008).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (Nast et al, 2015a). A total of 25 randomized trials (N=11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for REMICADE (infliximab), 11.97 (95% CI, 8.83 to 16.23) for COSENTYX (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for STELARA (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for HUMIRA (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for ENBREL (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for OTEZLA (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, HUMIRA (adalimumab), COSENTYX (secukinumab), and STELARA (ustekinumab) were characterized by high efficacy and tolerability, REMICADE (infliximab) and TALTZ (ixekizumab) were characterized by high efficacy and poorer tolerability, and ENBREL (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (Jabbar-Lopez et al, 2017).

**Psoriatic arthritis (PsA)**

- In two trials, PsA patients receiving HUMIRA (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 (P=0.012) in a trial (N=100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (P<0.001) (Genovese et al, 2007; Mease et al, 2005). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; P<0.001) (Mease et al, 2005).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of ENBREL (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo (P<0.0001). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 (P=0.0154) and 13% (P<0.0001) of placebo-treated patients (Mease et al, 2000). In a second trial, the mean annualized rate of change in the mTSS with ENBREL (etanercept) was -0.03 unit, compared to one unit with placebo (P<0.0001). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients (P=0.001). Additionally, HAQ 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) (Mease et al, 2004).
- The FDA approval of SIMPONI (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA 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 (Kavanaugh et al, 2009).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year five were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every four weeks (Kavanaugh et al, 2014b).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [(≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (Kavanaugh et al, 2016).

- In another trial, more REMICADE (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (P<0.001) (Antoni et al, 2005).
- The efficacy of CIMZIA (certolizumab) in the treatment of PsA was established in one multicenter, double-blind, placebo controlled trial (N=409). Patients were randomized to receive placebo, CIMZIA 200 mg every two weeks, or CIMZIA 400 mg every four weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (Mease et al, 2014).
- The FDA-approval of STELARA (ustekinumab) for PsA was based on the results of two randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In 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 (McInnes et al, 2013). Similar results were observed in the PSUMMIT 2 trial (N=312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (P<0.001) (Ritchlin et al, 2014).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (McInnes et al, 2013). At week 100 (Kavanaugh et al, 2015a), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on two multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 (Mease et al, 2015; McInnes et al, 2015). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; P<0.0001 vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (Kavanaugh et al, 2017).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively (P<0.0001 for secukinumab 300 mg and 150 mg; P<0.05 for 75 mg vs placebo).
    - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of OTEZLA (apremilast) was demonstrated in three placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the OTEZLA groups had ≥20% improvement in symptoms, as defined by ACR response criteria (Cutolo et al, 2013; Edwards et al, 2016; Kavanaugh et al, 2014a). Clinical improvements observed at 16 weeks were sustained at 52 weeks (Edwards et al, 2016; Kavanaugh et al, 2015b).
- ORENCIA (abatacept) gained FDA approval for the treatment of PsA based on two double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (Mease et al, 2011; Mease et al, 2017). In a phase 2 dose-finding trial (N=170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (two doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (Mease et al, 2011). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p=0.006) and 30/10 mg/kg (42%; p=0.022) but not 3 mg/kg (33%). A phase 3 trial (N=424) randomized patients to abatacept 125 mg weekly or placebo (Mease et al, 2017). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p<0.001).
- A small, single-center randomized trial (N=100) compared REMICADE (infliximab), ENBREL (etanercept), and HUMIRA (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (Atteno et al, 2010). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest

improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.

- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of HUMIRA (adalimumab), ENBREL (etanercept), REMICADE (infliximab), and SIMPONI (golimumab) over 24 weeks for the treatment of PsA (Fénix et al, 2013). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of nine randomized controlled trials and six observational studies evaluated HUMIRA (adalimumab), ENBREL (etanercept), SIMPONI (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (Lemos et al, 2014). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
    - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (Ungprasert et al, 2016a). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: ENBREL [etanercept], REMICADE [infliximab], HUMIRA [adalimumab], and SIMPONI [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving CIMZIA (certolizumab), OTEZLA (apremilast), or STELARA (ustekinumab). Patients receiving COSENTYX (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
    - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (ORENCIA [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (Ungprasert et al, 2016b). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
    - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

**Ulcerative colitis (UC)**

- Two trials (ACT 1 and ACT 2) evaluated REMICADE (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week eight was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all P<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (Rutgeerts et al, 2005). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (Hyams et al, 2012).
- In the ULTRA 2 study, significantly more patients taking HUMIRA (adalimumab) 160 mg at week zero, 80 mg at week two, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (Sandborn et al, 2012). These long term results confirm the findings of ULTRA 1. This eight-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical remission (Reinisch et al, 2011). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for two of the secondary end points at week eight, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week eight. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of three randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (Zhang et al, 2016).
- SIMPONI (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks zero and two were compared to patients receiving placebo. At week six, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; P<0.0001 for both comparisons) (Sandborn et al, 2014b). In a study enrolling patients who responded in a prior study with golimumab, 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 vs 31.2%; P<0.001 and P=0.01, respectively) (Sandborn et al, 2014a).

- The safety and efficacy of ENTYVIO (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of ENTYVIO-treated patients achieved or maintained clinical response and remission over placebo at weeks six and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (Feagan et al, 2013). A systematic review and meta-analysis (N=606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (Bickston et al, 2014; Mosli et al, 2015).

**Uveitis (UV)**

- The safety and efficacy of HUMIRA (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in two randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (N=217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (Jaffe et al, 2016). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
    - VISUAL II (N=226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (Nguyen et al, 2016a). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every two weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; P=0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

**Multiple indications**

- The efficacy of infliximab-dyyb (European Union formulation) in patients (N=481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (Jørgensen et al, 2017). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

**CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPs**

- The efficacy of KINERET (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n=11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (KINERET prescribing information, 2016). A cohort study of 26 patients followed for three to five years demonstrated sustained improvement in disease activity and inflammatory markers (Sibley et al, 2012).
- The efficacy and safety of ILARIS (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (ILARIS prescribing information, 2016). Published data supports the use of canakinumab for these various CAPS phenotypes (Koné-Paut et al, 2011; Kuemmerle-Deschner et al, 2011; Lachmann et al, 2009).
    - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period. Resolution of the flare was defined as a PGA score <2 (minimal or no

disease) and CRP within normal range (or reduction ≥70% from baseline) (ILARIS prescribing information, 2016).

- The efficacy and safety of ACTEMRA (tocilizumab) has been evaluated for treatment of GCA and CRS.
  - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (Stone et al, 2017). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo ($p<0.01$).
  - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (ACTEMRA prescribing information, 2017). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

**Treatment Guidelines**

- RA:
  - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (Singh et al, 2016c).
  - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (Smolen et al, 2017).
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (ACR, 2016).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- JIA:
  - The American College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (Beukelman et al, 2011; Ringold et al, 2013).
    - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (Beukelman et al, 2011).
    - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is one of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (Ringold et al, 2013).

- UC:
    - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (Kornbluth et al, 2010). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.
- CD:
    - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. Maintenance therapy with TNF inhibitors is effective. An update to these guidelines is currently in process (Lichtenstein et al, 2009).
    - The American Gastroenterological Association (AGA) recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (Nguyen et al, 2017).
    - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (Sandborn, 2014).
    - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (Gomollón et al, 2017).
- Pregnancy in inflammatory bowel disease:
    - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (Nguyen et al, 2016b).
- PsO and PsA:
    - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (Hsu et al, 2012).
    - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011). Biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (>5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
    - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (Nast et al, 2015b). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least one synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
    - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (Gottleib et al, 2008; Menter et al, 2009b; Menter et al, 2011).

  - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate (Gossec et al, 2016; Ramiro et al, 2016).
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (Coates et al, 2016).
- AS:
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (van der Heijde et al, 2017).
  - The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (Ward et al, 2016).
- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (Levy-Clarke et al, 2014). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (Ozen et al, 2016).
  - No recent guidelines were identified for CAPS, CRS, GCA, HIDS/MKD, or TRAPS.

**SAFETY SUMMARY**

- Contraindications:
  - ACTEMRA (tocilizumab), COSENTYX (secukinumab), ENTYVIO (vedolizumab), ILARIS (canakinumab), INFLECTRA (infliximab-dyyb), KEVZARA (sarilumab), KINERET (anakinra), OTEZLA (apremilast), REMICADE (infliximab), RENFLEXIS (infliximab-abda), STELARA (ustekinumab), and TALTZ (ixekizumab) use in patients with hypersensitivity to any component of the product.
  - SILIQ in patients with Crohn's disease because SILIQ may cause worsening of disease.
  - ENBREL (etanercept) in patients with sepsis.
  - KINERET (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - REMICADE (infliximab), INFLECTRA (infliximab-dyyb), and RENFLEXIS (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:

- ACTEMRA (tocilizumab), CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), KEVZARA (sarilumab), REMICADE (infliximab), RENFLEXIS (infliximab-abda), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ / XELJANZ XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
- In addition, CIMZIA (certolizumab), ENBREL (etanercept), HUMIRA (adalimumab), INFLECTRA (infliximab-dyyb), REMICADE (infliximab), RENFLEXIS (infliximab-abda), SIMPONI / SIMPONI ARIA (golimumab), and XELJANZ (tofacitinib) all have warnings for increased risk of malignancies.
- RITUXAN (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
- SILIQ has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.

- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Increased lipid parameters and liver function tests with ACTEMRA (tocilizumab), XELJANZ / XELJANZ XR (tofacitinib) and KEVZARA (sarilumab)
  - Increased incidence of CD and UC with COSENTYX (secukinumab) and TALTZ (ixekizumab); risk of new-onset CD or exacerbation of CD with SILIQ (brodalumab)
  - Diarrhea, nausea, and vomiting with OTEZLA (apremilast)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a five-year study in RA and a 10-year study in patients with early RA (Keystone et al, 2014a; Burmester et al, 2014b). In the five-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first six months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over five years in patients with RA (Keystone et al, 2014b). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 patient-years), and upper respiratory infections (rate of 7.3 per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.
    - Abatacept has been evaluated in two long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the seven year follow-up and a 52-week double-blind study (Westhovens et al, 2014). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 patient-years), malignancies (3.2 events per100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a five-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year one and year five, respectively.
    - Data from five RCTs of ACTEMRA (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to

severe RA received at least one dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (PY). The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (Genovese et al, 2013).

- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the ENBREL (etanercept) plus DMARD group and the DMARD alone group at six months, 12 months, and two years. At three years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at six months, flu-like syndrome at six months and two years, infection at six months and two years, malignancy at 12 months and two years, pneumonia at 12 months, and serious infection at 12 months and two years between the etanercept plus DMARD group and the DMARD group (Lethaby et al, 2013).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (Strand et al, 2015b). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.

o PsO

- A total of 3,117 patients treated with at least one dose of STELARA (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least four years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with greater than or equal to five years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year five. The causes of death were considered related to cardiovascular events (n=5), malignancy (n=5), infection (n=3) and other causes (n=7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year one to year five, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (Papp et al, 2013).
- In a five-year extension study, a total of 2,510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (Kimball et al, 2015). Serious AEs were reported as a cumulative incidence of the entire five-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month six and remained stable through five years.
- In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (Crowley et al, 2017). Serious AEs (≥ 2 patients) were coronary artery disease (n=6), acute myocardial infarction (n=4), osteoarthritis (n=4), and nephrolithiasis (n=4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (Kalb et al, 2015). Patients were followed for up to eight years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age,

diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; P<0.001) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; P=0.002) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over five years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (Kavanaugh et al, 2014b). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
- Multiple indications
  - One study looked at 23,458 patients who were treated with HUMIRA (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (Burmester et al, 2013b).
  - Pooled data from five Phase 3 trials of SQ golimumab over at least three years demonstrated a safety profile consistent with other TNF inhibitors (Kay et al, 2015). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (Capogrosso Sansone et al, 2015). All but one trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - Several recent meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up one to 36 months) and seven open-label extension studies (follow-up six to 48 months) (Minozzi et al, 2016). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up two to 36 months) and six open-label extension trials (follow-up six to 48 months) (Bonovas et al, 2016). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give two immunomodulators together.
  - For XELJANZ / XELJANZ XR (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
- Risk Evaluation and Mitigation Strategy (REMS)
  - SILIQ (brodalumab) is available only through the SILIQ REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.

- Patients must sign a patient-prescriber agreement form.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| ACTEMRA (tocilizumab) | Vials:<br>80 mg/4 mL;<br>200 mg/10 mL;<br>400 mg/20 mL<br><br>Prefilled syringe:<br>162 mg/0.9 mL | **RA:** 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose=800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response. >100 kg, 162 mg administered SQ every week.<br>**PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks.<br>**SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks.<br>**GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations.<br>**CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion. | **RA:** Can give with MTX or other DMARDs.<br>**PJIA and SJIA:** Can give with MTX.<br>**GCA:** Can use alone after discontinuation of glucocorticoids.<br>**CRS:** Can give with corticosteroids.<br>May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses.<br>**RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count and low ANC. | Give as a single 60-minute intravenous infusion.<br><30 kg, use a 50 mL infusion bag.<br>≥30 kg, use a 100 mL infusion bag.<br>Before infusion, allow bag to come to room temperature.<br>Do not administer with other drugs.<br><br>Patients can self-inject with the prefilled syringe. Rotate injection sites. |
| CIMZIA (certolizumab) | Powder for reconstitution: 200 mg<br>Prefilled syringe: 200 mg/mL | **CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks.<br>**RA, PsO:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks.<br>**AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks. | Patients can self-inject with the prefilled syringe. | When a 400 mg dose is required, give as two 200 mg SQ injections in separate sites in the thigh or abdomen. |
| COSENTYX (secukinumab) | Sensoready pen:<br>150 mg/1 mL<br>Prefilled syringe: | **PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by | **PsO:** For some patients, a dose of 150 mg may be | Each 300 mg dose is given as two subcutaneous |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | 150 mg/1 mL<br>Vial: 150 mg lyophilized powder | 300 mg every 4 weeks<br>**PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks | acceptable.<br><br>**PsA:**<br>For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed.<br><br>If active PsA continues, consider 300 mg dose. | injections of 150 mg.<br><br>Patients may self-administer with the pen or prefilled syringe.<br>The vial is for healthcare professional use only. |
| ENBREL (etanercept) | Prefilled syringe: 25 mg and 50 mg<br>Prefilled SureClick autoinjector: 50 mg<br>Multiple-use vial: 25 mg | **RA, AS, PsA:** 50 mg SQ weekly<br>**PsO (adults):** 50 mg SQ twice weekly for three months, then 50 mg weekly<br>**PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly | **RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued<br>**JIA:** NSAIDs glucocorticoids, or analgesics may be continued | Patients may be taught to self-inject.<br>May bring to room temperature prior to injecting. |
| ENTYVIO (vedolizumab) | Lyophilized cake for injection in single dose 20 mL vials: 300 mg | **CD and UC:** 300 mg administered by intravenous infusion at time zero, two and six weeks, and then every eight weeks thereafter.<br><br>Discontinue therapy if there is no evidence of therapeutic benefit by week 14. | All immunizations should be to date according to current guidelines prior to initial dose. | ENTYVIO should be reconstituted at room temperature and prepared by a trained medical professional.<br>It should be used as soon as possible after reconstitution and dilution. |
| HUMIRA (adalimumab) | Prefilled syringe:<br>10 mg/0.1 mL<br>10 mg/0.2 mL<br>20 mg/0.2 mL<br>20 mg/0.4 mL<br>40 mg/0.4 mL<br>40 mg/0.8 mL<br>80 mg/0.8 mL<br><br>Single-use pen:<br>80 mg/0.8 mL<br>40 mg/0.8 mL<br>40 mg/0.4 mL<br><br>Single-use vial:<br>40 mg/0.8 mL | **RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX.<br>**PJIA:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week<br>**CD, HS and UC:** 160 mg SQ on Day 1 (given in one day or split over two consecutive days), followed by 80 mg SQ two weeks later (Day | **RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued.<br>**JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.<br>**CD and UC:** aminosalicylates and/or corticosteroids may be continued. | Patients may be taught to self-inject.<br>Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites.<br>May bring to room temperature prior to injecting. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week.<br>**PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting one week after the initial dose.<br>**CD in pediatric patients ≥6 years and older:** 17 kg to <40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg two weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4.<br><br>≥40 kg: 160 mg on day (given in one day or split over two consecutive days) and 80 mg two weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4. | Azathioprine, 6-MP or MTX may be continued if necessary.<br>Needle cover of the syringe contains dry rubber (latex). | |
| ILARIS (canakinumab) | Vial: 150 mg (lyophilized powder and injection solution formulations) | **SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg).<br><br>**CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks<br><br>**TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks | For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg<br><br>For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg) | Do not inject into scar tissue. |
| INFLECTRA (infliximab-dyyb) | Vial: 100 mg | **CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen | **RA:** give with MTX<br><br>**CD:** If no response by week | Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg.<br>**RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks.<br>**AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks. | 14, consider discontinuation. | acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs. |
| KEVZARA (sarilumab) | Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL | **RA:** 200 mg SQ every 2 weeks. | **RA:** give with or without MTX or other conventional DMARDs<br><br>Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes. | Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting. Rotate injection sites. |
| KINERET (anakinra) | Prefilled syringe: 100 mg/0.67 mL | **RA:** 100 mg SQ once daily.<br>**CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day. | **NOMID**: dose can be given once or twice daily. | Patients may be taught to self-inject.<br>A new syringe must be used for each dose. |
| ORENCIA (abatacept) | Vial: 250 mg<br><br>Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL<br><br>ClickJect autoinjector: 125 mg/mL | **RA:**<br>IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter<br>SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. | | IV infusion should be over 30 minutes.<br>Use 100 mL bag for IV infusion.<br>Do not administer with other drugs.<br>Patients may be taught to self-inject the SQ dose.<br>For SQ, injection sites should be rotated. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | **PJIA:**<br>IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg.<br>SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly.<br><br>**PsA:**<br>IV: follow adult RA IV schedule.<br>SQ: 125 mg once weekly without IV dose. | | |
| OTEZLA (apremilast) | Tablet: 10 mg, 20 mg, and 30 mg | **PsA, PsO:**<br>Day 1: 10 mg in the morning<br>Day 2: 10 mg in the morning and in the evening<br>Day 3: 10 mg in the morning and 20 mg in evening<br>Day 4: 20 mg in the morning and evening<br>Day 5: 20 mg in the morning and 30 mg in the evening<br>Day 6 and thereafter: 30 mg twice daily | Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms.<br><br>Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded). | May be taken with or without food.<br><br>Do not crush, split, or chew the tablets. |
| REMICADE (infliximab) | Vial: 100 mg | **CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with | **RA:** give with MTX<br><br>**CD:** If no response by week 14, consider discontinuation. | Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids.<br>Use 250 mL 0.9% |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| | | CD who lose response, can increase dose to 10 mg/kg.<br>**RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks.<br>**AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks. | | sodium chloride for infusion.<br>Infuse over 2 hours.<br>Do not administer with other drugs. |
| RENFLEXIS | Vial: 100 mg | **CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg.<br>**RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks.<br>**AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks. | **RA:** give with MTX<br><br>**CD:** If no response by week 14, consider discontinuation. | Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids.<br>Use 250 mL 0.9% sodium chloride for infusion.<br>Infuse over 2 hours.<br>Do not administer with other drugs. |
| RITUXAN (rituximab) | Vial:<br>100 mg<br>500 mg | **RA:** 1,000 mg IV every 2 weeks times two doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks. | Give with MTX. | Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| SILIQ (brodalumab) | Prefilled syringe: 210 mg/1.5 mL | **PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks | **PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation | Patients may self-inject when appropriate and after proper training.<br><br>The syringe should be allowed to reach room temperature before injecting. |
| SIMPONI/ SIMPONI ARIA (golimumab) | SmartJect® autoinjector: 50 mg and 100 mg<br>Prefilled syringe: 50 mg and 100 mg<br><br>ARIA, Vial: 50 mg/4 mL | **RA, PsA, and AS**: 50 mg SQ once monthly<br>**UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks.<br><br>**ARIA**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. | **RA:** give with MTX<br>**PsA and AS**: may give with or without MTX or other DMARDs.<br><br>Needle cover of the syringe contains dry rubber (latex).<br><br>**ARIA**: give with MTX<br><br>Efficacy and safety of switching between IV and SQ formulations have not been established. | Patients may be taught to self-inject the SQ dose.<br>For SQ, injection sites should be rotated.<br>For SQ, bring to room temperature for 30 minutes prior to injecting.<br><br>**ARIA**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL.<br>Do not administer with other drugs. |
| STELARA (ustekinumab) | Prefilled syringe: 45 mg and 90 mg<br>Vial: 130 mg | **PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.<br><br>**CD**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight) | Needle cover of the syringe contains dry rubber (latex). | Patients may be taught to self-inject using the prefilled syringes.<br>STELARA for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least one hour.<br>Rotate injection sites. |
| TREMFYA (guselkumab) | Prefilled syringe: 100 mg | **PsO:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks | | Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Other Dosing Considerations | Administration Considerations |
|---|---|---|---|---|
| TALTZ (ixekizumab) | Prefilled syringe: 80 mg<br><br>Autoinjector: 80 mg | **PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks | | Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites. |
| XELJANZ / XELJANZ XR (tofacitinib) | Tablet: 5 mg<br>Extended release Tablet: 11 mg | **RA:** 5 mg PO twice daily or 11 mg PO once daily | Patients may switch from XELJANZ 5 mg twice daily to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg.<br><br>Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of XELJANZ in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended.<br><br>Dose interruption is recommended for management of lymphopenia (< 500 cells/$mm^3$), neutropenia (ANC < 500 cells/$mm^3$) and anemia.<br><br>Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors. | May take with or without food.<br><br>Swallow XELJANZ XR tablets whole; do not crush, split, or chew. |

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

## SPECIAL POPULATIONS

**Table 4. Special Populations**

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| ACTEMRA (tocilizumab) | Frequency of serious infection greater in ≥65 years. Use caution. | Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS. | No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment. | Not studied in patients with impairment. | Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered. |
| CIMZIA (certolizumab) | The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution. | Safety and effectiveness have not been established. | No data | No data | Unclassified† Limited data from ongoing pregnancy registry not sufficient to inform risks. Unknown whether excreted in breast milk, but data suggest systemic exposure to a breastfed infant is expected to be low; risks and benefits should be considered. |
| COSENTYX (secukinumab) | The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. | Safety and efficacy have not been established. | No data | No data | Pregnancy category B* Unknown whether excreted in breast milk; use with caution. |
| ENTYVIO (vedolizumab) | The number of patients ≥65 years in clinical trials was insufficient to determine differences. | Safety and efficacy have not been established. | Safety and efficacy have not been established. | Safety and efficacy have not been established. | Pregnancy category B* Unknown whether excreted in breast milk; use with caution. |
| ENBREL (etanercept) | Use caution. | Not studied in children <2 years with PJIA or <4 years with PsO. | No data | No data | Unclassified† Available studies do not reliably support association with major birth defects. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| | | | | | Present in low levels in breast milk; consider risks and benefits. |
| HUMIRA (adalimumab) | Frequency of serious infection and malignancies is greater in ≥65 years. Use caution. | Only studied in PJIA (ages 2 years and older) and CD (6 years and older). | No data | No data | Unclassified†<br><br>Present in low levels in breast milk; consider risks and benefits. |
| ILARIS (canakinumab) | The number of patients ≥65 years in clinical trials was insufficient to determine differences. | Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS). | No data | No data | Unclassified†<br><br>Limited data from postmarketing reports not sufficient to inform risks.<br><br>Unknown whether excreted in breast milk; consider risks and benefits. |
| INFLECTRA (infliximab-dyyb) | Frequency of serious infection is greater in ≥65 years. Use caution. | Not recom-mended in <6 years in children with CD. | No data | No data | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| KEVZARA (sarilumab) | Frequency of serious infection is greater in ≥ 65 years. Use caution. | Safety and efficacy not established. | Dosage adjustment not required in mild to moderate renal impairment. KEVZARA has not been studied in severe renal impairment. | No data. | Unclassified†<br><br>Data on use in pregnant women insufficient to inform risks.<br><br>Unknown whether excreted in breast milk; consider risks and benefits. |
| KINERET (anakinra) | Use caution. | For NOMID, has been used in all ages. Not possible to give a dose <20 mg. | CrCl<30 mL/min: give dose every other day | No data | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; use caution. |
| ORENCIA (abatacept) | Frequency of serious infection and malignancies is greater in ≥65 years. Use caution. | Not recom-mended in <2 years.<br><br>IV dosing has not been studied | No data | No data | Unclassified†<br><br>Data on use in pregnant women insufficient to inform risks. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| | | in patients < 6 years old.<br><br>ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years. | | | Unknown whether excreted in breast milk. |
| OTEZLA (apremilast) | No overall differences were observed in the safety profile of elderly patients. | Safety and efficacy have not been established. | The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30 mL/min). | No dosage adjustment necessary. | Pregnancy category C*<br><br>Unknown whether excreted in breast milk; use caution. |
| REMICADE (infliximab) | Frequency of serious infection is greater in ≥65 years. Use caution. | Not recom-mended in <6 years in children with CD or UC. | No data | No data | Pregnancy category B*<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| RENFLEXIS (infliximab-abda) | Frequency of serious infection is greater in ≥ 65 years. Use caution. | Not recom-mended in < 6 years in children with CD. | No data | No data | Unclassified†<br><br>Available data do not report clear association with adverse outcomes.<br><br>Unknown whether excreted in breast milk; consider risks and benefits. |
| RITUXAN (rituximab) | Rates of serious infections, malignancies, and cardiovascular events were higher in older patients. | Safety and effectiveness have not been established. | No data | No data | Pregnancy category C*<br><br>Unknown whether excreted in breast milk; risks and benefits should be weighed before use. |
| SILIQ (brodalumab) | No differences in safety or efficacy were observed between older and younger patients, but the number of | Safety and effectiveness in <18 years have not been established. | No data | No data | Unclassified†<br><br>There are no human data in pregnant women to inform risks. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| | patients ≥65 years was insufficient to determine any differences in response. | | | | Unknown whether excreted in breast milk; risks and benefits should be weighed before use. |
| SIMPONI/ SIMPONI ARIA (golimumab) | SQ: No differences in AEs observed between older and younger patients. Use caution.<br><br>IV ARIA: Use caution. | Effectiveness in <18 years has not been established (SIMPONI).<br><br>Safety and effectiveness in < 18 years have not been established (ARIA). | No data | No data | Pregnancy category B* (ARIA)<br><br>Unclassified†<br>No adequate and well-controlled trials in pregnant women. (SIMPONI).<br><br>Unknown whether excreted in breast milk. Discontinue nursing or discontinue the drug (ARIA). Consider risks and benefits (SIMPONI). |
| STELARA (ustekinumab) | No differences observed between older and younger patients. Use caution. | Safety and effectiveness have not been established. | No data | No data | Unclassified†<br><br>Limited data in pregnant women are insufficient to inform risks.<br><br>Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits. |
| TALTZ (ixekizumab) | No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences. | Safety and effectiveness have not been established. | No data | No data | Unclassified†<br><br>There are no available data in pregnant women to inform risks.<br><br>Unknown whether excreted in breast milk; consider risks and benefits. |
| TREMFYA (guselkumab) | No differences observed between older and younger patients; however, the number of | Safety and efficacy have not been established. | No data | No data | Unclassified†<br><br>No available data in pregnant women to inform risks. |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy and Nursing |
| | patients ≥ 65 years was not sufficient to determine differences. | | | | Unknown whether excreted in breast milk; consider risks and benefits. |
| XELJANZ / XELJANZ XR (tofacitinib) | Frequency of serious infection is greater in ≥65 years. Use caution. | Safety and effectiveness have not been established. | Reduce dose to 5 mg daily in moderate to severe impairment. | Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment. | Unclassified†<br><br>No adequate and well-controlled studies in pregnancy are available.<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |

CrCl=creatinine clearance; CRS=cytokine release syndrome; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

## CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at six months, but abatacept demonstrated greater efficacy after one year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (Schiff et al, 2008).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over two years in a single-blind study (Schiff et al, 2014).
    - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (Burmester et al, 2017). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (Gabay et al, 2013). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (Porter et al, 2016).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (Gottenberg et al, 2016). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population (Manders et al, 2015).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (Thaçi et al, 2015). The proportion of

patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; P<0.0001).
    - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; P<0.001) (Reich et al, 2017 [b]).
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (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 than ustekinumab (14.7% vs 0.7%) (Griffiths et al, 2010).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (Langley et al, 2014).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (Lebwohl et al, 2015).
    - In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab (Blauvelt et al, 2017; Reich et al, 2017[a]).
    - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (Park et al, 2013; Park et al, 2016; Park et al, 2017; Yoo et al, 2013; Yoo et al, 2016; Yoo et al, 2017). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (Choe et al, 2017; Shin et al, 2015).
    - In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (Jørgensen et al, 2017).
    - More comparative studies are needed.
- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (Singh et al, 2016c; Smolen et al, 2017). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (Götestam Skorpen et al, 2016).
- For the management of PsO, biologic agents are routinely used when one or more traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (Gottleib et al, 2008; Menter et al, 2008; Menter et al, 2009a; Menter et al, 2009b; Menter et al, 2010; Menter et al, 2011; Nast et al, 2015b). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX (Gossec et al, 2016; Ramiro et al, 2016). For patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (Coates et al, 2016).
- In patients with JIA and involvement of ≥5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (Beukelman et al, 2011). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (Ringold et al, 2013).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (Kornbluth et al, 2010). Other immunomodulators were not indicated for UC when these guidelines were written.
- Based on ACG guidelines, the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. These TNF inhibitors may also be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired (Lichtenstein et al, 2009). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (Terdiman et al, 2013). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF

inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (Gomollón et al, 2017).

- Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy (Nguyen et al, 2016b).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (Gulliver et al, 2016; Zouboulis et al, 2015).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (van der Heijde et al, 2017). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (Ward et al, 2016).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (Levy-Clarke et al, 2016).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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**Nevada Medicaid**
Symproic (naldemedine)
Pharmacy Coverage Guideline

| Brand Name | Generic Name |
|---|---|
| Symproic | naldemedine |

## CRITERIA FOR COVERAGE/NONCOVERAGE

### Indications

**Opioid-Induced Constipation (OIC)** Indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage

### Approval Criteria

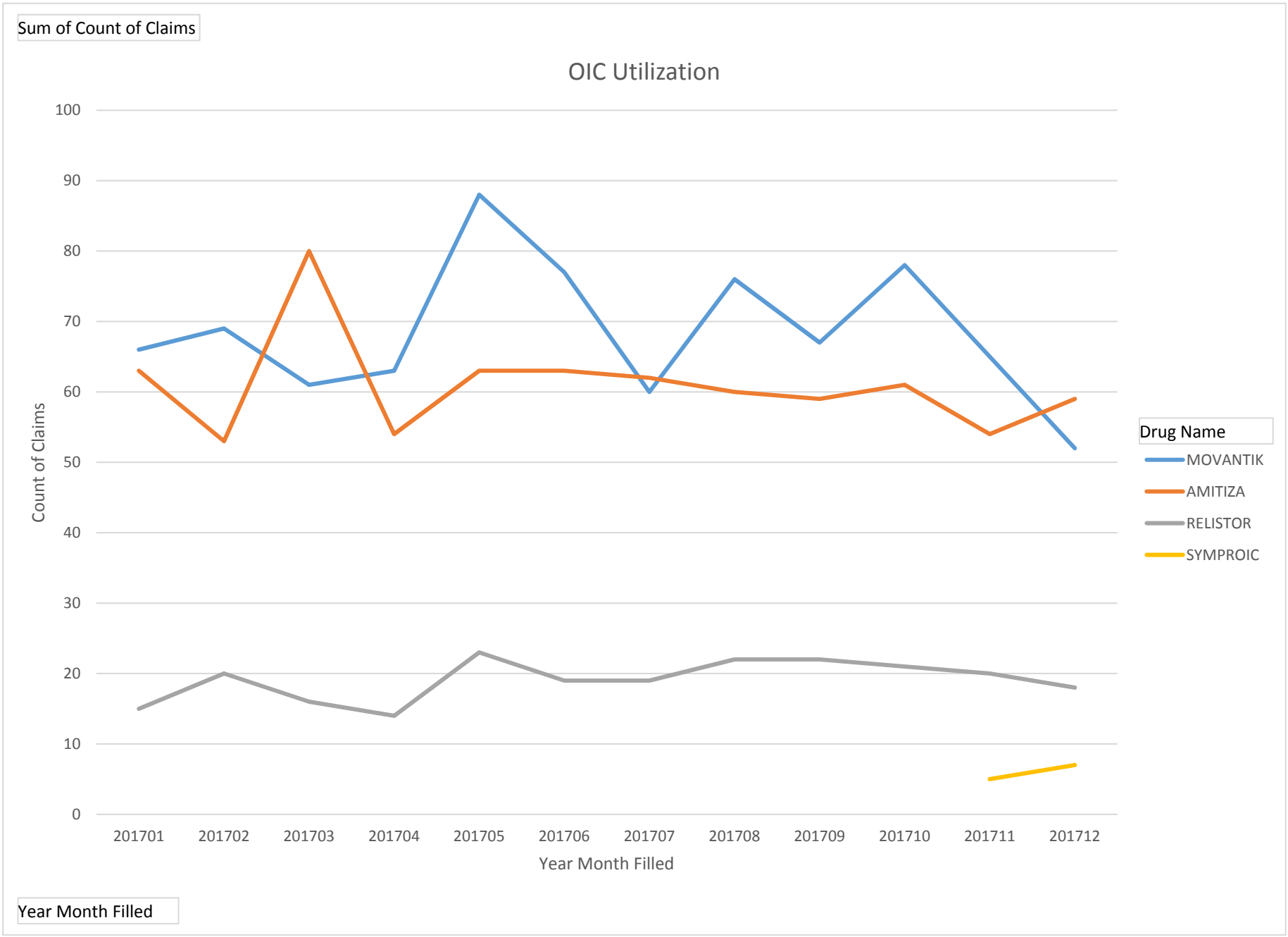
1. The recipient is 18 years of age or older and
2. The requested medication is being used for an FDA approved indication and
3. There is documentation in the recipient's medical record of an inadequate response, adverse reaction or contraindication to one agent from three of the four traditional laxative drug classes:
    a. Bulk forming laxatives
    b. Osmotic laxatives
    c. Saline laxatives
    d. Stimulant laxatives

**Approval Duration** - Up to one year

## Opioid Induced Contipation Utilization

Jan 1, 2017 - Dec 31, 2017

| Year Month Filled | Drug Name | Count of Members | Count of Claims | Sum of Days | Sum of Qty | Sum of Amt Paid |
|---|---|---|---|---|---|---|
| 201701 | AMITIZA | 55 | 63 | 1921 | 3370 | $ 6,604.61 |
| 201702 | AMITIZA | 51 | 53 | 1656 | 2892 | $ 8,477.00 |
| 201703 | AMITIZA | 71 | 80 | 2523 | 4504 | $ 15,319.27 |
| 201704 | AMITIZA | 50 | 54 | 1660 | 2811 | $ 9,455.91 |
| 201705 | AMITIZA | 59 | 63 | 1875 | 3480 | $ 11,481.98 |
| 201706 | AMITIZA | 60 | 63 | 2022 | 3723 | $ 13,039.44 |
| 201707 | AMITIZA | 59 | 62 | 2028 | 3433 | $ 9,008.68 |
| 201708 | AMITIZA | 58 | 60 | 1835 | 3240 | $ 11,840.39 |
| 201709 | AMITIZA | 54 | 59 | 1962 | 3573 | $ 15,652.84 |
| 201710 | AMITIZA | 54 | 61 | 1841 | 3441 | $ 14,535.49 |
| 201711 | AMITIZA | 52 | 54 | 1816 | 3512 | $ 16,240.30 |
| 201712 | AMITIZA | 55 | 59 | 1806 | 3280 | $ 13,335.01 |
| 201701 | MOVANTIK | 62 | 66 | 1980 | 1980 | $ 13,595.65 |
| 201702 | MOVANTIK | 65 | 69 | 2038 | 2038 | $ 14,757.76 |
| 201703 | MOVANTIK | 59 | 61 | 2002 | 2032 | $ 11,592.76 |
| 201704 | MOVANTIK | 62 | 63 | 2130 | 2130 | $ 16,267.79 |
| 201705 | MOVANTIK | 81 | 88 | 2841 | 2871 | $ 19,451.32 |
| 201706 | MOVANTIK | 72 | 77 | 2434 | 2449 | $ 20,094.13 |
| 201707 | MOVANTIK | 58 | 60 | 1845 | 1875 | $ 14,216.68 |
| 201708 | MOVANTIK | 64 | 76 | 2231 | 2261 | $ 17,046.07 |
| 201709 | MOVANTIK | 64 | 67 | 2250 | 2235 | $ 18,045.74 |
| 201710 | MOVANTIK | 74 | 78 | 2640 | 2625 | $ 20,728.14 |
| 201711 | MOVANTIK | 62 | 65 | 2001 | 2031 | $ 17,352.85 |
| 201712 | MOVANTIK | 49 | 52 | 1611 | 1611 | $ 14,540.31 |
| 201701 | RELISTOR | 14 | 15 | 332 | 538.8 | $ 10,105.00 |
| 201702 | RELISTOR | 20 | 20 | 563 | 1027.8 | $ 24,132.26 |
| 201703 | RELISTOR | 15 | 16 | 338 | 542.6 | $ 4,482.40 |
| 201704 | RELISTOR | 13 | 14 | 414 | 826.2 | $ 16,598.72 |
| 201705 | RELISTOR | 23 | 23 | 447 | 975.4 | $ 16,679.49 |
| 201706 | RELISTOR | 18 | 19 | 487 | 1143.4 | $ 21,501.82 |
| 201707 | RELISTOR | 18 | 19 | 495 | 1149.6 | $ 20,840.84 |
| 201708 | RELISTOR | 22 | 22 | 569 | 1264.8 | $ 27,723.32 |
| 201709 | RELISTOR | 22 | 22 | 513 | 1232.4 | $ 23,970.71 |
| 201710 | RELISTOR | 20 | 21 | 568 | 1311.6 | $ 28,319.76 |
| 201711 | RELISTOR | 19 | 20 | 540 | 1406.4 | $ 25,732.84 |
| 201712 | RELISTOR | 18 | 18 | 569 | 1345.8 | $ 23,511.72 |
| 201711 | SYMPROIC | 5 | 5 | 150 | 150 | $ 1,620.60 |
| 201712 | SYMPROIC | 7 | 7 | 210 | 210 | $ 2,268.84 |


Sum of Count of Claims
OIC Utilization
100
90
80
70
60
50
40
30
20
10
0
Count of Claims
201701
201702
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
Year Month Filled
Drug Name
MOVANTIK
AMITIZA
RELISTOR
SYMPROIC
Year Month Filled

WW. Irritable-Bowel Syndrome Agents

Therapeutic Class: Irritable-Bowel Syndrome Agents
Last Reviewed by the DUR Board: July 28, 2016
Viberzi® last reviewed April 28, 2016

Irritable-Bowel Syndrome Agents are subject to prior authorization and quantity limits based on the Application of Standards in Section 1927 of the 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

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

      1. The recipient is 18 years of age or older; and

      2. The requested agent is being prescribed based on FDA approved guidelines; and

         a. For requests for a diagnosis of Irritable-Bowel Syndrome with Constipation (IBS-C):

            1. For requests for lubiprostone, the recipient must be female.

            2. The requested dose is appropriate based on indication and age.

               a. Linaclotide: 290 μg daily.

               b. Lubiprostone: 16 μg daily.

         b. For requests for a diagnosis of Irritable-Bowel Syndrome with Diarrhea (IBS-D):

            1. The medication is being prescribed by or in consultation with a gastroenterologist; and

            2. The requested dose is appropriate based on indication and age.

               a. Alosetron: 0.5 mg twice daily or 1 mg twice daily.

               b. Eluxadoline: 75 mg twice daily or 100 mg twice daily.

               c. Rifaximin: 550 mg three times a day for 14 days.

2. Prior Authorization Guidelines

a. Prior authorization approval will be given for an appropriate length of therapy based on the requested agent and diagnosis, not to exceed one year.

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

LLL. Opioid-Induced Constipation Agents

Therapeutic Class: Opioid-Induced Constipation Agents
Last Reviewed by the DUR Board: April 28, 2016

Opioid-induced constipation agents are subject to prior authorization and quantity limits based on the Application of Standards in Section 1927 of the 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 all the following criteria are met and documented:

   a. The recipient is 18 years of age or older; and

   b. The requested medication is being used for an FDA approved indication; and

   c. The recipient must meet the following criteria:

      1. There is documentation in the recipient's medical record of an inadequate response, adverse reaction or contraindication to one agent from three of the four traditional laxative drug classes:

         a. Bulk forming laxatives;

         b. Osmotic laxatives;

         c. Saline laxatives;

         d. Stimulant laxatives

   d. And, requests for methylnaltrexone bromide that exceed the quantity limit must meet all of the following criteria:

      1. The recipient has opioid-induced constipation in advanced illness, is receiving palliative care, and is not enrolled in the DHCFP's hospice program; and

      2. The requested dose is 0.15 mg/kg; and

      3. The recipient's current weight is >114 kg.

2. Prior Authorization Guidelines

   a. Prior Authorization approval will be for one year.

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

# Therapeutic Class Overview
## Irritable Bowel Syndrome and Constipation Agents

### INTRODUCTION

- Irritable bowel syndrome (IBS) is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (Wald, 2017).
- IBS may consist of diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (Ford et al, 2014).
- IBS is a functional disorder of the gastrointestinal tract characterized by abdominal pain, discomfort, and bloating, as well as disturbed bowel habit. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (Ford, 2009; Andresen, 2008).
- Prevalence estimates of IBS range from 5% to 15%, and it typically occurs in young adulthood (Ford et al, 2014). IBS-D is more common in men, and IBS-C is more common in women (World Gastroenterology Organization [WGO], 2015).
- Symptoms of IBS often interfere with daily life and social functioning (WGO, 2015).
- The general goals of therapy are to alleviate the patient's symptoms and to target any specific exacerbating factors (e.g., medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist.
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (e.g., beans, prunes, brussel sprouts, bagels, etc.), trials of gluten avoidance, consumption of probiotics, as well as psychosocial therapies (e.g., hypnosis, biofeedback, etc.) (Ford et al, 2014).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include poorly absorbable antibiotics such as rifaximin; laxative agents, including stimulant laxatives (bisacodyl, etc.) and osmotic laxatives (polyethylene glycol [PEG], lactulose, etc.); antispasmodics (e.g., dicyclomine, hyoscine, etc.); selective chloride channel activators (e.g. lubiprostone); serotonin-3 receptor antagonists (e.g., alosetron); guanylate cyclase-c agonists (e.g., linaclotide); antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors; select probiotics; and peppermint oil (Ford et al, 2014).
- In addition to treatment of IBS-C, AMITIZA® (lubiprostone), LINZESS® (linaclotide), and TRULANCE™ (plecanatide) are indicated for the treatment of chronic idiopathic constipation (CIC). Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as fewer than three bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (American Gastroenterological Association [AGA] Medical Position Statement, 2013; Bharucha et al, 2013).
- AMITIZA (lubiprostone) is also Food and Drug Administration (FDA)-approved for the treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer related pain. OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (Brock et al, 2012).
- Three other products are approved for use in OIC:
  - RELISTOR® (methylnatrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. RELISTOR has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - MOVANTIK® (naloxegol) and SYMPROIC® (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORA) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.

- LOTRONEX® (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

- ZELNORM® (tegaserod) was approved in July 2002 for short-term treatment of IBS-C in women and in August 2004 for treatment of CIC in men and women <65 years of age. In March 2007, the FDA requested the manufacturer to discontinue the marketing of ZELNORM due to safety concerns related to increased rate of heart attack, stroke, and worsening heart-related chest pain. In July 2007, ZELNORM became available for use as a treatment investigational new drug (IND) protocol for IBS-C and CIC in women < 55 years of age meeting specific guidelines; however, in April 2008, the manufacturer discontinued the availability as a treatment IND. ZELNORM is currently available for use only in emergency situations with FDA authorization (Clinical Pharmacology, 2016).
- IBS-D is an IBS subtype characterized mainly by loose or watery stools at least 25% of the time. In May 2015, two new treatments with different mechanisms of action were approved for use in the treatment of IBS-D, VIBERZI® (eluxadoline) and XIFAXAN® (rifaximin). VIBERZI is a mu-opioid receptor agonist, and XIFAXAN is a rifamycin antibacterial (FDA News Release, 2015). VIBERZI is a schedule IV controlled substance.
- The scope of this review will focus upon AMITIZA (lubiprostone), LINZESS (linaclotide), LOTRONEX (alosetron), MOVANTIK (naloxegol), RELISTOR (methylnaltrexone bromide), SYMPROIC (naldemedine), TRULANCE (plecanatide), VIBERZI (eluxadoline), and XIFAXAN (rifaximin) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (TRULANCE); Gastrointestinal Chloride Channel Activators (AMITIZA); IBS Agents (LOTRONEX, LINZESS, VIBERZI); Peripheral Opioid Receptor Antagonists (MOVANTIK, RELISTOR, SYMPROIC); Anti-infective Agents – Misc (XIFAXAN)

**Table 1. Medications Included Within Class Review**

| Drug | Manufacturer | FDA Approval Date | Generic Availability |
|---|---|---|---|
| AMITIZA (lubiprostone) | Sucampo Pharmaceuticals, Inc./Takeda | 01/31/2006 | - |
| LINZESS (linaclotide) | Ironwood Pharmaceuticals/ Forest Pharmaceuticals | 08/30/2012 (145 and 290 mcg capsules)<br>1/25/2017 (72 mcg capsule) | - |
| LOTRONEX (alosetron) | Prometheus Laboratories, Inc. | 02/09/2000 | ✔ |
| MOVANTIK (naloxegol) | AstraZeneca | 09/16/2014 | - |
| RELISTOR (methylnaltrexone bromide) | Salix Pharmaceuticals | 04/24/2008 (injection)<br>07/19/2016 (tablet) | - |
| SYMPROIC® (naldemedine) | Shionogi Inc. | 3/23/2017 | - |
| TRULANCE (plecanatide) | Synergy Pharmaceuticals Inc. | 1/19/2017 | - |
| VIBERZI (eluxadoline) | Patheon Pharmaceuticals/Forest Pharmaceuticals (now Actavis) | 05/27/2015 | - |
| XIFAXAN (rifaximin) | Salix Pharmaceuticals | 05/25/2004 (200 mg tablet)<br>03/24/2010 (550 mg tablet) | - |

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

## INDICATIONS

**Table 2. FDA Approved Indications**

| Indication | AMITIZA (lubiprostone) | LINZESS (linaclotide) | LOTRONEX (alosetron) | MOVANTIK (naloxegol) | RELISTOR (methylnaltrexone bromide) | SYMPROIC (naldemedine) | TRULANCE (plecanatide) | VIBERZI (eluxadoline) | XIFAXAN (rifaximin) |
|---|---|---|---|---|---|---|---|---|---|
| Treatment of CIC in adults | ✔ | ✔ | | | | | ✔ | | |
| Treatment of OIC in adults with chronic, non-cancer pain | ✔* | | | ✔ | ✔ | ✔ | | | |
| Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation. | ✔ | | | ✔ | ✔ | ✔ | | | |
| Treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient or pain caused by active cancer which requires opioid dosage escalation for palliative care | | | | | ✔† | | | | |
| Treatment of IBS-C in women ≥18 years of age | ✔ | | | | | | | | |
| Treatment of IBS-C in adults | | ✔ | | | | | | | |
| Treatment of IBS-D in adults | | | | | | | | ✔ | ✔‡ |
| Women with severe IBS-D who have:<br>• chronic IBS symptoms (generally lasting six months or longer)<br>• had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§ | | | ✔ | | | | | | |

*Effectiveness of AMITIZA in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.

†Injection formulation only. Use of RELISTOR beyond four months in treatment of OIC in patients with advanced illness has not been studied.

‡XIFAXAN has additional indications for treatment of traveler's diarrhea (TD) caused by noninvasive strains of *Escherichia coli* in adult and pediatric patients 12 years of age and older, and reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults. Do not use XIFAXAN in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

§IBS-D is severe if it includes diarrhea and one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.

(Prescribing information: AMITIZA, 2017; LINZESS, 2017; LOTRONEX, 2016; MOVANTIK, 2017; RELISTOR, 2017; SYMPROIC 2017; TRULANCE, 2017; VIBERZI, 2017; XIFAXAN, 2017)

- LOTRONEX was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of LOTRONEX to treat only women with severe IBS-D. Physicians are required to complete training before prescribing alosetron to ensure that the benefits and risks of the agent are considered before administering it to patients (LOTRONEX FDA press release, 2016).

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

### CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥3 complete spontaneous bowel movements (CSBMs)/week compared with placebo with a relative risk (RR) of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥1 CSBM/week (RR 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (Nelson et al, 2017).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; P<0.001) (Li et al, 2016).
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (Videlock et al, 2013).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (Chey et al, 2012).
- For the recently approved linaclotide 72 mcg, a double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that linaclotide improved the weekly frequency of CSBMs compared with placebo, with 13% of linaclotide-treated patients meeting responder requirements compared with 9% in the placebo group (95% CI, 4.8% to 12.5%) (LINZESS prescribing information, 2017).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; P<0.001; Study 2: 20.1% vs 12.8%; P=0.004) (Miner et al [abstract], 2016; Miner et al, 2017).

### IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and CSBM frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (Atluri et al, 2014; Videlock et al, 2013). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; RR of failure to respond 0.80; 95% CI, 0.76 to 0.85).
- For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b). In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2008b).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Lembo et al, 2001; Lembo et al, 2004; Rahimi et al, 2008; Watson et al, 2001).
- A meta-analysis concluded that the 5-HT3 antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (Andresen et al, 2008).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (Cremonini et al, 2003).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in two randomized, multicenter, multinational, double-blind, placebo-controlled, phase 3 clinical trials in which 2,427 patients with IBS-D (meeting Rome III criteria), average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and

a Bristol Stool Scale (BSS) of 5.5 or greater with at least five days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (P=0.01) and 25.1% of patients in the 100 mg group (P=0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (P=0.11) and 29.3% in the 100 mg group (P<0.001) achieved the primary endpoint compared to 19% in the placebo group (Lembo et al, 2016).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in three double-blind, placebo-controlled trials.
  - In the first two trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg three times daily (n=624) or placebo (n=634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least two of four weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; P<0.05; Trial 2: 47% vs 36%; P<0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg three times daily (n=328) or placebo (n=308) for two additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; P<0.05) (ClinicalTrials.gov NCT01543178, 2016).

**OIC**

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n=274; n=277) or placebo (n=273; n=276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2mg experienced a significantly higher response compared to patients receiving placebo in both studies(COMPOSE-1 responders: 47.6% vs 34.6%; P=0.002 and COMPOSE-2 responders: 52.5% vs 33.6%; P<0.0001, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (Hale et al, 2017).
- A total of 1,300 patients were enrolled in three, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥1 SBM improvement over baseline for all treatment weeks and ≥3 SBMs per week for at least nine of the 12-week study period. Lubiprostone (27.1%) had a significantly higher “overall responder rate” than placebo (18.9%; P=0.03) (Jamal et al, 2015). Primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week eight. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo (P=0.004). In Study 3, the difference was not statistically significant; however, Study 3 was the only study, which enrolled patients who received diphenylheptane opioids such as methadone. Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as less than three SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n=210) or placebo (n=218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week eight. Changes from baseline in SBM frequency rates were significantly higher at week eight (P=0.005) and overall (P=0.004) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (Cryer et al, 2014).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments including methylnaltrexone, naloxone, and

alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (Ford et al, 2013).

- In 2014, another systematic review of 21 randomized clinical trials evaluated seven pharmacological treatments of OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within four hours, and time to first BM. Methylnatrexone showed improvements in all three OOMs. Randomized control trials in naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥ 12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. Although not FDA-approved, CB-5945 and prucalopride tended to increase BM frequency, especially for 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (Siemens et al, 2015).
- The efficacy of naloxegol has been established in K4 and K5, two replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least four weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥3 SBMs per week and an increase of ≥1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (P=0.001 and P=0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (P=0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (P=0.2) (Chey et al, 2014).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (P=0.002) and with naloxegol 12.5 mg vs placebo (P=0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (P=0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (P<0.001 for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, supporting the preservation of centrally mediated analgesia.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxation effects similar to SBMs and predictable timing (Bull et al, 2015; Thomas et al, 2008). Similar findings have been reported in patients with OIC with chronic non-cancer pain (Michna et al, 2011, Webster et al, 2017).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of four weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with three or more SBMs per week, with an increase of one or more SBMs per week over baseline, for at least three weeks in the four-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (P=0.03 vs placebo), 51.5% (P=0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (Rauck et al, 2017).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubriprostone, naldemedine, naloxegol, subcutaneous and oral methylnaltrexone, and 2 agents, alvimopan and prucalopride, not approved for OIC in the U.S. (Sridharan & Sivaramakrishan, 2017). Observations from 16 RCTs with 4,048 patients demonstrated lubriprostone, naldemedine, naloxegol, and subcutaneous and oral methyl naltrexone to perform better vs. placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with subcutaneous methyl naltrexone resulted in significantly improved RFBMs vs. lubiprostone, naloxegol, and oral methyl naltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while subcutaneous methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.

**IBS and CIC**

- An updated systematic review on IBS and CIC was commissioned by the American College of Gastroenterology to assess the efficacy of available therapies in treating IBS and CIC compared with placebo or no treatment. The secondary objectives included assessing the efficacy of available therapies in treating IBS according to predominant stool pattern reported (IBS-C, IBS-D, and IBS-M), as well as assessing adverse events with therapies for both IBS and CIC. Parallel-group, randomized controlled trials comparing active interventions with either placebo or no therapy were evaluated. Crossover trials were eligible for inclusion if extractable data were provided at the end of the first treatment period, before crossover. The following were identified as “strong” recommendations for IBS and CIC treatments:
  - IBS
    - There is insufficient evidence to recommend loperamide for use in IBS. Quality of evidence is very low.
    - Mixed 5-HT 4 agonists/5-HT 3 antagonists are not more effective than placebo at improving symptoms of IBS-C. Quality of evidence is low.
    - Linaclotide is superior to placebo for the treatment of IBS-C. Quality of evidence is high.
    - Lubiprostone is superior to placebo for the treatment of IBS-C. Quality of evidence is moderate.
  - CIC
    - Some medicinal and dietary fiber supplements increase stool frequency in patients with CIC. Quality of evidence is low.
    - PEG is effective in improving symptoms of CIC. Quality of evidence is high.
    - Lactulose is effective in improving symptoms of CIC. Quality of evidence is low.
    - Sodium picosulfate and bisacodyl are effective in CIC. Quality of evidence is moderate.
    - Prucalopride is more effective than placebo in improving symptoms of CIC. Quality of evidence is moderate.
    - Linaclotide is effective in CIC. It is generally safe, with the main adverse event being diarrhea. Quality of evidence is high.
    - Lubiprostone is effective in the treatment of CIC. Quality of evidence is high (Ford et al, 2014).

## CLINICAL GUIDELINES

- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as “rescue agents”. Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (Ford et al, 2014):
  - Rifaximin is effective in reducing total IBS symptoms and bloating in IBS-D (weak; moderate)
  - Alosetron is effective in females with IBS-D (weak; moderate)
  - Linaclotide is superior to placebo for the treatment of IBS-C (strong; high)
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is superior to placebo for the treatment of IBS-C (strong; moderate)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
- The AGA guideline on management of IBS makes the following statements (reported with strength of recommendation and quality of evidence, respectively) (Weinberg et al, 2014):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (WGO, 2015).
- In the 2014 Technical Review of the Pharmacological Management of Irritable Bowel Syndrome, the AGA Institute reviewed and graded the evidence for pharmacological interventions (linaclotide, lubiprostone, PEG laxative, rifaximin, alosetron, loperamide, tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors (SSRIs), and antispasmodics) for treatment of IBS. Review of the evidence for these pharmacological treatments showed that across all outcomes, evidence was high for linaclotide; moderate for lubiprostone, rifaximin, and alosetron; low for TCAs, SSRIs, and PEG; and very low for loperamide and antispasmodics (Chang et al, 2014).

## SAFETY SUMMARY

- AMITIZA is contraindicated with known or suspected mechanical gastrointestinal obstruction. LOTRONEX is associated with several contraindications, including history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment. LINZESS and TRULANCE are contraindicated in patients age 6 years or younger and in patients with known or suspected mechanical obstruction. MOVANTIK is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction. SYMPROIC is contraindicated in patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients. VIBERZI has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than three alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected hepatic duct obstruction; severe hepatic impairment; severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; or use in patients without a gallbladder. XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN.
  - On March 15, 2017, an FDA Drug Safety Communication was released warning that VIBERZI should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (FDA Drug Safety Communication, 2017). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
- LINZESS and TRULANCE have a Boxed Warning regarding the contraindication in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age.
- LOTRONEX has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, LOTRONEX should be discontinued. The agent should be used only in female patients with severe IBS-D who have not benefited from usual therapies (Lotronex – FDA MedWatch, 2016).
- LOTRONEX also has a Risk Evaluation and Mitigation Strategy (REMS) that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (Drugs@FDA, 2017).
- There are no known drug interactions with LINZESS. Diphenylheptane opioids such as methadone may interfere with the efficacy of AMITIZA. Clinically significant drug interactions associated with LOTRONEX include cytochrome P450 (CYP) 1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine.
- Concomitant use of MOVANTIK should be avoided with the following drug classes: moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (e.g., rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of MOVANTIK is warranted.
- Concomitant use of RELISTOR with other opioid antagonists should be avoided due to potentially additive effects that may increase risk of opioid withdrawal.
- Concomitant use of SYMPROIC should be avoided with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil) can increase SYMPROIC concentrations.
- A clinically important drug interaction with VIBERZI which potentially may result in clinically relevant interactions may occur with concomitant use of the following drug classes: OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (e.g., ciprofloxacin, fluconazole, clarithromycin,

paroxetine, bupropion, etc.), constipation-inducing drugs (e.g., alosetron, anticholinergics, opioids, etc.), OATP1Bi and BCRP substrate (rosuvastatin), and CYP3A substrates (e.g., alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus).

- Concomitant administration of drugs that are P-glycoprotein inhibitors with XIFAXAN can substantially increase the systemic exposure to rifaximin. Caution should be exercised when concomitant use of XIFAXAN and a P-glycoprotein inhibitor such as cyclosporine is needed.
- The IBS agents are most commonly associated with gastrointestinal-related adverse events.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Dosage Form: Strength | Usual Recommended Dose | Administration Considerations |
|---|---|---|---|
| AMITIZA (lubiprostone) | Capsule:<br>8 mcg<br>24 mcg | Treatment of CIC in adults and OIC:<br>Capsule: 24 mcg twice daily by mouth<br><br>Treatment of IBS-C in women ≥18 years of age:<br>Capsule: 8 mcg twice daily<br><br>Adjust dosing in moderate and severe hepatic impairment. | Take with food and water. |
| LINZESS (linaclotide) | Capsule: 72 mcg, 145 mcg, 290 mcg | IBS-C: 290 mcg once daily<br><br>CIC: 145 mcg once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability. | Take on an empty stomach at least 30 minutes before the first meal of the day. Swallow capsules whole; do not crush or chew. If unable to swallow, administer contents of capsule with applesauce or water.<br><br>No titration |
| LOTRONEX (alosetron) | Tablet:<br>0.5 mg<br>1 mg | Women with severe IBS-D:<br>Tablet: 0.5 mg twice daily for four weeks; if dosage is well tolerated but does not adequately control IBS symptoms after four weeks, the dose may be increased to up to 1 mg twice daily | Take with or without food.<br><br>Discontinue treatment in patients who have not had adequate control of IBS symptoms after four weeks of treatment with 1 mg twice daily. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Administration Considerations |
|---|---|---|---|
| MOVANTIK (naloxegol) | Tablets:<br>12.5 mg<br>25 mg | OIC in chronic non-cancer pain:<br>25 mg once daily; if not tolerated, may reduce to 12.5 mg once daily<br><br>• Renal Impairment (CrCl <60 mL/min): 12.5 mg once daily; if tolerated, may increase to 25 mg once daily | Discontinue maintenance laxative therapy prior to initiating therapy with MOVANTIK.<br><br>Take on an empty stomach at least one hour before or two hours after the first meal of the day.<br><br>For patients who are unable to swallow the tablet whole, the tablet can be crushed to a powder, mixed with 4 ounces of water, and drunk immediately. The glass should be refilled with an additional 4 ounces of water and drunk immediately. Crushed MOVANTIK can also be administered via a nasogastric tube.<br><br>Avoid ingestion of grapefruit or grapefruit juice.<br><br>Discontinue MOVANTIK when opioid pain medication is discontinued. |
| RELISTOR (methylnaltrex-one) | Single-use vial:<br>12 mg/0.6 mL solution for use with a 27 gauge x 0.5 inch needle and 1 mL syringe<br><br>Single-use pre-filled syringe:<br>8 mg/0.4 mL<br>12 mg/0.6 mL<br><br>Tablet: 150 mg | OIC in chronic non-cancer pain:<br>Injection: 12 mg subcutaneously once daily<br><br>Tablets: 450 mg orally once daily in the morning<br><br>• Moderate to severe renal impairment (CrCl <60 mL/min): reduce subcutaneous dose to 6 mg once daily (one-half usual dose); reduce oral dose to 150 mg once daily<br><br>• Hepatic impairment: for RELISTOR tablets in patients with moderate or severe hepatic impairment: 150 mg once daily. When considering dose adjustment of RELISTOR injection in patients with severe hepatic impairment, follow reduced weight-based dosing:<br>o Weight <38 kg: 0.075 mg/kg<br>o Weight 38 kg to <62 kg: 4 mg<br>o Weight 62 kg to 114 kg: 6 mg<br>o >114 kg: 0.075 mg/kg<br><br>OIC in advanced illness (injection; subcutaneous dosing): weight-based dosing once every other day, as needed (max of once daily): | Inject subcutaneously in the upper arm, abdomen, or thigh.<br><br>Rotate injection sites.<br><br>Be within close proximity to toilet facilities after administration.<br><br>Discontinue maintenance laxative therapy prior to initiating therapy with RELISTOR.<br><br>Discontinue RELISTOR when opioid pain medication is discontinued.<br><br>Pre-filled syringes only should be used for patients taking 8 mg or 12 mg dose.<br><br>Take RELISTOR tablets with water on an empty stomach at least 30 minutes before the first meal of the day. |

| Drug | Dosage Form: Strength | Usual Recommended Dose | Administration Considerations |
|---|---|---|---|
| | | • Weight <38 kg: 0.15 mg/kg<br>• Weight 38 kg to <62 kg: 8 mg<br>• Weight 62 kg to 114 kg: 12 mg<br>• >114 kg: 0.15 mg/kg<br><br>• Moderate to severe renal impairment (CrCl <60 mL/min): reduce to one subcutaneous dose every other day based on weight, as needed<br>o Weight <38 kg: 0.075 mg/kg<br>o Weight 38 kg to <62 kg: 4 mg<br>o Weight 62 kg to 114 kg: 6 mg<br>o >114 kg: 0.075 mg/kg | |
| SYMPROIC (naldemedine) | Tablet:<br>0.2 mg | OIC in chronic non-cancer pain:<br>0.2 mg once daily | Take with or without food.<br><br>Patients taking opioids < 4 weeks may be less responsive to treatment.<br><br>Discontinue SYMPROIC when opioid pain medication is discontinued. |
| TRULANCE (plecanatide) | Tablet:<br>3 mg | CIC: 3 mg once daily | Take with or without food.<br><br>For adult patients with swallowing difficulties, can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. |
| VIBERZI (eluxadoline) | Tablet:<br>75 mg<br>100 mg | Treatment of IBS-D in adults:<br>100 mg twice daily<br><br>75 mg twice daily in select patients who:<br>• do not have a gallbladder<br>• are unable to tolerate the 100 mg dose<br>• are receiving concomitant OATP1B1 inhibitors<br>• have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment | Take with food<br><br>Discontinue treatment in patients who develop severe constipation for more than four days. |
| XIFAXAN (rifaximin) | Tablet:<br>200 mg<br>550 mg | TD:<br>200 mg three times daily for three days<br><br>Hepatic encephalopathy:<br>550 mg twice daily<br><br>IBS-D:<br>550 mg three times daily for 14 days | Take with or without food.<br><br>Patients with IBS-D who experience recurrence may be retreated up to two times with the same regimen.<br><br>Do not use in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*. |

## SPECIAL POPULATIONS

**Table 4. Special Populations**

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy* and Nursing |
| AMITIZA (lubiprostone) | The efficacy among those ≥65 years was consistent with the overall study population of CIC. Clinical trials of OIC had insufficient numbers of older patients to determine if differences exist.<br><br>Safety profile among those ≥65 years was consistent with the overall study population of IBS-C. | Safety and efficacy have not been established. | No dosage adjustment required. | CIC or OIC with moderate impairment (Child-Pugh Class B): recommended dose is 16 mcg twice daily†<br><br>CIC or OIC with severe impairment (Child-Pugh Class D): recommended dose is 8 mcg twice daily†<br><br>IBS-C with severe impairment (Child-Pugh Class C): recommended dose is 8 mcg once daily† | Pregnancy Category C<br><br>Unknown whether excreted in breast milk; use with caution. |
| LINZESS (linaclotide) | Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients. | Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to <18 years. | No dosage adjustment required. | No dosage adjustment required. | Not categorized‡<br><br>Unknown whether excreted in breast milk; use with caution. |
| LOTRONEX (alosetron) | Use with caution in patients ≥65 years due to risk for constipation. | Safety and efficacy have not been established. | No dosage adjustment required. | Use with caution in mild or moderate impairment; avoid use in severe impairment. | Pregnancy category B<br><br>Unknown whether excreted in breast milk; use with caution. |
| MOVANTIK (naloxegol) | No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients.<br><br>No dosage adjustments are required in older patients. | Safety and efficacy have not been established. | Reduce starting dose to 12.5 once daily in patients with CrCl <60 mL/min. No dose adjustments are required for mild renal impairment. | Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment. | Pregnancy Category C<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. |
| RELISTOR (methylnal- | No overall differences in effectiveness were observed between patients | Safety and efficacy have | Reduce dose in patients with CrCl <60 | Reduce dose in patients with OIC in chronic non-cancer | Not categorized‡ |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy* and Nursing |
| trexone bromide) | at least 65 years of age and younger patients.<br><br>No dosage adjustments are required in older patients. | not been established. | mL/min (See Table 3). No dose adjustments are required for mild renal impairment. | pain and moderate or severe hepatic impairment (see Table 3). No dose adjustments are required for mild hepatic impairment. | Unknown whether excreted in breast milk; breastfeeding not recommended during treatment. |
| SYMPROIC (naldemedine) | No overall differences in safety or effectiveness between patients at least 65 years of age and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out. | Safety and efficacy have not been established. | No dosing adjustments necessary. | Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustments are required for mild or moderate hepatic impairment. | Not categorized‡<br><br>Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug. If drug is discontinued, breastfeeding can be resumed 3 days after the final dose. |
| TRULANCE (plecanatide) | Clinical studies did not include sufficient numbers of patients ≥65 years to determine whether they respond differently from younger patients. | Contra-indicated in <6 years. Boxed Warning to avoid use in children ages 6 to 17 years. | No dosing adjustments necessary. | No dosing adjustments necessary. | Not categorized‡<br><br>Unknown whether excreted in breast milk; use with caution. |
| VIBERZI (eluxadoline) | No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients. | Safety and efficacy have not been established. | No information available. | Reduce the dose to 75 mg twice daily with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment.<br><br>Do not use in patients with severe hepatic impairment (Child-Pugh Class C). | No studies in pregnant women.<br><br>Unknown whether excreted in breast milk; use with caution. |
| XIFAXAN (rifaximin) | No overall differences in effectiveness were observed between patients at least 65 years of age and younger patients. | Safety and efficacy have not been established in pediatric patients less | Studies in patients with renal impairment have not | No dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment. | No studies in pregnant women.<br><br>Unknown whether |

| Drug | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly | Pediatrics | Renal Dysfunction | Hepatic Dysfunction | Pregnancy* and Nursing |
| | Clinical studies with XIFAXAN for TD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects. | than 12 years of age with TD or in patients less than 18 years of age for HE and IBS-D. | been conducted. | | excreted in breast milk, effects on breastfed infant, or effects on milk production; use with caution. |

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of response.
‡In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

## CONCLUSION

- Irritable Bowel Syndrome (IBS) is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (WGO, 2015; Quigley et al, 2012).
- Irritable Bowel Syndrome has four subtypes depending on the change in bowel habits – Irritable Bowel Syndrome-Diarrhea (IBS-D), Irritable Bowel Syndrome-Constipation (IBS-C), mixed type having diarrhea and constipation (IBS-M), or unspecified (IBS-U). IBS-C symptoms include abdominal pain and bloating, less than three bowel movements per week, straining, and feeling of incomplete evacuation of bowels.
- Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (Andresen et al, 2008; Ford et al, 2009).
- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- Guidelines on management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents." Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (AGA, 2013; Bharucha et al, 2013; Chang et al, 2014; Lindberg et al, 2010).
- The American College of Gastroenterology monograph on the management of IBS and CIC notes that rifaximin is effective in reducing IBS symptoms and bloating in IBS-D; alosetron is effective in females with IBS-D; and linaclotide and lubiprostone are each superior to placebo for the treatment of IBS-C. In addition, linaclotide and lubiprostone are each effective for the treatment of CIC (Ford et al, 2014).
- AMITIZA (lubiprostone) is currently the only chloride channel activator commercially available. It selectively activates intestinal chloride channels, increasing intestinal fluid secretion and delaying gastric emptying.
- In clinical trials, AMITIZA has demonstrated efficacy in the treatment of CIC as well as IBS-C in women, with improvement in SBMs, straining, constipation severity, stool consistency, and global assessment of constipation (Drossman et al, 2007; Drossman et al, 2009; Johanson et al, 2004; Johanson et al, 2005; Johanson et al, 2007; Johanson et al, 2008a; Johanson et al, 2008b).
- LINZESS (linaclotide) is a guanylate cyclase-C agonist. LINZESS acts locally in the intestine to accelerate intestinal transit, increase intestinal secretions and reduce intestinal pain. LINZESS has been shown in placebo-controlled studies to be effective in improving constipation related to IBS-C and CIC (Li et al, 2016; Nelson et al, 2017; Videlock et al, 2013).
- TRULANCE (plecanatide) is approved by the FDA for treatment of CIC. Similar to LINZESS, it is a guanylate cyclase-C agonist. In two randomized control trials, TRULANCE 3 mg demonstrated a significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Miner et al [abstract], 2016; Miner et al, 2017).
- Agents approved for use in OIC include MOVANTIK (naloxegol), SYMPROIC (naldemedine), and RELISTOR (methylnaltrexone) in patients with chronic non-cancer pain. RELISTOR is also approved in patients with advanced illness (including cancer) receiving palliative care and unresponsive to laxative therapy. SYMPROIC, RELISTOR,

MOVANTIK and AMITIZA, are also indicated in patients with chronic pain related to prior cancer or its treatment in those who do not require frequent (e.g., weekly) opioid dosage escalation.

- LOTRONEX (alosetron), a 5-HT receptor antagonist, has been shown to reduce pain, abdominal discomfort, urgency, and diarrhea in patients with IBS as demonstrated in several placebo-controlled trials (Andresen et al, 2008; Bardhan et al, 2000; Camilleri et al, 2000; Camilleri et al, 2001; Chey et al, 2004; Cremonini et al, 2003; Ford et al, 2009; Lembo et al, 2001; Lembo et al, 2004; Krause et al, 2007; Rahimi et al, 2008; Watson et al, 2001).
- Use of LOTRONEX is limited to female patients with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, a boxed warning regarding gastrointestinal adverse events has been added to the alosetron prescribing information. The medication also has an approved REMS program.

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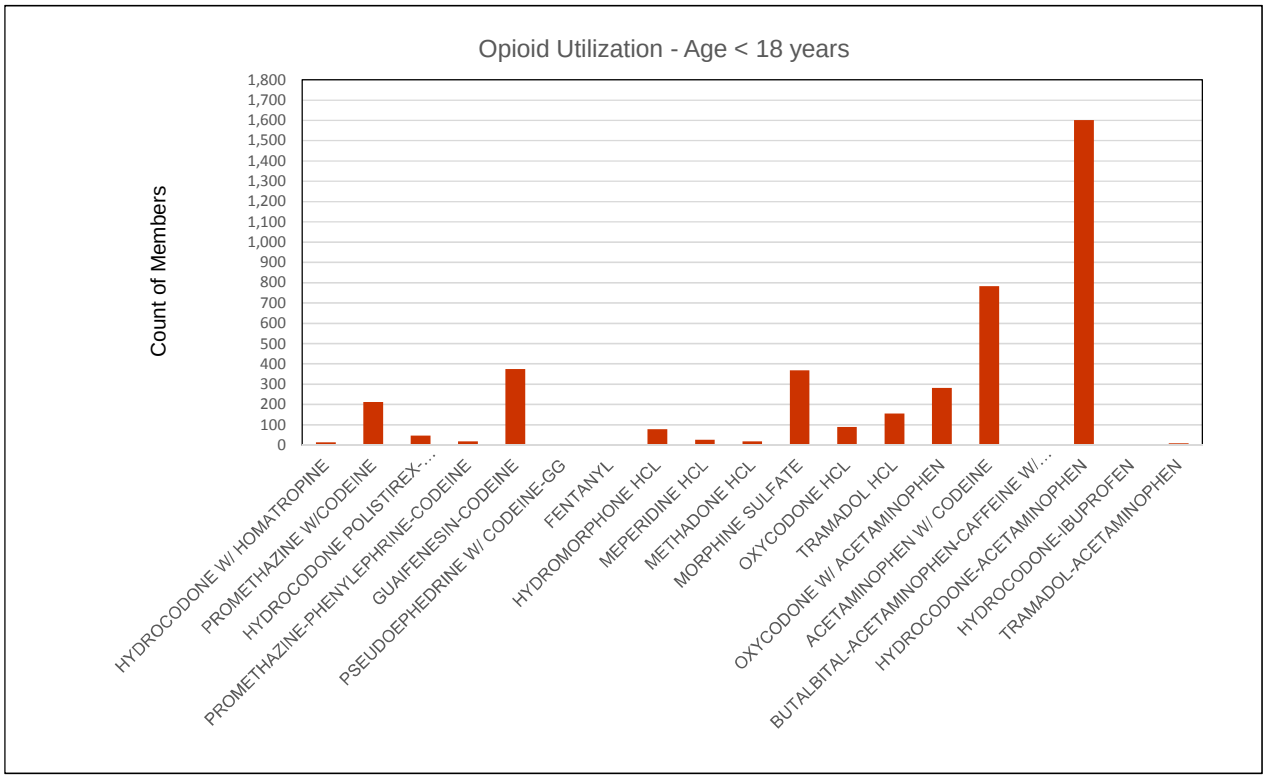
Publication Date: September 28, 2017

## Top 50 Orphan Drug

December 1, 2016 - November 30, 2017

| Row Labels | Sum of Pharmacy Due Amount | Sum of Total Rxs | Sum of Utilizing Members |
|---|---|---|---|
| HARVONI TAB 90-400MG | $ 7,146,234.06 | 418 | 126 |
| NOVOSEVEN RT INJ 5MG | $ 6,888,111.87 | 11 | 2 |
| SPINRAZA INJ 12MG/5ML | $ 4,250,284.76 | 28 | 10 |
| NOVOSEVEN RT INJ 2MG | $ 2,755,311.87 | 11 | 2 |
| EXONDYS 51 SOL 100/2ML | $ 2,373,115.27 | 31 | 4 |
| PULMOZYME SOL 1MG/ML | $ 2,229,050.81 | 683 | 140 |
| H.P. ACTHAR INJ 80UNIT | $ 2,108,163.95 | 35 | 11 |
| SOLIRIS INJ 10MG/ML | $ 1,990,537.00 | 88 | 5 |
| ELAPRASE INJ 6MG/3ML | $ 1,822,289.16 | 139 | 9 |
| GENOTROPIN INJ 12MG | $ 1,482,554.83 | 287 | 44 |
| ORKAMBI TAB 200-125 | $ 1,430,192.75 | 70 | 10 |
| NEULASTA INJ 6MG/0.6M | $ 1,288,978.28 | 254 | 128 |
| OCTAGAM INJ 10GM | $ 1,105,822.33 | 197 | 48 |
| LETAIRIS TAB 10MG | $ 931,287.62 | 106 | 17 |
| AVASTIN INJ | $ 881,344.66 | 1159 | 455 |
| TOBRAMYCIN NEB 300/5ML | $ 832,641.62 | 343 | 118 |
| BOTOX INJ 200UNIT | $ 825,854.11 | 509 | 284 |
| ACTIMMUNE INJ 2MU/0.5 | $ 805,229.73 | 17 | 3 |
| HUMIRA KIT 40MG/0.8 | $ 791,215.45 | 161 | 42 |
| OPDIVO INJ 40MG/4ML | $ 781,342.14 | 240 | 55 |
| HERCEPTIN INJ 440MG | $ 780,761.43 | 213 | 52 |
| KEYTRUDA INJ 100MG/4M | $ 757,072.92 | 100 | 34 |
| COPAXONE INJ 40MG/ML | $ 756,811.40 | 130 | 26 |
| PRIVIGEN INJ 20GRAMS | $ 728,168.16 | 48 | 6 |
| ONFI SUS 2.5MG/ML | $ 727,430.85 | 455 | 85 |
| HELIXATE FS INJ 2000UNIT | $ 689,363.13 | 6 | 2 |
| ONFI TAB 10MG | $ 679,777.03 | 663 | 128 |
| AFINITOR TAB 5MG | $ 642,279.22 | 42 | 7 |
| SABRIL POW 500MG | $ 608,228.80 | 66 | 12 |
| SOVALDI TAB 400MG | $ 602,452.76 | 28 | 8 |
| ONFI TAB 20MG | $ 591,969.57 | 440 | 79 |
| RITUXAN INJ 100MG | $ 583,348.03 | 141 | 54 |
| SUBOXONE MIS 8-2MG | $ 580,691.14 | 2390 | 392 |
| NORDITROPIN INJ 10/1.5ML | $ 564,043.13 | 155 | 23 |
| ALPROLIX INJ 4000UNIT | $ 547,499.55 | 11 | 2 |
| RAVICTI LIQ 1.1GM/ML | $ 537,247.72 | 16 | 2 |
| XIFAXAN TAB 550MG | $ 535,693.19 | 408 | 148 |
| ORFADIN CAP 20MG | $ 526,989.07 | 5 | 1 |
| REVLIMID CAP 10MG | $ 505,701.45 | 35 | 6 |
| EXONDYS 51 SOL 500/10ML | $ 480,050.85 | 5 | 1 |
| WILATE INJ | $ 465,592.47 | 15 | 6 |
| REMICADE INJ 100MG | $ 464,667.30 | 131 | 40 |
| BANZEL TAB 400MG | $ 450,986.59 | 201 | 32 |
| SABRIL TAB 500MG | $ 449,137.49 | 44 | 6 |
| CAYSTON INH 75MG | $ 437,503.43 | 63 | 23 |
| RITUXAN INJ 500MG | $ 435,563.42 | 95 | 40 |
| AVASTIN INJ 400/16ML | $ 433,526.82 | 110 | 40 |
| AFINITOR TAB 2.5MG | $ 421,193.02 | 35 | 4 |
| GENOTROPIN INJ 5MG | $ 414,062.37 | 118 | 17 |
| BANZEL SUS 40MG/ML | $ 411,219.86 | 229 | 25 |
| **Grand Total** | **$ 59,528,594.44** | **11185** | **2814** |

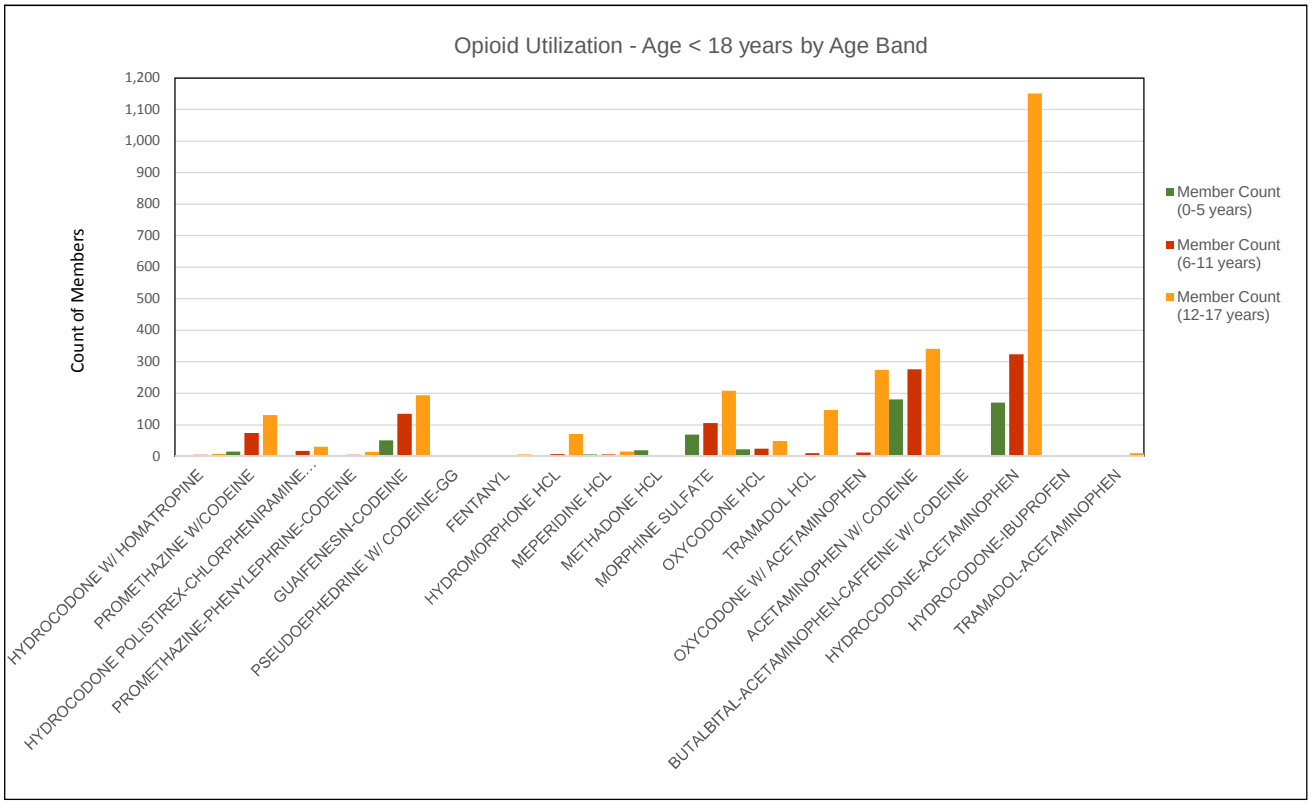
| Drug Name | Count of Utilizing Members |
|---|---|
| HYDROCODONE W/ HOMATROPINE | 14 |
| PROMETHAZINE W/CODEINE | 214 |
| HYDROCODONE POLISTIREX-CHLORPHENIRAMINE POLISTIREX | 47 |
| PROMETHAZINE-PHENYLEPHRINE-CODEINE | 19 |
| GUAIFENESIN-CODEINE | 375 |
| PSEUDOEPHEDRINE W/ CODEINE-GG | 1 |
| FENTANYL | 4 |
| HYDROMORPHONE HCL | 79 |
| MEPERIDINE HCL | 27 |
| METHADONE HCL | 19 |
| MORPHINE SULFATE | 369 |
| OXYCODONE HCL | 91 |
| TRAMADOL HCL | 156 |
| OXYCODONE W/ ACETAMINOPHEN | 282 |
| ACETAMINOPHEN W/ CODEINE | 784 |
| BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE | 4 |
| HYDROCODONE-ACETAMINOPHEN | 1,601 |
| HYDROCODONE-IBUPROFEN | 1 |
| TRAMADOL-ACETAMINOPHEN | 10 |



Opioid Utilization for Members Under 18 Years Old

November 1, 2016 - October 31, 2017

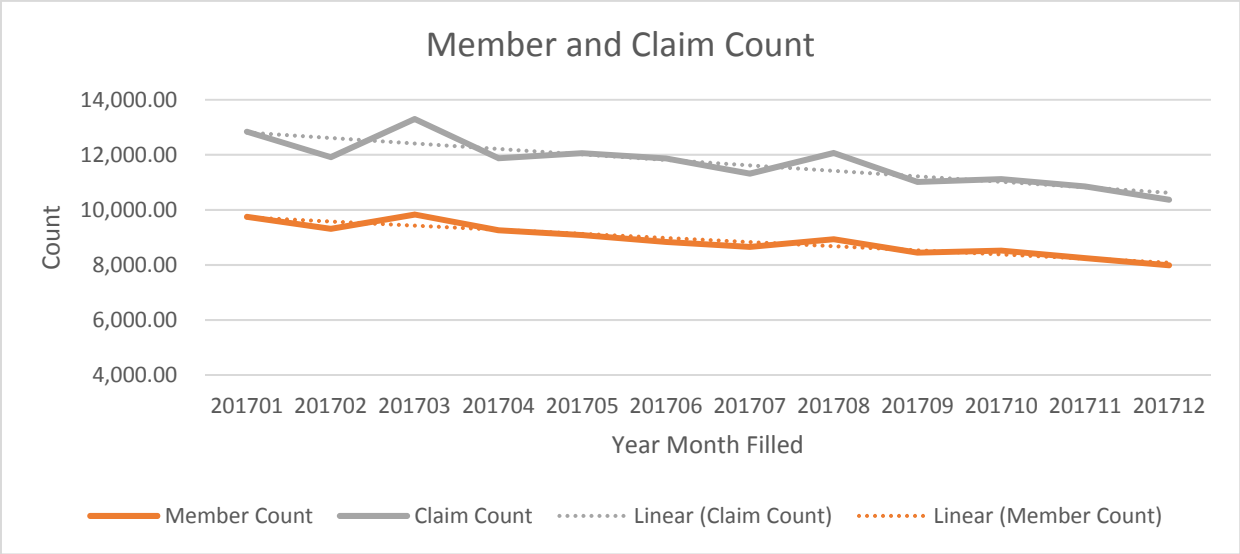
| Drug Name | Member Count (0-5 years) | Member Count (6-11 years) | Member Count (12-17 years) |
|---|---|---|---|
| HYDROCODONE W/ HOMATROPINE | 1 | 5 | 8 |
| PROMETHAZINE W/CODEINE | 15 | 74 | 131 |
| HYDROCODONE POLISTIREX-CHLORPHENIRAMINE POLISTIREX | 2 | 17 | 30 |
| PROMETHAZINE-PHENYLEPHRINE-CODEINE | 1 | 5 | 14 |
| GUAIFENESIN-CODEINE | 51 | 135 | 194 |
| PSEUDOEPHEDRINE W/ CODEINE-GG | 1 | 0 | 0 |
| FENTANYL | 0 | 0 | 6 |
| HYDROMORPHONE HCL | 4 | 7 | 71 |
| MEPERIDINE HCL | 6 | 6 | 15 |
| METHADONE HCL | 19 | 0 | 3 |
| MORPHINE SULFATE | 69 | 106 | 208 |
| OXYCODONE HCL | 22 | 24 | 49 |
| TRAMADOL HCL | 0 | 10 | 147 |
| OXYCODONE W/ ACETAMINOPHEN | 2 | 12 | 274 |
| ACETAMINOPHEN W/ CODEINE | 181 | 276 | 341 |
| BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE | 0 | 0 | 4 |
| HYDROCODONE-ACETAMINOPHEN | 171 | 324 | 1,151 |
| HYDROCODONE-IBUPROFEN | 0 | 1 | 0 |
| TRAMADOL-ACETAMINOPHEN | 0 | 0 | 10 |

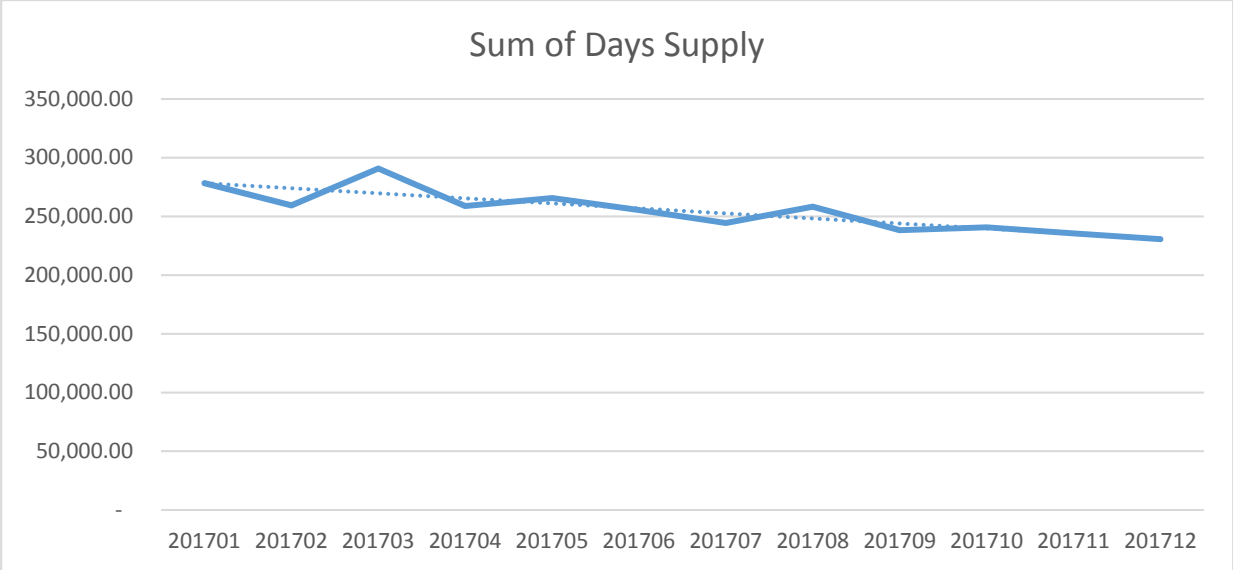


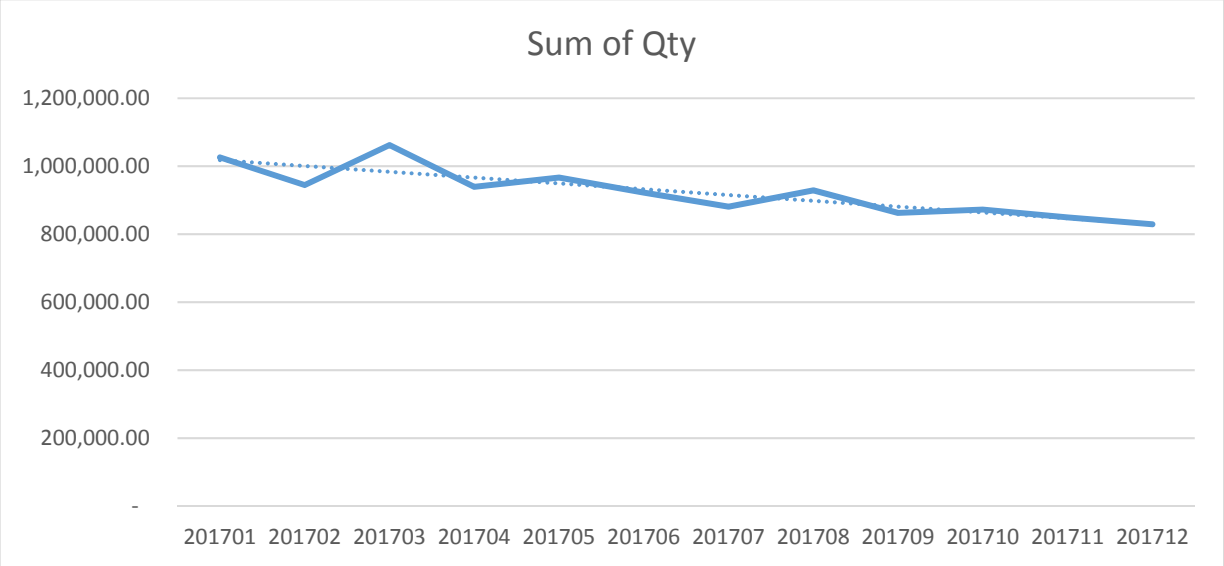
**Opioid Utilization**

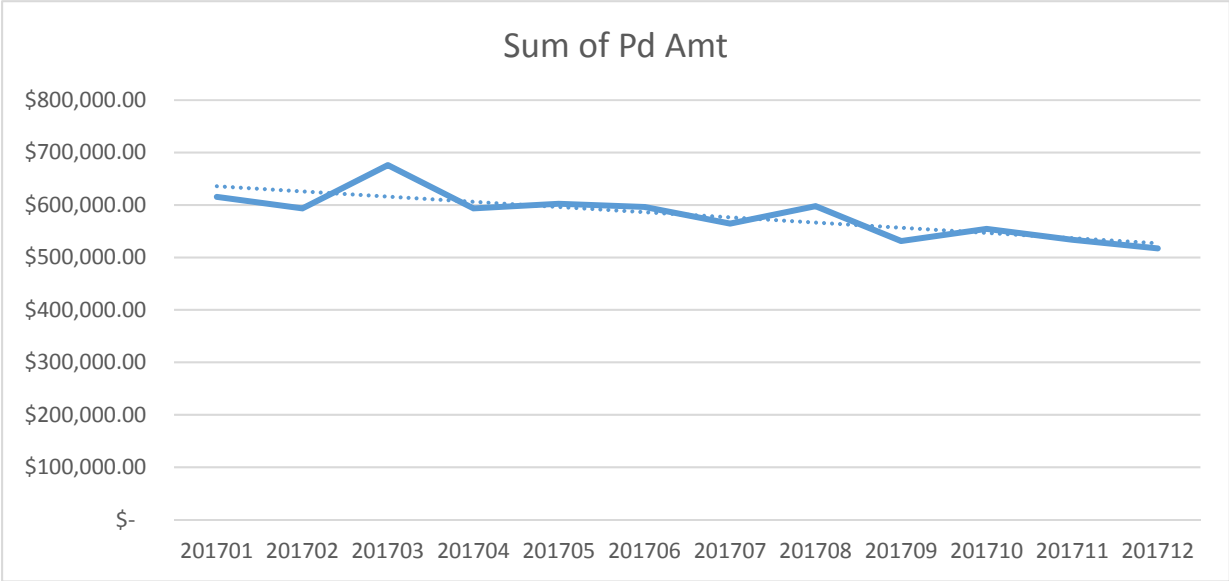
January 1, 2017 - December 31, 2017

| Year Month Filled | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| 201701 | 9,745.00 | 12,841.00 | 278,303.00 | 1,026,048.00 | $ 615,550.09 |
| 201702 | 9,311.00 | 11,913.00 | 259,460.00 | 944,694.25 | $ 593,640.48 |
| 201703 | 9,831.00 | 13,302.00 | 290,813.00 | 1,062,291.70 | $ 676,039.89 |
| 201704 | 9,258.00 | 11,876.00 | 258,869.00 | 939,597.70 | $ 593,564.85 |
| 201705 | 9,084.00 | 12,061.00 | 265,723.00 | 966,720.70 | $ 602,405.47 |
| 201706 | 8,832.00 | 11,867.00 | 255,450.00 | 922,730.00 | $ 596,342.97 |
| 201707 | 8,655.00 | 11,317.00 | 244,339.00 | 881,363.50 | $ 564,725.24 |
| 201708 | 8,931.00 | 12,064.00 | 258,247.00 | 929,117.00 | $ 597,967.30 |
| 201709 | 8,446.00 | 11,015.00 | 238,251.00 | 862,621.50 | $ 531,185.37 |
| 201710 | 8,522.00 | 11,118.00 | 240,713.00 | 872,643.00 | $ 554,505.93 |
| 201711 | 8,248.00 | 10,849.00 | 235,519.00 | 849,795.00 | $ 533,627.50 |
| 201712 | 7,987.00 | 10,368.00 | 230,656.00 | 829,227.44 | $ 517,223.51 |




Sum of Qty
1,200,000.00
1,000,000.00
800,000.00
600,000.00
400,000.00
200,000.00
-
201701 201702 201703 201704 201705 201706 201707 201708 201709 201710 201711 201712


Sum of Pd Amt
$800,000.00
$700,000.00
$600,000.00
$500,000.00
$400,000.00
$300,000.00
$200,000.00
$100,000.00
$-
201701 201702 201703 201704 201705 201706 201707 201708 201709 201710 201711 201712

Top 10 Opioids by Quantity
January 1, 2017 - December 31, 2017

| Sum of MetricDecimalQty | Column Labels | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Row Labels** | **201701** | **201702** | **201703** | **201704** | **201705** | **201706** | **201707** | **201708** | **201709** | **201710** | **201711** | **201712** | **Grand Total** |
| HYDROCODONE/ACETAMINOPHEN | 351,025.00 | 318,954.00 | 358,938.00 | 322,154.00 | 329,219.00 | 310,465.00 | 299,574.00 | 314,383.00 | 288,162.00 | 296,866.00 | 286,193.00 | 280,538.00 | 3,756,471.00 |
| OXYCODONE HCL | 198,055.00 | 185,739.75 | 211,073.20 | 188,869.20 | 191,556.80 | 192,452.00 | 179,857.00 | 190,653.00 | 178,594.00 | 182,465.00 | 178,940.00 | 176,991.00 | 2,255,245.95 |
| OXYCODONE/ACETAMINOPHEN | 194,619.00 | 184,844.00 | 201,696.00 | 177,672.00 | 185,087.00 | 179,265.00 | 169,303.00 | 179,807.00 | 168,354.00 | 168,391.00 | 158,269.00 | 154,760.00 | 2,122,067.00 |
| TRAMADOL HCL | 86,768.00 | 84,000.00 | 92,599.00 | 81,938.00 | 85,610.00 | 79,200.00 | 78,508.00 | 87,318.00 | 77,749.00 | 74,803.00 | 76,884.00 | 70,356.00 | 975,733.00 |
| MORPHINE SULFATE ER | 54,030.00 | 50,231.00 | 57,618.00 | 48,301.00 | 50,699.00 | 49,315.00 | 47,365.00 | 47,823.00 | 45,210.00 | 44,193.00 | 42,819.00 | 41,976.00 | 579,580.00 |
| METHADONE HCL | 26,981.00 | 24,881.00 | 27,535.00 | 25,951.00 | 26,241.30 | 22,538.00 | 22,328.00 | 23,160.00 | 21,242.00 | 22,436.00 | 20,968.00 | 21,436.90 | 285,698.20 |
| HYDROCODONE BITARTRATE/AC | 29,969.00 | 22,818.00 | 29,272.00 | 21,164.00 | 25,737.00 | 20,031.00 | 21,606.00 | 18,023.00 | 21,188.00 | 21,021.00 | 20,173.00 | 18,361.00 | 269,363.00 |
| ACETAMINOPHEN/CODEINE | 17,624.00 | 15,427.00 | 17,970.00 | 17,207.00 | 14,357.00 | 11,815.50 | 11,251.00 | 13,109.50 | 11,735.00 | 11,235.00 | 11,784.00 | 10,269.04 | 163,784.04 |
| MORPHINE SULFATE | 11,970.00 | 10,416.00 | 12,323.00 | 10,924.00 | 12,009.00 | 12,069.00 | 10,199.00 | 11,756.00 | 10,425.00 | 9,016.00 | 10,220.00 | 11,889.00 | 133,216.00 |
| HYDROMORPHONE HCL | 13,167.00 | 10,880.00 | 12,109.00 | 10,129.00 | 11,483.00 | 10,883.00 | 8,456.00 | 8,858.00 | 8,653.00 | 8,580.00 | 7,853.00 | 7,945.00 | 118,996.00 |
| **Grand Total** | **984,208.00** | **908,190.75** | **1,021,133.20** | **904,309.20** | **931,999.10** | **888,033.50** | **848,447.00** | **894,890.50** | **831,312.00** | **839,006.00** | **814,103.00** | **794,521.94** | **10,660,154.19** |

**Top 10 Prescriber of Opioids**

Jan 1, 2017 - Dec 31, 2017

**By member count**

| Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| E | 875 | 981 | 4,218 | 16,953 | $ 10,964.86 |
| S | 410 | 489 | 1,907 | 11,865 | $ 6,723.21 |
| O | 298 | 815 | 23,306 | 77,268 | $ 26,983.03 |
| T | 266 | 663 | 19,480 | 65,507 | $ 26,539.18 |
| B | 246 | 514 | 15,312 | 52,684 | $ 20,711.70 |
| P | 238 | 1,549 | 25,869 | 141,168 | $ 46,849.07 |
| J | 238 | 354 | 940 | 5,253 | $ 4,130.41 |
| R | 237 | 516 | 15,163 | 51,089 | $ 19,134.84 |
| G | 234 | 524 | 14,366 | 44,595 | $ 17,530.38 |
| U | 234 | 478 | 13,815 | 43,405 | $ 16,578.46 |

**by count of claims**

| Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| W | 201 | 1,958 | 57,811 | 183,411 | $ 166,361.98 |
| P | 238 | 1,549 | 25,869 | 141,168 | $ 46,849.07 |
| Z | 124 | 1,529 | 44,949 | 173,153 | $ 89,818.90 |
| L | 172 | 1,389 | 40,862 | 124,182 | $ 124,862.41 |
| N | 124 | 1,249 | 33,626 | 101,633 | $ 399,682.40 |
| A | 187 | 1,243 | 36,047 | 144,347 | $ 105,463.19 |
| I | 167 | 1,207 | 33,660 | 115,530 | $ 90,066.58 |
| Y | 182 | 1,205 | 33,664 | 116,582 | $ 69,450.65 |
| K | 230 | 1,194 | 35,238 | 102,952 | $ 87,510.23 |
| C | 187 | 1,085 | 32,511 | 105,064 | $ 85,365.53 |

**By Days Supply**

| Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| W | 201 | 1,958 | 57,811 | 183,411 | $ 166,361.98 |
| Z | 124 | 1,529 | 44,949 | 173,153 | $ 89,818.90 |
| L | 172 | 1,389 | 40,862 | 124,182 | $ 124,862.41 |
| A | 187 | 1,243 | 36,047 | 144,347 | $ 105,463.19 |
| K | 230 | 1,194 | 35,238 | 102,952 | $ 87,510.23 |
| Y | 182 | 1,205 | 33,664 | 116,582 | $ 69,450.65 |
| I | 167 | 1,207 | 33,660 | 115,530 | $ 90,066.58 |
| N | 124 | 1,249 | 33,626 | 101,633 | $ 399,682.40 |
| C | 187 | 1,085 | 32,511 | 105,064 | $ 85,365.53 |
| V | 136 | 1,036 | 29,380 | 101,195 | $ 60,685.15 |

**By Sum of Qty**

| Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| W | 201 | 1,958 | 57,811 | 183,411 | $ 166,361.98 |
| Z | 124 | 1,529 | 44,949 | 173,153 | $ 89,818.90 |
| A | 187 | 1,243 | 36,047 | 144,347 | $ 105,463.19 |
| P | 238 | 1,549 | 25,869 | 141,168 | $ 46,849.07 |
| L | 172 | 1,389 | 40,862 | 124,182 | $ 124,862.41 |
| Y | 182 | 1,205 | 33,664 | 116,582 | $ 69,450.65 |
| I | 167 | 1,207 | 33,660 | 115,530 | $ 90,066.58 |
| C | 187 | 1,085 | 32,511 | 105,064 | $ 85,365.53 |
| K | 230 | 1,194 | 35,238 | 102,952 | $ 87,510.23 |
| N | 124 | 1,249 | 33,626 | 101,633 | $ 399,682.40 |

**By Pharmacy Paid Amt**

| Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|
| N | 124 | 1,249 | 33,626 | 101,633 | $ 399,682.40 |
| H | 10 | 64 | 1,678 | 7,010 | $ 236,519.05 |
| D | 37 | 352 | 10,013 | 33,295 | $ 182,083.73 |
| W | 201 | 1,958 | 57,811 | 183,411 | $ 166,361.98 |
| L | 172 | 1,389 | 40,862 | 124,182 | $ 124,862.41 |
| M | 29 | 74 | 1,697 | 5,801 | $ 121,564.62 |
| Q | 75 | 740 | 11,565 | 27,006 | $ 110,064.26 |
| X | 81 | 545 | 15,710 | 52,766 | $ 106,203.64 |
| A | 187 | 1,243 | 36,047 | 144,347 | $ 105,463.19 |
| F | 14 | 189 | 5,408 | 21,215 | $ 102,402.51 |

**Top 10 Prescriber with Specialty**

Jan 1, 2017 - Dec 31, 2017

**By count of claims**

| Specialty | Degree | City | Prescriber ID | Member Count | Claim Count | Sum of Days Supply | Sum of Qty | Sum of Pd Amt |
|---|---|---|---|---|---|---|---|---|
| Pain Management | NP | Las Vegas | W | 201 | 1,958 | 57,811 | 183,411 | $ 166,361.98 |
| | NP | Fallon | P | 238 | 1,549 | 25,869 | 141,168 | $ 46,849.07 |
| | PA | Las Vegas | Z | 124 | 1,529 | 44,949 | 173,153 | $ 89,818.90 |
| | PA | Las Vegas | L | 172 | 1,389 | 40,862 | 124,182 | $ 124,862.41 |
| Pain Management | MD | Carson City | N | 124 | 1,249 | 33,626 | 101,633 | $ 399,682.40 |
| Anesthesiology | DO | Reno | A | 187 | 1,243 | 36,047 | 144,347 | $ 105,463.19 |
| | PA | Las Vegas | I | 167 | 1,207 | 33,660 | 115,530 | $ 90,066.58 |
| | PA | Las Vegas | Y | 182 | 1,205 | 33,664 | 116,582 | $ 69,450.65 |
| | PA | Las Vegas | K | 230 | 1,194 | 35,238 | 102,952 | $ 87,510.23 |
| Pain Management | MD | Las Vegas | C | 187 | 1,085 | 32,511 | 105,064 | $ 85,365.53 |

## Top 10 Drug Group by Paid Amt

### Q1 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 85 | HEMATOLOGICAL AGENTS - MISC.* | 3,662 | $ 9,325,628.04 |
| 12 | ANTIVIRALS* | 5,203 | $ 7,266,435.97 |
| 27 | ANTIDIABETICS* | 27,611 | $ 6,425,317.42 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 32,411 | $ 5,892,304.25 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 44,908 | $ 4,796,359.79 |
| 21 | ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES | 4,068 | $ 3,991,362.58 |
| 72 | ANTICONVULSANTS* | 46,753 | $ 3,945,512.52 |
| 30 | ENDOCRINE AND METABOLIC AGENTS - MISC.* | 4,017 | $ 2,759,685.73 |
| 62 | PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT | 5,400 | $ 2,322,888.21 |
| 61 | ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX | 10,959 | $ 2,284,652.13 |

### Q2 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 85 | HEMATOLOGICAL AGENTS - MISC.* | 3,457 | $ 10,924,453.46 |
| 12 | ANTIVIRALS* | 4,246 | $ 7,675,577.73 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 31,299 | $ 5,609,573.39 |
| 27 | ANTIDIABETICS* | 20,020 | $ 5,235,915.50 |
| 21 | ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES | 4,240 | $ 5,147,044.39 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 41,941 | $ 4,762,202.79 |
| 72 | ANTICONVULSANTS* | 45,627 | $ 3,982,719.66 |
| 74 | NEUROMUSCULAR AGENTS* | 337 | $ 2,794,526.15 |
| 30 | ENDOCRINE AND METABOLIC AGENTS - MISC.* | 3,899 | $ 2,601,347.46 |
| 62 | PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT | 5,248 | $ 2,268,181.85 |

### Q3 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 85 | HEMATOLOGICAL AGENTS - MISC.* | 3,278 | $ 10,640,081.06 |
| 12 | ANTIVIRALS* | 3,884 | $ 6,931,296.33 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 31,096 | $ 5,817,206.78 |
| 27 | ANTIDIABETICS* | 18,872 | $ 5,324,357.36 |
| 21 | ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES | 4,225 | $ 5,248,531.03 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 38,520 | $ 4,618,115.93 |
| 72 | ANTICONVULSANTS* | 44,913 | $ 4,004,509.88 |
| 30 | ENDOCRINE AND METABOLIC AGENTS - MISC.* | 3,688 | $ 3,169,159.32 |
| 90 | DERMATOLOGICALS* | 17,632 | $ 2,176,520.77 |
| 62 | PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT | 5,151 | $ 2,173,017.99 |

## Top 10 Drug Group by Claim Count

### Q1 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 65 | ANALGESICS - OPIOID* | 59,662 | $ 2,086,447.21 |
| 72 | ANTICONVULSANTS* | 46,753 | $ 3,945,512.52 |
| 58 | ANTIDEPRESSANTS* | 46,102 | $ 901,813.95 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 44,908 | $ 4,796,359.79 |
| 36 | ANTIHYPERTENSIVES* | 33,497 | $ 535,039.24 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 32,411 | $ 5,892,304.25 |
| 27 | ANTIDIABETICS* | 27,611 | $ 6,425,317.42 |
| 39 | ANTIHYPERLIPIDEMICS* | 27,327 | $ 773,511.80 |
| 57 | ANTIANXIETY AGENTS* | 26,161 | $ 291,756.42 |
| 49 | ULCER DRUGS* | 25,806 | $ 1,240,036.94 |

### Q2 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 65 | ANALGESICS - OPIOID* | 57,647 | $ 1,960,118.79 |
| 72 | ANTICONVULSANTS* | 45,627 | $ 3,982,719.66 |
| 58 | ANTIDEPRESSANTS* | 43,789 | $ 846,962.47 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 41,941 | $ 4,762,202.79 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 31,299 | $ 5,609,573.39 |
| 57 | ANTIANXIETY AGENTS* | 25,761 | $ 283,662.72 |
| 49 | ULCER DRUGS* | 24,549 | $ 1,176,384.46 |
| 36 | ANTIHYPERTENSIVES* | 24,325 | $ 359,353.24 |
| 39 | ANTIHYPERLIPIDEMICS* | 24,318 | $ 722,355.35 |
| 66 | ANALGESICS - ANTI-INFLAMMATORY* | 23,771 | $ 1,871,181.95 |

### Q3 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 65 | ANALGESICS - OPIOID* | 55,736 | $ 1,824,685.78 |
| 72 | ANTICONVULSANTS* | 44,913 | $ 4,004,509.88 |
| 58 | ANTIDEPRESSANTS* | 42,299 | $ 846,772.67 |
| 44 | ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 38,520 | $ 4,618,115.93 |
| 59 | ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 31,096 | $ 5,817,206.78 |
| 57 | ANTIANXIETY AGENTS* | 25,552 | $ 280,676.13 |
| 49 | ULCER DRUGS* | 23,688 | $ 1,128,662.84 |
| 36 | ANTIHYPERTENSIVES* | 23,578 | $ 369,229.85 |
| 66 | ANALGESICS - ANTI-INFLAMMATORY* | 23,256 | $ 1,915,622.40 |
| 39 | ANTIHYPERLIPIDEMICS* | 22,456 | $ 716,877.01 |

## Top 10 Drug Classes by Paid Amt

### Q1 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 8510 | ANTIHEMOPHILIC PRODUCTS** | 118 | $ 8,909,353.08 |
| 2710 | INSULIN** | 8,943 | $ 4,283,103.71 |
| 1235 | HEPATITIS AGENTS** | 328 | $ 3,929,771.33 |
| 4420 | SYMPATHOMIMETICS** | 30,551 | $ 3,170,155.87 |
| 1210 | ANTIRETROVIRALS** | 2,535 | $ 3,157,821.11 |
| 7260 | ANTICONVULSANTS - MISC.** | 34,315 | $ 2,705,834.35 |
| 5907 | BENZISOXAZOLES** | 7,659 | $ 2,163,906.94 |
| 6240 | MULTIPLE SCLEROSIS AGENTS** | 324 | $ 1,751,131.75 |
| 5940 | ANTIPSYCHOTICS - MISC.** | 3,090 | $ 1,472,868.59 |
| 2153 | ANTINEOPLASTIC ENZYME INHIBITORS** | 174 | $ 1,366,624.72 |

### Q2 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 8510 | ANTIHEMOPHILIC PRODUCTS** | 95 | $ 10,279,220.11 |
| 1235 | HEPATITIS AGENTS** | 343 | $ 4,431,089.27 |
| 2710 | INSULIN** | 6,311 | $ 3,446,189.72 |
| 4420 | SYMPATHOMIMETICS** | 28,438 | $ 3,166,342.54 |
| 1210 | ANTIRETROVIRALS** | 2,196 | $ 3,128,703.60 |
| 7260 | ANTICONVULSANTS - MISC.** | 33,660 | $ 2,706,848.12 |
| 5907 | BENZISOXAZOLES** | 7,364 | $ 2,091,603.88 |
| 7470 | SPINAL MUSCULAR ATROPHY AGENTS (SMA)** | 13 | $ 2,000,132.21 |
| 2135 | ANTINEOPLASTIC - ANTIBODIES** | 333 | $ 1,799,186.78 |
| 6240 | MULTIPLE SCLEROSIS AGENTS** | 304 | $ 1,671,342.11 |

### Q3 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 8510 | ANTIHEMOPHILIC PRODUCTS** | 100 | $ 9,946,107.33 |
| 1235 | HEPATITIS AGENTS** | 281 | $ 3,791,464.82 |
| 2710 | INSULIN** | 6,088 | $ 3,318,260.58 |
| 4420 | SYMPATHOMIMETICS** | 26,233 | $ 3,078,454.32 |
| 1210 | ANTIRETROVIRALS** | 2,136 | $ 3,047,759.79 |
| 7260 | ANTICONVULSANTS - MISC.** | 33,010 | $ 2,812,377.81 |
| 5907 | BENZISOXAZOLES** | 7,244 | $ 2,189,734.24 |
| 2153 | ANTINEOPLASTIC ENZYME INHIBITORS** | 230 | $ 1,578,071.49 |
| 2135 | ANTINEOPLASTIC - ANTIBODIES** | 364 | $ 1,564,842.71 |
| 6240 | MULTIPLE SCLEROSIS AGENTS** | 315 | $ 1,555,193.63 |

## Top 10 Drug Classes by Claim Count

### Q1 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 7260 | ANTICONVULSANTS - MISC.** | 34,315 | $ 2,705,834.35 |
| 6599 | OPIOID COMBINATIONS** | 33,578 | $ 810,834.57 |
| 4420 | SYMPATHOMIMETICS** | 30,551 | $ 3,170,155.87 |
| 6610 | NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* | 25,202 | $ 321,555.13 |
| 6510 | OPIOID AGONISTS** | 25,168 | $ 1,063,262.89 |
| 3940 | HMG COA REDUCTASE INHIBITORS** | 22,722 | $ 428,842.94 |
| 5816 | SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)** | 22,212 | $ 270,607.46 |
| 5710 | BENZODIAZEPINES** | 18,734 | $ 189,624.66 |
| 7510 | CENTRAL MUSCLE RELAXANTS** | 16,795 | $ 290,601.35 |
| 2210 | GLUCOCORTICOSTEROIDS** | 14,370 | $ 180,288.84 |

### Q2 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 7260 | ANTICONVULSANTS - MISC.** | 45,637 | $ 3,667,824.50 |
| 6599 | OPIOID COMBINATIONS** | 43,574 | $ 998,712.92 |
| 4420 | SYMPATHOMIMETICS** | 39,281 | $ 4,329,537.64 |
| 6510 | OPIOID AGONISTS** | 34,049 | $ 1,406,192.97 |
| 6610 | NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* | 32,205 | $ 408,779.15 |
| 5816 | SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)** | 28,866 | $ 360,187.39 |
| 3940 | HMG COA REDUCTASE INHIBITORS** | 28,068 | $ 543,311.48 |
| 5710 | BENZODIAZEPINES** | 25,010 | $ 249,237.17 |
| 7510 | CENTRAL MUSCLE RELAXANTS** | 21,710 | $ 372,188.71 |
| 2210 | GLUCOCORTICOSTEROIDS** | 18,266 | $ 355,741.10 |

### Q3 2017

| Class | Drug Class Name | Count of Claims | Pharmacy Paid |
|---|---|---|---|
| 7260 | ANTICONVULSANTS - MISC.** | 33,010 | $ 2,812,377.81 |
| 6599 | OPIOID COMBINATIONS** | 30,381 | $ 651,846.97 |
| 4420 | SYMPATHOMIMETICS** | 26,233 | $ 3,078,454.32 |
| 6510 | OPIOID AGONISTS** | 24,446 | $ 944,031.43 |
| 6610 | NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)* | 22,729 | $ 279,932.70 |
| 5816 | SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)** | 20,136 | $ 258,890.76 |
| 3940 | HMG COA REDUCTASE INHIBITORS** | 18,681 | $ 381,431.02 |
| 5710 | BENZODIAZEPINES** | 18,205 | $ 178,287.81 |
| 7510 | CENTRAL MUSCLE RELAXANTS** | 15,346 | $ 256,906.13 |
| 5025 | 5-HT3 RECEPTOR ANTAGONISTS** | 12,956 | $ 196,647.93 |

**Top 50 Drugs by Amount - Q1 2017**

| Drug Code | Drug Name | Claim Count | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|
| 8510001025 | ANTIHEMOPHILIC FACTOR RAHF-PFM | 18 | $ 3,839,329.14 | 84,192 | 12 |
| 8510001020 | ANTIHEMOPHILIC FACTOR (RECOMBINANT) | 26 | $ 2,342,506.36 | 54,693 | 23 |
| 8510002620 | COAGULATION FACTOR VIIA (RECOMBINANT) | 4 | $ 1,747,240.68 | 70,000 | 10 |
| 1235990240 | LEDIPASVIR-SOFOSBUVIR | 110 | $ 1,667,082.78 | 14 | 14 |
| 5907005010 | PALIPERIDONE PALMITATE | 870 | $ 1,540,505.35 | 1 | 21 |
| 2710400300 | INSULIN GLARGINE | 3562 | $ 1,500,640.34 | 14 | 30 |
| 1235990265 | SOFOSBUVIR-VELPATASVIR | 110 | $ 1,369,292.39 | 10 | 10 |
| 7460003500 | ETEPLIRSEN | 15 | $ 1,304,152.55 | 24 | 5 |
| 1950206000 | PALIVIZUMAB | 476 | $ 1,279,326.33 | 1 | 23 |
| 5940002310 | LURASIDONE HCL | 1297 | $ 1,254,908.36 | 19 | 16 |
| 4420101010 | ALBUTEROL SULFATE | 20177 | $ 1,134,441.48 | 36 | 14 |
| 9410003000 | GLUCOSE BLOOD | 7239 | $ 984,523.11 | 75 | 23 |
| 7260005700 | PREGABALIN | 2943 | $ 940,770.95 | 49 | 21 |
| 4420990270 | FLUTICASONE-SALMETEROL | 3098 | $ 940,038.25 | 42 | 23 |
| 6627001500 | ADALIMUMAB | 216 | $ 901,309.53 | 1 | 10 |
| 2710400500 | INSULIN LISPRO | 1515 | $ 885,555.96 | 13 | 25 |
| 4927002510 | ESOMEPRAZOLE MAGNESIUM | 3726 | $ 855,958.62 | 22 | 21 |
| 5925001500 | ARIPIPRAZOLE | 4802 | $ 807,374.79 | 16 | 15 |
| 3010002000 | SOMATROPIN | 196 | $ 759,977.48 | 2 | 11 |
| 2710400200 | INSULIN ASPART | 1351 | $ 724,327.84 | 14 | 26 |
| 5915307010 | QUETIAPINE FUMARATE | 8615 | $ 721,499.51 | 30 | 20 |
| 1910002010 | IMMUNE GLOBULIN (HUMAN) IV | 114 | $ 629,454.96 | 530 | 4 |
| 1210990429 | ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE | 276 | $ 590,289.02 | 20 | 20 |
| 4410008010 | TIOTROPIUM BROMIDE MONOHYDRATE | 2313 | $ 581,000.18 | 23 | 25 |
| 2710400600 | INSULIN DETEMIR | 1285 | $ 549,479.14 | 13 | 25 |
| 4420990241 | BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE | 2721 | $ 540,719.19 | 8 | 24 |
| 4530402000 | DORNASE ALFA | 160 | $ 527,980.89 | 49 | 17 |
| 7260003600 | LACOSAMIDE | 992 | $ 522,831.76 | 55 | 14 |
| 2153253000 | EVEROLIMUS | 28 | $ 508,688.67 | 14 | 9 |
| 6135303010 | GUANFACINE HCL (ADHD) | 1861 | $ 507,517.53 | 20 | 19 |
| 7470005000 | NUSINERSEN | 3 | $ 500,030.51 | 1 | 3 |
| 9310002500 | DEFERASIROX | 68 | $ 494,704.90 | 21 | 10 |
| 6110002510 | LISDEXAMFETAMINE DIMESYLATE | 1953 | $ 491,320.59 | 22 | 22 |
| 6240552500 | DIMETHYL FUMARATE | 73 | $ 483,939.47 | 14 | 7 |
| 7210000700 | CLOBAZAM | 390 | $ 467,317.24 | 67 | 15 |
| 1210990230 | EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE | 364 | $ 450,240.89 | 21 | 20 |
| 8240157000 | PEGFILGRASTIM | 83 | $ 447,135.96 | 0 | 4 |
| 6629003000 | ETANERCEPT | 113 | $ 446,375.49 | 2 | 12 |
| 3090685000 | IDURSULFASE | 24 | $ 432,964.43 | 14 | 6 |
| 6140002010 | METHYLPHENIDATE HCL | 2404 | $ 427,317.93 | 34 | 19 |
| 6599000220 | OXYCODONE W/ ACETAMINOPHEN | 10650 | $ 405,381.61 | 58 | 15 |
| 3090404500 | NITISINONE | 6 | $ 397,514.34 | 51 | 13 |
| 6510007510 | OXYCODONE HCL | 8937 | $ 393,651.50 | 72 | 18 |
| 9085006000 | LIDOCAINE | 1887 | $ 386,563.39 | 65 | 15 |
| 8510001510 | ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN) | 23 | $ 382,498.53 | 5,552 | 11 |
| 2755007010 | SITAGLIPTIN PHOSPHATE | 1190 | $ 379,463.48 | 29 | 29 |
| 1235308000 | SOFOSBUVIR | 17 | $ 368,836.29 | 8 | 8 |
| 3030001000 | CORTICOTROPIN | 6 | $ 363,881.02 | 2 | 2 |
| 6599170210 | HYDROCODONE-ACETAMINOPHEN | 21026 | $ 352,175.15 | 60 | 15 |
| 0700007000 | TOBRAMYCIN | 102 | $ 347,845.19 | 119 | 13 |

**Top 50 Drugs by Amount - Q2 2017**

| Drug Code | Drug Name | Claim Count | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|
| 8510001025 | ANTIHEMOPHILIC FACTOR RAHF-PFM | 19 | $ 4,369,916.59 | 99,132 | 14 |
| 8510002620 | COAGULATION FACTOR VIIA (RECOMBINANT) | 6 | $ 2,620,861.02 | 210,000 | 30 |
| 1235990240 | LEDIPASVIR-SOFOSBUVIR | 116 | $ 2,048,837.39 | 8 | 8 |
| 7470005000 | NUSINERSEN | 13 | $ 2,000,132.21 | 5 | 21 |
| 8510001020 | ANTIHEMOPHILIC FACTOR (RECOMBINANT) | 12 | $ 1,977,028.26 | 105,864 | 25 |
| 1235990265 | SOFOSBUVIR-VELPATASVIR | 118 | $ 1,786,388.20 | 7 | 7 |
| 5907005010 | PALIPERIDONE PALMITATE | 763 | $ 1,518,854.65 | 1 | 24 |
| 5940002310 | LURASIDONE HCL | 1,109 | $ 1,186,130.47 | 17 | 15 |
| 2710400300 | INSULIN GLARGINE | 2,384 | $ 1,115,309.42 | 15 | 34 |
| 4420101010 | ALBUTEROL SULFATE | 18,298 | $ 1,086,491.30 | 36 | 15 |
| 9410003000 | GLUCOSE BLOOD | 6,959 | $ 982,791.69 | 75 | 24 |
| 7260005700 | PREGABALIN | 2,793 | $ 929,163.42 | 44 | 19 |
| 4420990270 | FLUTICASONE-SALMETEROL | 2,867 | $ 918,205.04 | 43 | 23 |
| 6627001500 | ADALIMUMAB | 191 | $ 881,404.72 | 1 | 9 |
| 4927002510 | ESOMEPRAZOLE MAGNESIUM | 3,293 | $ 840,872.98 | 22 | 22 |
| 3010002000 | SOMATROPIN | 206 | $ 765,718.19 | 2 | 10 |
| 2710400500 | INSULIN LISPRO | 1,029 | $ 747,245.48 | 15 | 27 |
| 5925001500 | ARIPIPRAZOLE | 4,750 | $ 733,191.61 | 18 | 17 |
| 1910002010 | IMMUNE GLOBULIN (HUMAN) IV | 108 | $ 675,973.90 | 515 | 3 |
| 1210990429 | ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE | 259 | $ 633,591.95 | 19 | 19 |
| 5915307010 | QUETIAPINE FUMARATE | 8,209 | $ 589,994.06 | 28 | 20 |
| 7460003500 | ETEPLIRSEN | 8 | $ 582,481.36 | 19 | 6 |
| 2153253000 | EVEROLIMUS | 35 | $ 578,474.20 | 12 | 9 |
| 4410008010 | TIOTROPIUM BROMIDE MONOHYDRATE | 2,113 | $ 570,614.56 | 24 | 25 |
| 2710400200 | INSULIN ASPART | 969 | $ 567,788.62 | 15 | 29 |
| 1235990230 | ELBASVIR-GRAZOPREVIR | 48 | $ 545,144.71 | 14 | 14 |
| 4420990241 | BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE | 2,541 | $ 540,079.03 | 8 | 24 |
| 4530402000 | DORNASE ALFA | 163 | $ 536,405.25 | 47 | 16 |
| 7260003600 | LACOSAMIDE | 1,027 | $ 534,377.91 | 51 | 13 |
| 8580005000 | ECULIZUMAB | 23 | $ 525,948.00 | 107 | 1 |
| 6135303010 | GUANFACINE HCL (ADHD) | 1,810 | $ 513,496.77 | 20 | 19 |
| 7210000700 | CLOBAZAM | 401 | $ 498,776.01 | 61 | 14 |
| 9310002500 | DEFERASIROX | 67 | $ 496,752.14 | 24 | 11 |
| 6110002510 | LISDEXAMFETAMINE DIMESYLATE | 1,872 | $ 478,678.04 | 22 | 21 |
| 6240552500 | DIMETHYL FUMARATE | 70 | $ 463,542.76 | 15 | 7 |
| 9085006000 | LIDOCAINE | 2,129 | $ 459,717.09 | 85 | 16 |
| 8510001510 | ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN) | 22 | $ 452,702.31 | 8,886 | 12 |
| 1210990230 | EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE | 317 | $ 442,135.71 | 21 | 21 |
| 6140002010 | METHYLPHENIDATE HCL | 2,391 | $ 436,009.44 | 34 | 19 |
| 8240157000 | PEGFILGRASTIM | 79 | $ 433,288.68 | 0 | 3 |
| 3090685000 | IDURSULFASE | 40 | $ 423,739.34 | 8 | 3 |
| 6629003000 | ETANERCEPT | 97 | $ 419,174.40 | 2 | 12 |
| 2710400600 | INSULIN DETEMIR | 951 | $ 405,721.20 | 16 | 30 |
| 3030001000 | CORTICOTROPIN | 6 | $ 400,263.02 | 2 | 5 |
| 9037403530 | DICLOFENAC SODIUM (ACTINIC KERATOSES) | 457 | $ 398,615.67 | 217 | 20 |
| 2135303200 | IPILIMUMAB | 7 | $ 376,015.51 | 118 | 1 |
| 2133502000 | BEVACIZUMAB | 326 | $ 358,038.97 | 6 | 1 |
| 6599000220 | OXYCODONE W/ ACETAMINOPHEN | 10,154 | $ 350,216.66 | 56 | 15 |
| 6510007510 | OXYCODONE HCL | 8,512 | $ 347,380.03 | 71 | 18 |
| 2135304100 | NIVOLUMAB | 83 | $ 334,212.12 | 138 | 1 |

**Top 50 Drugs by Amount - Q3 2017**

| Drug Code | Drug Name | Claim Count | | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|---|
| 8510001025 | ANTIHEMOPHILIC FACTOR RAHF-PFM | 18.00 | $ | 3,899,376.74 | 91,616 | 14 |
| 8510002620 | COAGULATION FACTOR VIIA (RECOMBINANT) | 6.00 | $ | 2,620,861.02 | 210,000 | 30 |
| 1235990240 | LEDIPASVIR-SOFOSBUVIR | 118.00 | $ | 2,133,254.01 | 11 | 11 |
| 8510001020 | ANTIHEMOPHILIC FACTOR (RECOMBINANT) | 12.00 | $ | 1,998,921.64 | 91,780 | 20 |
| 5907005010 | PALIPERIDONE PALMITATE | 755.00 | $ | 1,653,655.12 | 1 | 24 |
| 1235990265 | SOFOSBUVIR-VELPATASVIR | 102.00 | $ | 1,476,501.70 | 8 | 8 |
| 5940002310 | LURASIDONE HCL | 1,080.00 | $ | 1,272,259.09 | 18 | 15 |
| 2710400300 | INSULIN GLARGINE | 2,277.00 | $ | 1,077,244.58 | 15 | 35 |
| 4420101010 | ALBUTEROL SULFATE | 16,649.00 | $ | 1,037,850.13 | 33 | 16 |
| 7260005700 | PREGABALIN | 2,669.00 | $ | 988,670.56 | 46 | 19 |
| 9410003000 | GLUCOSE BLOOD | 6,779.00 | $ | 973,265.80 | 76 | 25 |
| 6627001500 | ADALIMUMAB | 183.00 | $ | 894,868.87 | 1 | 9 |
| 4420990270 | FLUTICASONE-SALMETEROL | 2,642.00 | $ | 893,321.42 | 43 | 23 |
| 4927002510 | ESOMEPRAZOLE MAGNESIUM | 3,034.00 | $ | 805,679.93 | 23 | 22 |
| 5925001500 | ARIPIPRAZOLE | 4,663.00 | $ | 731,882.96 | 18 | 17 |
| 3030001000 | CORTICOTROPIN | 15.00 | $ | 727,792.55 | 2 | 3 |
| 1910002010 | IMMUNE GLOBULIN (HUMAN) IV | 137.00 | $ | 713,444.05 | 417 | 3 |
| 2710400500 | INSULIN LISPRO | 1,023.00 | $ | 709,724.40 | 15 | 28 |
| 3010002000 | SOMATROPIN | 203.00 | $ | 684,273.28 | 2 | 9 |
| 1210990429 | ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE | 320.00 | $ | 614,478.43 | 17 | 17 |
| 2153253000 | EVEROLIMUS | 37.00 | $ | 606,155.30 | 11 | 9 |
| 5915307010 | QUETIAPINE FUMARATE | 8,142.00 | $ | 595,131.16 | 29 | 20 |
| 4410008010 | TIOTROPIUM BROMIDE MONOHYDRATE | 1,924.00 | $ | 568,204.09 | 23 | 25 |
| 8240157000 | PEGFILGRASTIM | 102.00 | $ | 563,850.93 | 1 | 1 |
| 8580005000 | ECULIZUMAB | 25.00 | $ | 562,596.00 | 90 | 1 |
| 8510001510 | ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN) | 22.00 | $ | 553,982.60 | 15,450 | 19 |
| 7260003600 | LACOSAMIDE | 1,024.00 | $ | 553,165.70 | 53 | 13 |
| 4530402000 | DORNASE ALFA | 175.00 | $ | 550,790.62 | 42 | 14 |
| 2710400200 | INSULIN ASPART | 976.00 | $ | 540,071.62 | 13 | 27 |
| 4420990241 | BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE | 2,417.00 | $ | 538,996.09 | 8 | 24 |
| 7210000700 | CLOBAZAM | 392.00 | $ | 525,704.10 | 60 | 14 |
| 3090685000 | IDURSULFASE | 38.00 | $ | 498,015.68 | 10 | 4 |
| 6135303010 | GUANFACINE HCL (ADHD) | 1,800.00 | $ | 495,255.80 | 19 | 18 |
| 6629003000 | ETANERCEPT | 100.00 | $ | 477,040.91 | 2 | 13 |
| 9037403530 | DICLOFENAC SODIUM (ACTINIC KERATOSES) | 581.00 | $ | 463,675.54 | 207 | 19 |
| 6110002510 | LISDEXAMFETAMINE DIMESYLATE | 1,748.00 | $ | 445,462.31 | 22 | 21 |
| 2133502000 | BEVACIZUMAB | 316.00 | $ | 420,783.81 | 7 | 1 |
| 6140002010 | METHYLPHENIDATE HCL | 2,250.00 | $ | 412,423.83 | 34 | 19 |
| 9085006000 | LIDOCAINE | 2,216.00 | $ | 401,866.39 | 87 | 15 |
| 2135304100 | NIVOLUMAB | 93.00 | $ | 400,638.80 | 15 | 3 |
| 1210990230 | EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE | 293.00 | $ | 385,355.74 | 18 | 18 |
| 9310002500 | DEFERASIROX | 57.00 | $ | 382,737.38 | 20 | 10 |
| 4530990230 | LUMACAFTOR-IVACAFTOR | 19.00 | $ | 376,784.20 | 33 | 8 |
| 7470005000 | NUSINERSEN | 3.00 | $ | 375,030.51 | 2 | 14 |
| 2710400600 | INSULIN DETEMIR | 868.00 | $ | 374,256.46 | 13 | 27 |
| 6240552500 | DIMETHYL FUMARATE | 54.00 | $ | 368,829.18 | 16 | 8 |
| 7460003500 | ETEPLIRSEN | 6.00 | $ | 364,861.02 | 21 | 8 |
| 2755007010 | SITAGLIPTIN PHOSPHATE | 836.00 | $ | 345,196.73 | 33 | 33 |
| 1210301510 | DOLUTEGRAVIR SODIUM | 239.00 | $ | 326,196.14 | 19 | 19 |
| 6510007510 | OXYCODONE HCL | 8,229.00 | $ | 319,867.13 | 67 | 17 |

**Top 50 Drugs by Claim Count - Q1 2017**

| Drug Code | Drug Name | Claim Count | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|
| 6599170210 | HYDROCODONE-ACETAMINOPHEN | 21026 | $ 352,175.15 | 60 | 15 |
| 4420101010 | ALBUTEROL SULFATE | 20177 | $ 1,134,441.48 | 36 | 14 |
| 7260003000 | GABAPENTIN | 13926 | $ 194,129.29 | 71 | 23 |
| 3610003000 | LISINOPRIL | 12603 | $ 100,453.99 | 40 | 36 |
| 6610002000 | IBUPROFEN | 12049 | $ 110,434.50 | 47 | 13 |
| 3940001010 | ATORVASTATIN CALCIUM | 11798 | $ 122,816.93 | 27 | 27 |
| 6599000220 | OXYCODONE W/ ACETAMINOPHEN | 10650 | $ 405,381.61 | 58 | 15 |
| 5710001000 | ALPRAZOLAM | 10585 | $ 109,483.61 | 50 | 22 |
| 2810001010 | LEVOTHYROXINE SODIUM | 10274 | $ 151,489.65 | 29 | 30 |
| 3400000310 | AMLODIPINE BESYLATE | 10098 | $ 73,020.04 | 36 | 35 |
| 2725005000 | METFORMIN HCL | 9709 | $ 290,240.42 | 68 | 33 |
| 6510007510 | OXYCODONE HCL | 8937 | $ 393,651.50 | 72 | 18 |
| 5915307010 | QUETIAPINE FUMARATE | 8615 | $ 721,499.51 | 30 | 20 |
| 5812008010 | TRAZODONE HCL | 8561 | $ 93,315.60 | 30 | 22 |
| 0120001010 | AMOXICILLIN | 7821 | $ 83,475.39 | 63 | 6 |
| 4220003230 | FLUTICASONE PROPIONATE (NASAL) | 7490 | $ 86,066.49 | 12 | 23 |
| 4450505010 | MONTELUKAST SODIUM | 7416 | $ 119,008.11 | 22 | 22 |
| 9410003000 | GLUCOSE BLOOD | 7239 | $ 984,523.11 | 75 | 23 |
| 5816007010 | SERTRALINE HCL | 7109 | $ 76,036.66 | 27 | 22 |
| 6510005510 | MORPHINE SULFATE | 6640 | $ 160,160.00 | 26 | 11 |
| 0340001000 | AZITHROMYCIN | 6555 | $ 86,352.66 | 7 | 4 |
| 5025006505 | ONDANSETRON HCL | 6455 | $ 37,693.16 | 5 | 2 |
| 6410001000 | ASPIRIN | 6434 | $ 34,570.31 | 23 | 22 |
| 3320003010 | METOPROLOL TARTRATE | 6414 | $ 52,266.28 | 59 | 32 |
| 7720203200 | CHOLECALCIFEROL | 6181 | $ 46,380.73 | 24 | 22 |
| 4927007010 | PANTOPRAZOLE SODIUM | 6149 | $ 57,699.94 | 21 | 21 |
| 5907007000 | RISPERIDONE | 5968 | $ 101,042.46 | 37 | 21 |
| 2210004500 | PREDNISONE | 5749 | $ 48,602.15 | 16 | 9 |
| 3940007500 | SIMVASTATIN | 5730 | $ 42,726.75 | 31 | 31 |
| 4920002010 | RANITIDINE HCL | 5625 | $ 70,155.71 | 46 | 23 |
| 5816004000 | FLUOXETINE HCL | 5563 | $ 93,185.41 | 30 | 23 |
| 4155003000 | LORATADINE | 5408 | $ 58,871.07 | 34 | 21 |
| 7510005010 | CYCLOBENZAPRINE HCL | 5388 | $ 54,584.87 | 39 | 17 |
| 6510009510 | TRAMADOL HCL | 5315 | $ 48,457.17 | 58 | 16 |
| 7210001000 | CLONAZEPAM | 5280 | $ 52,585.02 | 44 | 21 |
| 5025006500 | ONDANSETRON | 5073 | $ 55,526.12 | 7 | 3 |
| 7250001010 | DIVALPROEX SODIUM | 4875 | $ 211,227.34 | 56 | 20 |
| 3720003000 | FUROSEMIDE | 4852 | $ 35,588.32 | 38 | 30 |
| 3615004020 | LOSARTAN POTASSIUM | 4826 | $ 39,490.01 | 37 | 35 |
| 5925001500 | ARIPIPRAZOLE | 4802 | $ 807,374.79 | 16 | 15 |
| 6610005200 | MELOXICAM | 4669 | $ 39,791.60 | 27 | 24 |
| 3620101010 | CLONIDINE HCL | 4634 | $ 67,221.11 | 50 | 29 |
| 7510009010 | TIZANIDINE HCL | 4537 | $ 103,551.25 | 51 | 21 |
| 7720203000 | ERGOCALCIFEROL | 4535 | $ 47,908.25 | 4 | 25 |
| 7975001000 | SODIUM CHLORIDE | 4469 | $ 11,103.14 | 454 | 1 |
| 5816002010 | CITALOPRAM HYDROBROMIDE | 4469 | $ 39,656.51 | 26 | 25 |
| 4155002010 | CETIRIZINE HCL | 4459 | $ 49,592.44 | 42 | 20 |
| 7260004000 | LAMOTRIGINE | 4356 | $ 226,335.99 | 42 | 21 |
| 5710006000 | LORAZEPAM | 4213 | $ 39,458.32 | 22 | 10 |
| 6020408010 | ZOLPIDEM TARTRATE | 4186 | $ 38,016.79 | 24 | 24 |

**Top 50 Drugs by Claim Count - Q2 2017**

| Drug Code | Drug Name | Claim Count | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|
| 6599170210 | HYDROCODONE-ACETAMINOPHEN | 19967 | $ 317,947.99 | 58 | 15 |
| 4420101010 | ALBUTEROL SULFATE | 18298 | $ 1,086,491.30 | 36 | 15 |
| 7260003000 | GABAPENTIN | 13551 | $ 181,760.42 | 72 | 23 |
| 3940001010 | ATORVASTATIN CALCIUM | 10892 | $ 112,588.26 | 27 | 26 |
| 6610002000 | IBUPROFEN | 10837 | $ 97,499.04 | 43 | 13 |
| 5710001000 | ALPRAZOLAM | 10250 | $ 105,012.40 | 50 | 21 |
| 6599000220 | OXYCODONE W/ ACETAMINOPHEN | 10154 | $ 350,216.66 | 56 | 15 |
| 2810001010 | LEVOTHYROXINE SODIUM | 9441 | $ 145,862.61 | 30 | 30 |
| 3610003000 | LISINOPRIL | 8945 | $ 66,304.67 | 41 | 37 |
| 6510007510 | OXYCODONE HCL | 8512 | $ 347,380.03 | 71 | 18 |
| 5915307010 | QUETIAPINE FUMARATE | 8209 | $ 589,994.06 | 28 | 20 |
| 5812008010 | TRAZODONE HCL | 8131 | $ 89,113.53 | 30 | 22 |
| 5025006505 | ONDANSETRON HCL | 7412 | $ 36,721.93 | 4 | 2 |
| 4220003230 | FLUTICASONE PROPIONATE (NASAL) | 7377 | $ 83,623.08 | 12 | 24 |
| 3400000310 | AMLODIPINE BESYLATE | 7273 | $ 42,720.36 | 40 | 38 |
| 4450505010 | MONTELUKAST SODIUM | 7212 | $ 110,790.63 | 23 | 22 |
| 6510005510 | MORPHINE SULFATE | 7026 | $ 137,661.23 | 21 | 9 |
| 9410003000 | GLUCOSE BLOOD | 6959 | $ 982,791.69 | 75 | 24 |
| 2725005000 | METFORMIN HCL | 6886 | $ 232,635.80 | 77 | 38 |
| 5816007010 | SERTRALINE HCL | 6866 | $ 73,542.78 | 28 | 23 |
| 6410001000 | ASPIRIN | 6475 | $ 34,222.78 | 23 | 22 |
| 7720203200 | CHOLECALCIFEROL | 6183 | $ 47,835.76 | 26 | 24 |
| 0120001010 | AMOXICILLIN | 6010 | $ 62,758.77 | 56 | 6 |
| 5907007000 | RISPERIDONE | 5870 | $ 95,601.79 | 36 | 21 |
| 4927007010 | PANTOPRAZOLE SODIUM | 5799 | $ 53,914.30 | 21 | 20 |
| 7975001000 | SODIUM CHLORIDE | 5677 | $ 14,969.13 | 469 | 1 |
| 4155003000 | LORATADINE | 5449 | $ 60,149.79 | 32 | 20 |
| 5025006500 | ONDANSETRON | 5291 | $ 56,766.01 | 7 | 3 |
| 4920002010 | RANITIDINE HCL | 5256 | $ 67,650.17 | 49 | 24 |
| 5816004000 | FLUOXETINE HCL | 5207 | $ 92,346.65 | 30 | 23 |
| 7510005010 | CYCLOBENZAPRINE HCL | 5011 | $ 51,405.23 | 42 | 19 |
| 7210001000 | CLONAZEPAM | 4996 | $ 50,998.40 | 44 | 22 |
| 6510009510 | TRAMADOL HCL | 4995 | $ 44,401.99 | 56 | 16 |
| 2210004500 | PREDNISONE | 4877 | $ 42,034.53 | 16 | 9 |
| 3940007500 | SIMVASTATIN | 4848 | $ 35,080.47 | 33 | 33 |
| 5925001500 | ARIPIPRAZOLE | 4750 | $ 733,191.61 | 18 | 17 |
| 4155002010 | CETIRIZINE HCL | 4716 | $ 51,359.83 | 41 | 20 |
| 7250001010 | DIVALPROEX SODIUM | 4689 | $ 182,064.27 | 56 | 20 |
| 3320003010 | METOPROLOL TARTRATE | 4443 | $ 33,076.91 | 56 | 30 |
| 7260004000 | LAMOTRIGINE | 4381 | $ 216,349.22 | 44 | 22 |
| 0340001000 | AZITHROMYCIN | 4365 | $ 56,749.34 | 7 | 3 |
| 5710006000 | LORAZEPAM | 4293 | $ 38,248.63 | 20 | 10 |
| 7720203000 | ERGOCALCIFEROL | 4265 | $ 45,392.53 | 4 | 26 |
| 7510009010 | TIZANIDINE HCL | 4252 | $ 94,135.97 | 50 | 20 |
| 6610005200 | MELOXICAM | 4235 | $ 35,246.25 | 27 | 24 |
| 5816002010 | CITALOPRAM HYDROBROMIDE | 4146 | $ 37,724.15 | 27 | 26 |
| 4920003000 | FAMOTIDINE | 4012 | $ 32,014.24 | 25 | 15 |
| 7260004300 | LEVETIRACETAM | 4008 | $ 176,681.52 | 127 | 20 |
| 5830004010 | BUPROPION HCL | 3938 | $ 84,795.78 | 32 | 23 |
| 6020408010 | ZOLPIDEM TARTRATE | 3869 | $ 37,015.76 | 24 | 24 |

**Top 50 Drugs by Claim Count - Q3 2017**

| Drug Code | Drug Name | Claim Count | Pharmacy Paid | Avg Qty/Rx | Avg Day Supply |
|---|---|---|---|---|---|
| 6599170210 | HYDROCODONE-ACETAMINOPHEN | 18956 | $ 294,328.10 | 54 | 14 |
| 4420101010 | ALBUTEROL SULFATE | 16649 | $ 1,037,850.13 | 33 | 16 |
| 7260003000 | GABAPENTIN | 13293 | $ 178,773.71 | 72 | 23 |
| 3940001010 | ATORVASTATIN CALCIUM | 10533 | $ 109,591.74 | 30 | 29 |
| 6610002000 | IBUPROFEN | 10310 | $ 92,146.81 | 39 | 11 |
| 5710001000 | ALPRAZOLAM | 9907 | $ 103,862.69 | 48 | 21 |
| 6599000220 | OXYCODONE W/ ACETAMINOPHEN | 9803 | $ 318,971.65 | 52 | 14 |
| 2810001010 | LEVOTHYROXINE SODIUM | 8974 | $ 142,492.98 | 31 | 31 |
| 3610003000 | LISINOPRIL | 8605 | $ 64,890.20 | 43 | 39 |
| 6510007510 | OXYCODONE HCL | 8229 | $ 319,867.13 | 67 | 17 |
| 5915307010 | QUETIAPINE FUMARATE | 8142 | $ 595,131.16 | 29 | 20 |
| 5812008010 | TRAZODONE HCL | 7803 | $ 85,596.76 | 29 | 22 |
| 5025006505 | ONDANSETRON HCL | 7780 | $ 33,770.95 | 4 | 1 |
| 3400000310 | AMLODIPINE BESYLATE | 7058 | $ 42,305.37 | 40 | 38 |
| 6510005510 | MORPHINE SULFATE | 7028 | $ 127,788.57 | 20 | 9 |
| 9410003000 | GLUCOSE BLOOD | 6779 | $ 973,265.80 | 76 | 25 |
| 5816007010 | SERTRALINE HCL | 6603 | $ 72,312.75 | 28 | 23 |
| 2725005000 | METFORMIN HCL | 6485 | $ 297,320.90 | 78 | 38 |
| 4450505010 | MONTELUKAST SODIUM | 6462 | $ 97,049.66 | 24 | 24 |
| 6410001000 | ASPIRIN | 6440 | $ 33,814.79 | 23 | 22 |
| 7975001000 | SODIUM CHLORIDE | 6299 | $ 15,761.89 | 470 | 1 |
| 7720203200 | CHOLECALCIFEROL | 6225 | $ 47,403.26 | 25 | 24 |
| 4220003230 | FLUTICASONE PROPIONATE (NASAL) | 6213 | $ 70,245.88 | 12 | 25 |
| 5907007000 | RISPERIDONE | 5826 | $ 90,098.45 | 36 | 21 |
| 4927007010 | PANTOPRAZOLE SODIUM | 5496 | $ 51,971.56 | 22 | 22 |
| 4920002010 | RANITIDINE HCL | 4946 | $ 63,013.12 | 48 | 24 |
| 5816004000 | FLUOXETINE HCL | 4919 | $ 90,438.22 | 31 | 24 |
| 7510005010 | CYCLOBENZAPRINE HCL | 4860 | $ 53,081.39 | 45 | 18 |
| 120001010 | AMOXICILLIN | 4855 | $ 50,472.11 | 54 | 6 |
| 6510009510 | TRAMADOL HCL | 4851 | $ 44,358.31 | 56 | 16 |
| 4155003000 | LORATADINE | 4807 | $ 52,645.06 | 32 | 22 |
| 7250001010 | DIVALPROEX SODIUM | 4805 | $ 169,686.47 | 53 | 19 |
| 7210001000 | CLONAZEPAM | 4786 | $ 48,562.42 | 38 | 19 |
| 5025006500 | ONDANSETRON | 4746 | $ 49,894.55 | 7 | 3 |
| 5710006000 | LORAZEPAM | 4670 | $ 38,977.22 | 17 | 8 |
| 5925001500 | ARIPIPRAZOLE | 4663 | $ 731,882.96 | 18 | 17 |
| 2210004500 | PREDNISONE | 4377 | $ 38,296.73 | 16 | 9 |
| 7260004000 | LAMOTRIGINE | 4372 | $ 207,100.68 | 43 | 21 |
| 3320003010 | METOPROLOL TARTRATE | 4350 | $ 33,181.04 | 59 | 32 |
| 4920003000 | FAMOTIDINE | 4336 | $ 33,295.51 | 20 | 13 |
| 3940007500 | SIMVASTATIN | 4171 | $ 31,022.25 | 30 | 30 |
| 4155002010 | CETIRIZINE HCL | 4106 | $ 44,810.65 | 43 | 22 |
| 7510009010 | TIZANIDINE HCL | 4091 | $ 90,470.96 | 48 | 19 |
| 6610005200 | MELOXICAM | 4089 | $ 32,437.67 | 28 | 25 |
| 7260004300 | LEVETIRACETAM | 3907 | $ 167,522.66 | 125 | 20 |
| 7720203000 | ERGOCALCIFEROL | 3864 | $ 41,381.49 | 4 | 27 |
| 5816002010 | CITALOPRAM HYDROBROMIDE | 3850 | $ 36,158.37 | 26 | 25 |
| 5830004010 | BUPROPION HCL | 3774 | $ 82,217.70 | 31 | 22 |
| 3720003000 | FUROSEMIDE | 3647 | $ 25,700.33 | 39 | 30 |
| 4650001030 | DOCUSATE SODIUM | 3622 | $ 26,786.40 | 38 | 19 |

CONFIDENTIAL

# RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31



## Client Totals:

| Total Rxs | Plan Paid | Member Paid |
|---|---|---|
| 769,702 | $78,090,741 | $0 |

## DUR Information as a percent of total:

| DUR Type | Total Rxs | Percent of Total Rxs - Paid | Cases | Rejected Rxs | Percent of Total Rxs - Rejects |
|---|---|---|---|---|---|
| Total Claims Paid | 769,702 | 0.0% | 0 | 0 | 0.0% |
| Cases / Rxs | 367,423 | 47.7% | 323,381 | 254,287 | 33.0% |
| TD - Therapeutic Duplication | 107,656 | 14.0% | 90,863 | 109,640 | 14.2% |
| LR - Underuse Precaution | 64,369 | 8.4% | 64,769 | 8,063 | 1.0% |
| ID - Ingredient Duplication | 55,795 | 7.2% | 21,111 | 55,727 | 7.2% |
| DD - Drug-Drug Interaction | 51,923 | 6.7% | 59,733 | 67,948 | 8.8% |
| LD - Low Dose Alert | 35,131 | 4.6% | 34,893 | 4,874 | 0.6% |
| MN - Insufficnt Duration Alert | 22,759 | 3.0% | 22,388 | 1,316 | 0.2% |
| HD - High Dose Alert | 20,176 | 2.6% | 19,883 | 4,041 | 0.5% |
| MX - Excessive Duration Alert | 9,550 | 1.2% | 9,669 | 2,674 | 0.3% |
| PA - Drug-Age Precaution | 58 | 0.0% | 66 | 3 | 0.0% |
| SX - Drug Gender Alert | 6 | 0.0% | 6 | 1 | 0.0% |

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

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# RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31



## DD

| Curr Rank | Top Drug Drug Interaction | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | TRAZODONE HCL - QUETIAPINE | Message Only | 1,092 | 301 | $13,009.86 | $11.91 | $0.00 | 28.15 | 38.76 |
| 2 | TRAZODONE - QUETIAPINE FUMARATE | Message Only | 1,044 | 267 | $16,036.62 | $15.36 | $0.00 | 28.35 | 44.80 |
| 3 | SPIRONOLACTONE - LISINOPRIL | Message Only | 648 | 155 | $6,959.49 | $10.74 | $0.00 | 43.02 | 46.98 |
| 4 | TRAZODONE - CITALOPRAM HYDROBROMIDE | Message Only | 622 | 181 | $5,341.86 | $8.59 | $0.00 | 30.57 | 31.72 |
| 5 | TRAZODONE HCL - CITALOPRAM | Message Only | 612 | 203 | $6,682.12 | $10.92 | $0.00 | 31.08 | 41.68 |
| 6 | SPIRONOLACT - LISINOPRIL | Message Only | 611 | 146 | $4,516.55 | $7.39 | $0.00 | 40.91 | 47.89 |
| 7 | DIVALPROEX - CLONAZEPAM | Message Only | 605 | 260 | $4,979.97 | $8.23 | $0.00 | 24.24 | 49.45 |
| 8 | TRAZODONE - ONDANSETRON HCL | Message Only | 548 | 20 | $303.07 | $0.55 | $0.00 | 1.11 | 2.29 |
| 9 | QUETIAPINE - CITALOPRAM HYDROBROMIDE | Message Only | 516 | 156 | $4,892.47 | $9.48 | $0.00 | 30.09 | 32.38 |
| 10 | SIMVASTATIN - FENOFIBRATE | Message Only | 515 | 152 | $6,870.56 | $13.34 | $0.00 | 35.81 | 36.00 |
| All Others | | | 52,920 | 66,107 | $6,030,125.51 | $113.95 | $0.00 | 25.13 | 45.69 |
| Summary | | | 59,733 | 67,948 | $6,099,718.08 | $102.12 | $0.00 | 25.62 | 44.84 |

## HD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ZOLPIDEM TARTRATE | GERIATRIC MAX DLY = .50UN | Message Only | 478 | 40 | $1,086.50 | $2.27 | $0.00 | 29.63 | 29.63 |
| 2 | KETOROLAC TROMETHAMINE | GERIATRIC MAX DLY = 2.00UN | Message Only | 451 | 14 | $6,505.72 | $14.43 | $0.00 | 1.00 | 7.60 |
| 3 | HYDROCODONE/ ACETAMINOPHEN | ADULT MAX DLY = 6.00 UN | Message Only | 400 | 64 | $10,833.97 | $27.08 | $0.00 | 14.90 | 115.22 |
| 4 | GRANISETRON HCL | GERIATRIC MAX DLY = .85UN | Message Only | 288 | 8 | $4,416.62 | $15.34 | $0.00 | 1.00 | 1.16 |
| 5 | INVEGA SUSTENNA | ADULT MAX DLY = .05 UN | Message Only | 226 | 0 | $561,235.30 | $2,483.34 | $0.00 | 23.92 | 1.85 |
| 5 | MIDAZOLAM HCL | GERIATRIC MAX DLY = 3.50UN | Message Only | 226 | 5 | $692.64 | $3.06 | $0.00 | 1.00 | 9.15 |
| 7 | MIDAZOLAM HCL | GERIATRIC MAX DLY = .70UN | Message Only | 219 | 3 | $268.94 | $1.23 | $0.00 | 1.00 | 1.42 |
| 8 | IBUPROFEN | ADULT MAX DLY = 4.00 UN | Message Only | 216 | 13 | $2,273.41 | $10.53 | $0.00 | 7.67 | 34.57 |
| 9 | BETAMETHASONE SODIUM PHOS | GERIATRIC MAX DLY = 1.50UN | Message Only | 202 | 2 | $5,033.42 | $24.92 | $0.00 | 1.00 | 5.03 |
| 10 | DEXAMETHASONE SODIUM PHOS | GERIATRIC MAX DLY = 4.00UN | Message Only | 199 | 8 | $3,558.34 | $17.88 | $0.00 | 1.00 | 36.81 |
| All Others | | | | 16,978 | 3,884 | $9,186,884.10 | $541.11 | $0.00 | 16.63 | 145.47 |
| HD | | | | 19,883 | 4,041 | $9,782,788.96 | $492.02 | $0.00 | 15.65 | 128.38 |

CONFIDENTIAL

# RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31



## ID

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PROVENTIL HFA | PROVENTIL AER HFA | Message Only | 346 | 20 | $31,780.04 | $91.85 | $0.00 | 25.68 | 7.82 |
| 2 | GABAPENTIN | GABAPENTIN CAP 300MG | Message Only | 291 | 17 | $4,081.99 | $14.03 | $0.00 | 37.98 | 118.51 |
| 3 | TRAZODONE HCL | TRAZODONE TAB 100MG | Message Only | 195 | 7 | $2,197.53 | $11.27 | $0.00 | 31.67 | 43.48 |
| 4 | HYDROCODONE/ ACETAMINOPHEN | HYDROCO/APAP TAB 5-325MG | Message Only | 180 | 0 | $46.65 | $0.26 | $0.00 | 1.00 | 2.00 |
| 5 | AMLODIPINE BESYLATE | AMLODIPINE TAB 10MG | Message Only | 176 | 12 | $1,803.88 | $10.25 | $0.00 | 50.64 | 51.59 |
| 6 | ONDANSETRON ODT | ONDANSETRON TAB 4MG ODT | Message Only | 168 | 0 | $61.57 | $0.37 | $0.00 | 1.00 | 1.01 |
| 7 | SERTRALINE HCL | SERTRALINE TAB 100MG | Message Only | 163 | 4 | $2,048.41 | $12.57 | $0.00 | 33.42 | 47.62 |
| 8 | FLUTICASONE PROPIONATE | FLUTICASONE SPR 50MCG | Message Only | 157 | 12 | $2,043.45 | $13.02 | $0.00 | 33.50 | 16.61 |
| 9 | TRAZODONE HCL | TRAZODONE TAB 50MG | Message Only | 156 | 9 | $1,683.18 | $10.79 | $0.00 | 33.15 | 42.60 |
| 10 | CLONIDINE HCL | CLONIDINE TAB 0.1MG | Message Only | 152 | 13 | $1,784.89 | $11.74 | $0.00 | 46.82 | 84.66 |
| 10 | PREDNISONE | PREDNISONE TAB 20MG | Message Only | 152 | 0 | $52.73 | $0.35 | $0.00 | 1.00 | 2.49 |
| All Others | | | | 18,975 | 55,633 | $2,983,942.04 | $157.26 | $0.00 | 33.23 | 91.23 |
| ID | | | | 21,111 | 55,727 | $3,031,526.36 | $143.60 | $0.00 | 32.64 | 86.05 |

## LD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ONDANSETRON ODT | GERIATRIC MIN DLY = 2.00UN | Message Only | 1,343 | 26 | $602.77 | $0.45 | $0.00 | 1.39 | 1.32 |
| 2 | ONDANSETRON HCL | GERIATRIC MIN DLY = 2.00UN | Message Only | 1,222 | 73 | $322.07 | $0.26 | $0.00 | 1.82 | 1.89 |
| 3 | IPRATROPIUM BROMIDE/ ALBUT | GERIATRIC MIN DLY = 9.00UN | Message Only | 1,042 | 17 | $624.67 | $0.60 | $0.00 | 1.68 | 7.34 |
| 4 | HEPARIN SODIUM | GERIATRIC MIN DLY = 4.00UN | Message Only | 728 | 4 | $2,206.55 | $3.03 | $0.00 | 1.36 | 2.47 |
| 5 | ALBUTEROL SULFATE | GERIATRIC MIN DLY = 9.00UN | Message Only | 705 | 27 | $908.89 | $1.29 | $0.00 | 3.07 | 14.89 |
| 6 | METFORMIN HCL | ADULT MIN DLY = 1.70 UN | Message Only | 547 | 99 | $4,811.65 | $8.80 | $0.00 | 50.44 | 49.70 |
| 7 | VITAMIN D | ADULT MIN DLY = .14 UN | Message Only | 527 | 54 | $5,296.75 | $10.05 | $0.00 | 35.10 | 3.72 |
| 8 | GABAPENTIN | ADULT MIN DLY = 3.00 UN | Message Only | 467 | 76 | $4,616.89 | $9.89 | $0.00 | 33.30 | 54.74 |
| 9 | PROPRANOLOL HCL | ADULT MIN DLY = 3.00 UN | Message Only | 372 | 63 | $6,567.33 | $17.65 | $0.00 | 38.73 | 64.34 |
| 10 | ALBUTEROL SULFATE | PEDIATRIC MIN DLY = 9.00UN | Message Only | 369 | 16 | $5,857.51 | $15.87 | $0.00 | 24.66 | 121.50 |
| All Others | | | | 27,571 | 4,419 | $4,046,737.32 | $146.78 | $0.00 | 26.45 | 45.32 |
| LD | | | | 34,893 | 4,874 | $4,078,552.40 | $116.89 | $0.00 | 23.60 | 40.03 |

## LR

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ATORVASTATIN CALCIUM | 8 DAYS LATE REFILLING | Message Only | 85 | 9 | $935.42 | $11.00 | $0.00 | 30.42 | 30.60 |
| 2 | LISINOPRIL | 7 DAYS LATE REFILLING | Message Only | 83 | 7 | $709.45 | $8.55 | $0.00 | 41.59 | 44.69 |
| 3 | ATORVASTATIN CALCIUM | 7 DAYS LATE REFILLING | Message Only | 82 | 10 | $842.71 | $10.28 | $0.00 | 29.50 | 29.50 |
| 4 | LEVOTHYROXINE SODIUM | 7 DAYS LATE REFILLING | Message Only | 73 | 4 | $859.20 | $11.77 | $0.00 | 30.40 | 30.05 |
| 4 | GABAPENTIN | 7 DAYS LATE REFILLING | Message Only | 73 | 5 | $886.59 | $12.15 | $0.00 | 28.97 | 99.97 |
| 6 | AMLODIPINE BESYLATE | 7 DAYS LATE REFILLING | Message Only | 68 | 7 | $507.25 | $7.46 | $0.00 | 41.13 | 44.66 |
| 7 | PROVENTIL HFA | 11 DAYS LATE REFILLING | Message Only | 61 | 3 | $5,167.66 | $84.72 | $0.00 | 19.21 | 6.92 |
| 7 | GABAPENTIN | 8 DAYS LATE REFILLING | Message Only | 61 | 7 | $822.04 | $13.48 | $0.00 | 29.16 | 92.10 |
| 9 | LISINOPRIL | 8 DAYS LATE REFILLING | Message Only | 60 | 7 | $509.28 | $8.49 | $0.00 | 44.00 | 49.50 |
| 10 | PROVENTIL HFA | 12 DAYS LATE REFILLING | Message Only | 57 | 6 | $4,775.29 | $83.78 | $0.00 | 19.63 | 6.94 |
| 10 | AMLODIPINE BESYLATE | 9 DAYS LATE REFILLING | Message Only | 57 | 0 | $440.86 | $7.73 | $0.00 | 41.30 | 44.70 |
| 10 | AMLODIPINE BESYLATE | 8 DAYS LATE REFILLING | Message Only | 57 | 5 | $485.92 | $8.52 | $0.00 | 40.25 | 40.25 |
| 10 | LEVOTHYROXINE SODIUM | 8 DAYS LATE REFILLING | Message Only | 57 | 4 | $811.47 | $14.24 | $0.00 | 31.00 | 30.12 |
| All Others | | | | 63,895 | 7,989 | $7,595,022.23 | $118.87 | $0.00 | 32.18 | 58.81 |
| LR | | | | 64,769 | 8,063 | $7,612,775.37 | $117.54 | $0.00 | 32.19 | 58.59 |

## MN

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | IPRATROPIUM BROMIDE/ALBUT | MIN. DAYS THERAPY = 30 | Message Only | 2,065 | 204 | $15,062.53 | $7.29 | $0.00 | 4.71 | 61.94 |
| 2 | LISINOPRIL | MIN. DAYS THERAPY = 7 | Message Only | 844 | 11 | $70.61 | $0.08 | $0.00 | 1.03 | 1.24 |
| 3 | PANTOPRAZOLE SODIUM | MIN. DAYS THERAPY = 7 | Message Only | 768 | 8 | $111.15 | $0.14 | $0.00 | 1.02 | 1.07 |
| 4 | METOPROLOL TARTRATE | MIN. DAYS THERAPY = 7 | Message Only | 622 | 20 | $132.34 | $0.21 | $0.00 | 1.06 | 1.40 |
| 5 | AMLODIPINE BESYLATE | MIN. DAYS THERAPY = 7 | Message Only | 500 | 2 | $79.50 | $0.16 | $0.00 | 1.05 | 1.19 |
| 6 | LEVETIRACETAM | MIN. DAYS THERAPY = 14 | Message Only | 486 | 30 | $2,955.71 | $6.08 | $0.00 | 2.61 | 31.60 |
| 7 | ATORVASTATIN CALCIUM | MIN. DAYS THERAPY = 7 | Message Only | 442 | 11 | $172.71 | $0.39 | $0.00 | 1.08 | 1.19 |
| 8 | QUETIAPINE FUMARATE | MIN. DAYS THERAPY = 7 | Message Only | 414 | 34 | $422.46 | $1.02 | $0.00 | 1.24 | 3.28 |
| 9 | CARVEDILOL | MIN. DAYS THERAPY = 7 | Message Only | 403 | 7 | $99.24 | $0.25 | $0.00 | 1.04 | 1.53 |
| 10 | KLOR-CON M20 | MIN. DAYS THERAPY = 7 | Message Only | 394 | 3 | $181.43 | $0.46 | $0.00 | 1.00 | 1.90 |
| All Others | | | | 15,450 | 986 | $1,256,149.08 | $81.30 | $0.00 | 2.27 | 20.00 |
| MN | | | | 22,388 | 1,316 | $1,275,436.76 | $56.97 | $0.00 | 2.26 | 20.50 |

## MX

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 2,796 | 1,889 | $28,144.65 | $10.07 | $0.00 | 30.81 | 66.08 |
| 2 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 1,634 | 0 | $17,086.26 | $10.46 | $0.00 | 30.98 | 71.12 |
| 3 | FLUCONAZOLE | MAX DAYS THERAPY = 1 | Message Only | 527 | 178 | $6,516.00 | $12.36 | $0.00 | 6.69 | 2.84 |
| 4 | AZITHROMYCIN | MAX DAYS THERAPY = 5 | Message Only | 313 | 68 | $6,471.38 | $20.68 | $0.00 | 12.22 | 19.33 |
| 5 | MAPAP | MAX DAYS THERAPY = 10 | Message Only | 274 | 17 | $2,504.74 | $9.14 | $0.00 | 26.06 | 114.49 |
| 6 | DIPHENOXYLATE/ ATROPINE | MAX DAYS THERAPY = 14 | Message Only | 233 | 20 | $7,227.86 | $31.02 | $0.00 | 28.63 | 110.45 |
| 7 | EPIPEN 2-PAK | MAX DAYS THERAPY = 1 | Message Only | 231 | 13 | $145,369.87 | $629.31 | $0.00 | 11.22 | 2.43 |
| 8 | CEFDINIR | MAX DAYS THERAPY = 10 | Message Only | 178 | 15 | $6,857.96 | $38.53 | $0.00 | 16.66 | 87.08 |
| 9 | POLYETHYLENE GLYCOL 3350 | MAX DAYS THERAPY = 14 | Message Only | 177 | 7 | $6,292.04 | $35.55 | $0.00 | 31.08 | 33.60 |
| 10 | SENEXON-S | MAX DAYS THERAPY = 14 | Message Only | 175 | 25 | $1,679.81 | $9.60 | $0.00 | 31.58 | 57.60 |
| All Others | | | | 3,131 | 442 | $992,229.98 | $316.91 | $0.00 | 25.34 | 60.91 |
| MX | | | | 9,669 | 2,674 | $1,220,380.55 | $126.22 | $0.00 | 26.25 | 60.86 |

## PA

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PROMETHAZINE-DM | AGE LESS THAN 4 | Message Only | 19 | 2 | $150.40 | $7.92 | $0.00 | 9.00 | 70.53 |
| 2 | PROMETHAZINE HCL PLAIN | AGE LESS THAN 4 | Message Only | 11 | 0 | $53.63 | $4.88 | $0.00 | 6.91 | 99.36 |
| 3 | NITROFURANTOIN | AGE LESS THAN 4 | Message Only | 10 | 0 | $867.13 | $86.71 | $0.00 | 27.10 | 155.00 |
| 4 | PROMETHAZINE HCL | AGE LESS THAN 4 | Message Only | 8 | 0 | $67.13 | $8.39 | $0.00 | 10.50 | 111.62 |
| 5 | PROMETHAZINE/ DEXTROMETHOR | AGE LESS THAN 4 | Message Only | 7 | 1 | $77.93 | $11.13 | $0.00 | 9.29 | 86.43 |
| 6 | NITROFURANTOIN MACROCRYST | AGE LESS THAN 4 | Message Only | 4 | 0 | $381.55 | $95.39 | $0.00 | 25.00 | 21.25 |
| 7 | PHENYLEPHRINE HCL | AGE LESS THAN 4 | Message Only | 3 | 0 | $241.63 | $80.54 | $0.00 | 49.67 | 11.67 |
| 8 | INFANRIX | AGE GREATER THAN 64 | Message Only | 2 | 0 | $44.80 | $22.40 | $0.00 | 1.00 | 0.50 |
| 9 | PROMETHAZINE/ CODEINE | AGE LESS THAN 4 | Message Only | 1 | 0 | $8.95 | $8.95 | $0.00 | 8.00 | 120.00 |
| 9 | PROMETHAZINE VC PLAIN | AGE LESS THAN 4 | Message Only | 1 | 0 | $15.70 | $15.70 | $0.00 | 3.00 | 50.00 |
| PA | | | | 66 | 3 | $1,908.85 | $28.92 | $0.00 | 14.08 | 87.45 |

## SX

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | BICALUTAMIDE | GENERAL CONTRAINDICATION | Message Only | 6 | 1 | $115.74 | $19.29 | $0.00 | 12.67 | 33.33 |
| SX | | | | 6 | 1 | $115.74 | $19.29 | $0.00 | 12.67 | 33.33 |

## TD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | QUETIAPINE FUMARATE | ORAL ANTIPSYCHOTICS | Message Only | 2,551 | 0 | $39,253.86 | $15.39 | $0.00 | 29.34 |
| 2 | RISPERIDONE | ORAL ANTIPSYCHOTICS | Message Only | 1,605 | 0 | $20,786.34 | $12.95 | $0.00 | 28.86 |
| 3 | MORPHINE SULFATE | SHORT ACTING NARCOTIC ANALGESI | Message Only | 1,524 | 92 | $4,107.74 | $2.70 | $0.00 | 1.00 |
| 4 | GABAPENTIN | GABAPENTIN AND RELATED | Message Only | 1,237 | 0 | $20,174.02 | $16.31 | $0.00 | 34.38 |
| 5 | ARIPIPRAZOLE | ORAL ANTIPSYCHOTICS | Message Only | 1,086 | 0 | $85,522.23 | $78.75 | $0.00 | 29.42 |
| 6 | LISINOPRIL | ANGIOTENSIN BLOCKERS | Message Only | 967 | 0 | $9,076.75 | $9.39 | $0.00 | 53.66 |
| 7 | HYDROMORPHONE HCL | SHORT ACTING NARCOTIC ANALGESI | Message Only | 930 | 132 | $4,696.61 | $5.05 | $0.00 | 1.00 |
| 8 | OLANZAPINE | ORAL ANTIPSYCHOTICS | Message Only | 905 | 0 | $14,995.26 | $16.57 | $0.00 | 29.00 |
| 9 | LEVOTHYROXINE SODIUM | THYROID HORMONES | Message Only | 901 | 0 | $14,245.09 | $15.81 | $0.00 | 42.83 |
| 10 | HYDROCODONE/ ACETAMINOPHEN | SHORT ACTING NARCOTIC ANALGESI | Message Only | 845 | 107 | $15,220.05 | $18.01 | $0.00 | 19.24 |
| All Others | | | | 78,312 | 109,309 | $12,753,581.20 | $162.86 | $0.00 | 25.59 |
| TD | | | | 90,863 | 109,640 | $12,981,659.15 | $142.87 | $0.00 | 25.70 |

## TD

| Quantity Per Rx |
|---|
| 42.81 |
| 48.80 |
| 1.58 |
| 110.92 |
| 35.26 |
| 58.59 |
| 2.81 |
| 36.46 |
| 41.28 |
| 76.65 |
| 70.23 |
| 66.69 |

## Selected Filters

**Client(s): Nevada Medicaid - HPES**

**Carrier(s): NVM-NEVADA MEDICAID**

**Account(s): ALL**

**Group(s): ALL**

| | |
|---|---|
| **Date Type:** | Date Filled Submitted |
| **Start Date:** | 2017-01-01 |
| **End Date:** | 2017-03-31 |
| **Relative Description:** | Previous Quarter |
| **Display Report Description:** | No |
| **Top Values to Display:** | 10 |

CONFIDENTIAL

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## Client Totals:

| Total Rxs | Plan Paid | Member Paid |
|---|---|---|
| 702,122 | $78,464,924 | $0 |

## DUR Information as a percent of total:

| DUR Type | Total Rxs | Percent of Total Rxs - Paid | Cases | Rejected Rxs | Percent of Total Rxs - Rejects |
|---|---|---|---|---|---|
| Total Claims Paid | 702,122 | 0.0% | 0 | 0 | 0.0% |
| Cases / Rxs | 508,986 | 72.5% | 621,766 | 339,014 | 48.3% |
| DD - Drug-Drug Interaction | 198,957 | 28.3% | 367,009 | 145,228 | 20.7% |
| TD - Therapeutic Duplication | 111,783 | 15.9% | 93,854 | 114,296 | 16.3% |
| ID - Ingredient Duplication | 58,493 | 8.3% | 22,795 | 58,893 | 8.4% |
| LR - Underuse Precaution | 56,332 | 8.0% | 56,600 | 7,339 | 1.0% |
| LD - Low Dose Alert | 33,782 | 4.8% | 32,539 | 5,958 | 0.8% |
| MN - Insufficnt Duration Alert | 22,872 | 3.3% | 22,410 | 1,319 | 0.2% |
| HD - High Dose Alert | 17,849 | 2.5% | 17,603 | 3,531 | 0.5% |
| MX - Excessive Duration Alert | 8,872 | 1.3% | 8,906 | 2,448 | 0.3% |
| PA - Drug-Age Precaution | 46 | 0.0% | 50 | 2 | 0.0% |

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## DD

| Curr Rank | Top Drug Drug Interaction | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | HYDROCODONE/ ACETAMINOPHEN - ALPRAZOLAM | Message Only | 3,513 | 611 | $61,411.85 | $17.48 | $0.00 | 21.73 | 84.35 |
| 2 | SIMVASTATIN - LISINOPRIL | Message Only | 2,837 | 684 | $20,158.26 | $7.11 | $0.00 | 48.64 | 51.32 |
| 3 | LISINOPRIL - FUROSEMIDE | Message Only | 2,783 | 905 | $19,503.44 | $7.01 | $0.00 | 50.96 | 60.86 |
| 4 | HYDROCO/APAP - ALPRAZOLAM | Message Only | 2,691 | 579 | $24,485.03 | $9.10 | $0.00 | 25.88 | 60.42 |
| 5 | ONDANSETRON HCL - HYDROCO/APAP | Message Only | 2,325 | 61 | $6,525.06 | $2.81 | $0.00 | 2.46 | 5.48 |
| 6 | OXYCODONE HCL - ALPRAZOLAM | Message Only | 1,995 | 445 | $51,418.62 | $25.77 | $0.00 | 25.49 | 102.66 |
| 7 | LISINOPRIL - IBUPROFEN | Message Only | 1,926 | 497 | $17,198.32 | $8.93 | $0.00 | 35.53 | 67.73 |
| 8 | OXYCODONE - ALPRAZOLAM | Message Only | 1,816 | 488 | $18,172.11 | $10.01 | $0.00 | 26.26 | 65.85 |
| 9 | OXYCODONE/ ACETAMINOPHEN - ALPRAZOLAM | Message Only | 1,710 | 329 | $57,714.91 | $33.75 | $0.00 | 21.94 | 86.76 |
| 10 | MORPHINE SULFATE ER - GABAPENTIN | Message Only | 1,604 | 335 | $42,901.66 | $26.75 | $0.00 | 24.79 | 52.90 |
| All Others | | | 343,809 | 140,294 | $19,623,050.59 | $57.08 | $0.00 | 29.90 | 56.53 |
| **Summary** | | | **367,009** | **145,228** | **$19,942,539.85** | **$54.34** | **$0.00** | **29.85** | **56.97** |

## HD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ZOLPIDEM TARTRATE | GERIATRIC MAX DLY = .50UN | Message Only | 453 | 41 | $841.74 | $1.86 | $0.00 | 29.21 | 29.21 |
| 2 | KETOROLAC TROMETHAMINE | GERIATRIC MAX DLY = 2.00UN | Message Only | 395 | 12 | $5,789.34 | $14.66 | $0.00 | 1.00 | 7.08 |
| 3 | HYDROCODONE/ ACETAMINOPHEN | ADULT MAX DLY = 6.00 UN | Message Only | 298 | 30 | $8,002.90 | $26.86 | $0.00 | 14.99 | 117.91 |
| 4 | MIDAZOLAM HCL | GERIATRIC MAX DLY = 3.50UN | Message Only | 240 | 11 | $645.98 | $2.69 | $0.00 | 1.00 | 7.92 |
| 5 | GRANISETRON HCL | GERIATRIC MAX DLY = .85UN | Message Only | 239 | 6 | $4,349.48 | $18.20 | $0.00 | 1.00 | 1.38 |
| 6 | BETAMETHASONE SODIUM PHOS | GERIATRIC MAX DLY = 1.50UN | Message Only | 202 | 1 | $5,534.64 | $27.40 | $0.00 | 1.00 | 5.44 |
| 7 | CEFTRIAXONE SODIUM | GERIATRIC MAX DLY = 4.00UN | Message Only | 200 | 4 | $9,935.91 | $49.68 | $0.00 | 1.00 | 172.52 |
| 8 | DEXAMETHASONE SODIUM PHOS | GERIATRIC MAX DLY = 4.00UN | Message Only | 191 | 3 | $3,365.64 | $17.62 | $0.00 | 1.00 | 290.86 |
| 9 | INVEGA SUSTENNA | ADULT MAX DLY = .05 UN | Message Only | 184 | 129 | $379,876.69 | $2,064.55 | $0.00 | 27.35 | 1.50 |
| 10 | IBUPROFEN | ADULT MAX DLY = 4.00 UN | Message Only | 174 | 21 | $1,875.61 | $10.78 | $0.00 | 8.22 | 37.97 |
| All Others | | | | 15,027 | 3,273 | $9,186,466.36 | $611.33 | $0.00 | 16.65 | 376.16 |
| **HD** | | | | **17,603** | **3,531** | **$9,606,684.29** | **$545.74** | **$0.00** | **15.67** | **329.71** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## ID

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PROVENTIL HFA | PROVENTIL AER HFA | Message Only | 409 | 23 | $39,307.30 | $96.11 | $0.00 | 27.62 | 8.08 |
| 2 | GABAPENTIN | GABAPENTIN CAP 300MG | Message Only | 247 | 21 | $3,239.56 | $13.12 | $0.00 | 36.45 | 110.97 |
| 3 | CLONIDINE HCL | CLONIDINE TAB 0.1MG | Message Only | 204 | 22 | $2,646.82 | $12.97 | $0.00 | 75.65 | 130.24 |
| 3 | SERTRALINE HCL | SERTRALINE TAB 100MG | Message Only | 204 | 12 | $2,483.96 | $12.18 | $0.00 | 34.72 | 47.91 |
| 5 | LISINOPRIL | LISINOPRIL TAB 20MG | Message Only | 195 | 9 | $2,239.60 | $11.49 | $0.00 | 78.74 | 90.56 |
| 6 | AMLODIPINE BESYLATE | AMLODIPINE TAB 10MG | Message Only | 175 | 17 | $1,815.75 | $10.38 | $0.00 | 74.33 | 73.65 |
| 7 | ONDANSETRON ODT | ONDANSETRON TAB 4MG ODT | Message Only | 174 | 0 | $63.13 | $0.36 | $0.00 | 1.00 | 1.06 |
| 7 | TRAZODONE HCL | TRAZODONE TAB 50MG | Message Only | 174 | 4 | $1,936.33 | $11.13 | $0.00 | 33.84 | 46.23 |
| 9 | METFORMIN HCL | METFORMIN TAB 500MG | Message Only | 173 | 10 | $1,909.31 | $11.04 | $0.00 | 78.01 | 155.55 |
| 10 | TRAZODONE HCL | TRAZODONE TAB 100MG | Message Only | 167 | 8 | $1,899.19 | $11.37 | $0.00 | 36.38 | 50.54 |
| All Others | | | | 20,673 | 58,767 | $5,060,240.43 | $244.78 | $0.00 | 39.29 | 122.65 |
| **ID** | | | | **22,795** | **58,893** | **$5,117,781.38** | **$224.51** | **$0.00** | **39.88** | **117.43** |

## LD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ONDANSETRON ODT | GERIATRIC MIN DLY = 2.00UN | Message Only | 1,285 | 18 | $628.73 | $0.49 | $0.00 | 1.30 | 1.24 |
| 2 | IPRATROPIUM BROMIDE/ ALBUT | GERIATRIC MIN DLY = 9.00UN | Message Only | 935 | 7 | $709.63 | $0.76 | $0.00 | 1.98 | 8.83 |
| 3 | HEPARIN SODIUM | GERIATRIC MIN DLY = 4.00UN | Message Only | 815 | 13 | $2,041.66 | $2.51 | $0.00 | 1.40 | 2.41 |
| 4 | HEPARIN SODIUM | GERIATRIC MIN DLY = 20.00UN | Message Only | 751 | 891 | $3,424.07 | $4.56 | $0.00 | 1.00 | 3.01 |
| 5 | ALBUTEROL SULFATE | GERIATRIC MIN DLY = 9.00UN | Message Only | 533 | 23 | $1,187.65 | $2.23 | $0.00 | 5.23 | 26.53 |
| 6 | ONDANSETRON HCL | GERIATRIC MIN DLY = 2.00UN | Message Only | 529 | 57 | $290.79 | $0.55 | $0.00 | 2.79 | 2.79 |
| 7 | VITAMIN D | ADULT MIN DLY = .14 UN | Message Only | 524 | 56 | $5,321.45 | $10.16 | $0.00 | 37.87 | 4.12 |
| 8 | GABAPENTIN | ADULT MIN DLY = 3.00 UN | Message Only | 482 | 85 | $4,897.75 | $10.16 | $0.00 | 33.44 | 55.30 |
| 9 | METFORMIN HCL | ADULT MIN DLY = 1.70 UN | Message Only | 379 | 114 | $3,145.47 | $8.30 | $0.00 | 59.60 | 59.02 |
| 10 | METFORMIN HCL | GERIATRIC MIN DLY = 1.70UN | Message Only | 353 | 40 | $624.54 | $1.77 | $0.00 | 40.10 | 39.11 |
| All Others | | | | 25,953 | 4,654 | $3,563,066.08 | $137.29 | $0.00 | 28.18 | 49.00 |
| **LD** | | | | **32,539** | **5,958** | **$3,585,337.82** | **$110.19** | **$0.00** | **25.01** | **41.99** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## LR

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ATORVASTATIN CALCIUM | 7 DAYS LATE REFILLING | Message Only | 67 | 5 | $676.96 | $10.10 | $0.00 | 30.87 | 30.87 |
| 1 | LEVOTHYROXINE SODIUM | 7 DAYS LATE REFILLING | Message Only | 67 | 6 | $747.78 | $11.16 | $0.00 | 29.97 | 29.97 |
| 3 | PROVENTIL HFA | 12 DAYS LATE REFILLING | Message Only | 65 | 6 | $5,871.68 | $90.33 | $0.00 | 20.42 | 7.52 |
| 4 | GABAPENTIN | 7 DAYS LATE REFILLING | Message Only | 61 | 5 | $817.48 | $13.40 | $0.00 | 29.39 | 92.49 |
| 5 | TRAZODONE HCL | 7 DAYS LATE REFILLING | Message Only | 60 | 21 | $588.95 | $9.82 | $0.00 | 29.17 | 41.65 |
| 6 | ATORVASTATIN CALCIUM | 8 DAYS LATE REFILLING | Message Only | 58 | 7 | $615.40 | $10.61 | $0.00 | 32.10 | 32.10 |
| 6 | GABAPENTIN | 9 DAYS LATE REFILLING | Message Only | 58 | 3 | $637.86 | $11.00 | $0.00 | 28.93 | 91.76 |
| 8 | ATORVASTATIN CALCIUM | 9 DAYS LATE REFILLING | Message Only | 56 | 10 | $607.08 | $10.84 | $0.00 | 30.79 | 30.79 |
| 9 | PROVENTIL HFA | 11 DAYS LATE REFILLING | Message Only | 55 | 4 | $4,457.41 | $81.04 | $0.00 | 20.16 | 6.70 |
| 10 | MONTELUKAST SODIUM | 7 DAYS LATE REFILLING | Message Only | 54 | 2 | $1,174.12 | $21.74 | $0.00 | 30.00 | 30.56 |
| 10 | LEVOTHYROXINE SODIUM | 8 DAYS LATE REFILLING | Message Only | 54 | 4 | $692.71 | $12.83 | $0.00 | 30.02 | 30.02 |
| All Others | | | | 55,945 | 7,266 | $6,968,670.60 | $124.56 | $0.00 | 31.71 | 59.18 |
| **LR** | | | | **56,600** | **7,339** | **$6,985,558.03** | **$123.42** | **$0.00** | **31.67** | **58.94** |

## MN

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | IPRATROPIUM BROMIDE/ALBUT | MIN. DAYS THERAPY = 30 | Message Only | 1,854 | 240 | $14,385.58 | $7.76 | $0.00 | 5.22 | 65.94 |
| 2 | LISINOPRIL | MIN. DAYS THERAPY = 7 | Message Only | 940 | 10 | $84.20 | $0.09 | $0.00 | 1.03 | 1.35 |
| 3 | PANTOPRAZOLE SODIUM | MIN. DAYS THERAPY = 7 | Message Only | 808 | 5 | $127.82 | $0.16 | $0.00 | 1.02 | 1.07 |
| 4 | METOPROLOL TARTRATE | MIN. DAYS THERAPY = 7 | Message Only | 713 | 7 | $120.75 | $0.17 | $0.00 | 1.06 | 1.48 |
| 5 | AMLODIPINE BESYLATE | MIN. DAYS THERAPY = 7 | Message Only | 636 | 11 | $73.21 | $0.12 | $0.00 | 1.04 | 1.16 |
| 6 | LEVETIRACETAM | MIN. DAYS THERAPY = 14 | Message Only | 612 | 27 | $3,268.50 | $5.34 | $0.00 | 2.60 | 30.25 |
| 7 | KLOR-CON M20 | MIN. DAYS THERAPY = 7 | Message Only | 586 | 7 | $343.25 | $0.59 | $0.00 | 1.06 | 2.13 |
| 8 | ATORVASTATIN CALCIUM | MIN. DAYS THERAPY = 7 | Message Only | 551 | 4 | $157.18 | $0.29 | $0.00 | 1.06 | 1.16 |
| 9 | CARVEDILOL | MIN. DAYS THERAPY = 7 | Message Only | 470 | 16 | $27.97 | $0.06 | $0.00 | 1.01 | 1.37 |
| 10 | CLONIDINE HCL | MIN. DAYS THERAPY = 7 | Message Only | 436 | 37 | $497.64 | $1.14 | $0.00 | 1.26 | 3.48 |
| All Others | | | | 14,804 | 955 | $1,187,349.13 | $80.20 | $0.00 | 2.02 | 35.87 |
| **MN** | | | | **22,410** | **1,319** | **$1,206,435.23** | **$53.83** | **$0.00** | **2.08** | **30.33** |

## MX

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 2,421 | 1,766 | $25,011.69 | $10.33 | $0.00 | 31.54 | 66.38 |
| 2 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 1,461 | 0 | $15,094.83 | $10.33 | $0.00 | 32.20 | 72.54 |
| 3 | FLUCONAZOLE | MAX DAYS THERAPY = 1 | Message Only | 500 | 159 | $6,442.39 | $12.88 | $0.00 | 7.69 | 3.05 |
| 4 | EPIPEN 2-PAK | MAX DAYS THERAPY = 1 | Message Only | 365 | 8 | $232,394.92 | $636.70 | $0.00 | 10.83 | 2.27 |
| 5 | AZITHROMYCIN | MAX DAYS THERAPY = 5 | Message Only | 265 | 70 | $5,814.26 | $21.94 | $0.00 | 11.47 | 20.98 |
| 6 | EPINEPHRINE | MAX DAYS THERAPY = 1 | Message Only | 251 | 10 | $77,655.31 | $309.38 | $0.00 | 14.49 | 2.46 |
| 7 | DIPHENOXYLATE/ ATROPINE | MAX DAYS THERAPY = 14 | Message Only | 197 | 7 | $5,903.85 | $29.97 | $0.00 | 27.97 | 95.22 |
| 7 | POLYETHYLENE GLYCOL 3350 | MAX DAYS THERAPY = 14 | Message Only | 197 | 14 | $5,836.07 | $29.62 | $0.00 | 31.45 | 32.09 |
| 9 | SENEXON-S | MAX DAYS THERAPY = 14 | Message Only | 182 | 14 | $1,717.78 | $9.44 | $0.00 | 32.14 | 62.90 |
| 10 | MAPAP | MAX DAYS THERAPY = 10 | Message Only | 164 | 8 | $1,582.96 | $9.65 | $0.00 | 26.52 | 135.23 |
| All Others | | | | 2,903 | 392 | $748,210.60 | $257.74 | $0.00 | 29.47 | 68.13 |
| **MX** | | | | **8,906** | **2,448** | **$1,125,664.66** | **$126.39** | **$0.00** | **27.55** | **59.70** |

## PA

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PROMETHAZINE HCL | AGE LESS THAN 4 | Message Only | 16 | 0 | $183.15 | $11.45 | $0.00 | 8.12 | 177.75 |
| 2 | PROMETHAZINE HCL PLAIN | AGE LESS THAN 4 | Message Only | 10 | 0 | $57.37 | $5.74 | $0.00 | 9.60 | 105.00 |
| 2 | NITROFURANTOIN | AGE LESS THAN 4 | Message Only | 10 | 2 | $1,613.65 | $161.36 | $0.00 | 24.80 | 154.50 |
| 4 | PROMETHAZINE/ DEXTROMETHOR | AGE LESS THAN 4 | Message Only | 5 | 0 | $54.41 | $10.88 | $0.00 | 11.20 | 78.80 |
| 4 | PROMETHAZINE-DM | AGE LESS THAN 4 | Message Only | 5 | 0 | $57.57 | $11.51 | $0.00 | 11.60 | 126.00 |
| 6 | PROMETHEGAN | AGE LESS THAN 4 | Message Only | 2 | 0 | $157.63 | $78.82 | $0.00 | 3.00 | 8.50 |
| 7 | PHENYLEPHRINE HCL | AGE LESS THAN 4 | Message Only | 1 | 0 | $100.17 | $100.17 | $0.00 | 30.00 | 15.00 |
| 7 | BENZTROPINE MESYLATE | AGE LESS THAN 4 | Message Only | 1 | 0 | $13.69 | $13.69 | $0.00 | 30.00 | 60.00 |
| **PA** | | | | **50** | **2** | **$2,237.64** | **$44.75** | **$0.00** | **13.08** | **131.10** |

## TD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | QUETIAPINE FUMARATE | ORAL ANTIPSYCHOTICS | Message Only | 2,700 | 1 | $41,363.12 | $15.32 | $0.00 | 29.31 |
| 2 | RISPERIDONE | ORAL ANTIPSYCHOTICS | Message Only | 1,653 | 0 | $20,443.59 | $12.37 | $0.00 | 29.85 |
| 3 | MORPHINE SULFATE | SHORT ACTING NARCOTIC ANALGESI | Message Only | 1,577 | 49 | $4,344.98 | $2.76 | $0.00 | 1.00 |
| 4 | LISINOPRIL | ANGIOTENSIN BLOCKERS | Message Only | 1,153 | 0 | $11,780.89 | $10.22 | $0.00 | 69.99 |
| 5 | GABAPENTIN | GABAPENTIN AND RELATED | Message Only | 1,148 | 0 | $18,455.19 | $16.08 | $0.00 | 35.02 |
| 6 | ARIPIPRAZOLE | ORAL ANTIPSYCHOTICS | Message Only | 1,079 | 0 | $59,319.66 | $54.98 | $0.00 | 30.68 |
| 7 | LEVOTHYROXINE SODIUM | THYROID HORMONES | Message Only | 932 | 0 | $16,731.01 | $17.95 | $0.00 | 49.28 |
| 8 | OLANZAPINE | ORAL ANTIPSYCHOTICS | Message Only | 878 | 0 | $14,087.72 | $16.05 | $0.00 | 28.60 |
| 9 | HYDROMORPHONE HCL | SHORT ACTING NARCOTIC ANALGESI | Message Only | 871 | 48 | $3,914.04 | $4.49 | $0.00 | 1.00 |
| 10 | SERTRALINE HCL | SSRIS AND SNRIS | Message Only | 808 | 0 | $9,785.66 | $12.11 | $0.00 | 34.27 |
| All Others | | | | 81,055 | 114,198 | $14,680,252.55 | $181.11 | $0.00 | 29.45 |
| **TD** | | | | **93,854** | **114,296** | **$14,880,478.41** | **$158.55** | **$0.00** | **29.52** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## TD

| Quantity Per Rx |
|---|
| 41.78 |
| 49.40 |
| 1.70 |
| 75.67 |
| 112.64 |
| 35.33 |
| 47.82 |
| 37.16 |
| 2.44 |
| 42.18 |
| 75.92 |
| **71.59** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30



## Selected Filters

**Client(s): Nevada Medicaid - HPES**

**Carrier(s): NVM-NEVADA MEDICAID**

**Account(s): ALL**

**Group(s): ALL**

| | |
|---|---|
| **Date Type:** | Date Filled Submitted |
| **Start Date:** | 2017-04-01 |
| **End Date:** | 2017-06-30 |
| **Relative Description:** | Select Date Range |
| **Display Report Description:** | No |
| **Top Values to Display:** | 10 |

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# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30

Jan 18, 2018 1:02:56 PM

## Client Totals:

| Total Rxs | Plan Paid | Member Paid |
|---|---|---|
| 679,937 | $77,230,033 | $0 |

## DUR Information as a percent of total:

| DUR Type | Total Rxs | Percent of Total Rxs - Paid | Cases | Rejected Rxs | Percent of Total Rxs - Rejects |
|---|---|---|---|---|---|
| Total Claims Paid | 679,937 | 0.0% | 0 | 0 | 0.0% |
| Cases / Rxs | 538,406 | 79.2% | 695,978 | 350,217 | 51.5% |
| DD - Drug-Drug Interaction | 231,967 | 34.1% | 444,670 | 162,503 | 23.9% |
| TD - Therapeutic Duplication | 111,132 | 16.3% | 93,788 | 110,214 | 16.2% |
| ID - Ingredient Duplication | 57,356 | 8.4% | 21,883 | 57,233 | 8.4% |
| LR - Underuse Precaution | 53,036 | 7.8% | 53,178 | 7,034 | 1.0% |
| LD - Low Dose Alert | 33,104 | 4.9% | 31,316 | 5,967 | 0.9% |
| MN - Insufficnt Duration Alert | 25,079 | 3.7% | 24,712 | 1,289 | 0.2% |
| HD - High Dose Alert | 17,885 | 2.6% | 17,515 | 3,499 | 0.5% |
| MX - Excessive Duration Alert | 8,749 | 1.3% | 8,815 | 2,471 | 0.4% |
| PA - Drug-Age Precaution | 97 | 0.0% | 100 | 7 | 0.0% |
| SX - Drug Gender Alert | 1 | 0.0% | 1 | 0 | 0.0% |

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

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# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## DD

| Curr Rank | Top Drug Drug Interaction | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | HYDROCODONE/ ACETAMINOPHEN - ALPRAZOLAM | Message Only | 3,909 | 638 | $71,506.49 | $18.29 | $0.00 | 22.19 | 86.57 |
| 2 | LISINOPRIL - FUROSEMIDE | Message Only | 3,597 | 1,037 | $23,345.83 | $6.49 | $0.00 | 45.62 | 53.92 |
| 3 | SIMVASTATIN - LISINOPRIL | Message Only | 3,431 | 824 | $25,190.44 | $7.34 | $0.00 | 50.94 | 53.08 |
| 4 | HYDROCO/APAP - ALPRAZOLAM | Message Only | 3,189 | 647 | $29,988.84 | $9.40 | $0.00 | 26.59 | 62.21 |
| 5 | ONDANSETRON HCL - HYDROCO/APAP | Message Only | 2,939 | 65 | $8,823.55 | $3.00 | $0.00 | 2.32 | 5.27 |
| 6 | OXYCODONE HCL - ALPRAZOLAM | Message Only | 2,501 | 523 | $62,710.56 | $25.07 | $0.00 | 24.92 | 100.52 |
| 7 | LISINOPRIL - IBUPROFEN | Message Only | 2,399 | 580 | $21,956.49 | $9.15 | $0.00 | 34.55 | 67.06 |
| 8 | OXYCODONE/ ACETAMINOPHEN - ALPRAZOLAM | Message Only | 2,329 | 380 | $73,086.80 | $31.38 | $0.00 | 21.39 | 81.08 |
| 9 | OXYCODONE - ALPRAZOLAM | Message Only | 2,272 | 599 | $22,291.94 | $9.81 | $0.00 | 25.62 | 64.06 |
| 10 | MORPHINE SULFATE ER - GABAPENTIN | Message Only | 1,980 | 447 | $52,742.96 | $26.64 | $0.00 | 26.09 | 55.27 |
| All Others | | | 416,124 | 156,763 | $24,380,208.00 | $58.59 | $0.00 | 29.82 | 56.42 |
| **Summary** | | | **444,670** | **162,503** | **$24,771,851.90** | **$55.71** | **$0.00** | **29.75** | **56.82** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## HD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ZOLPIDEM TARTRATE | GERIATRIC MAX DLY = .50UN | Message Only | 385 | 22 | $647.62 | $1.68 | $0.00 | 29.80 | 29.80 |
| 2 | KETOROLAC TROMETHAMINE | GERIATRIC MAX DLY = 2.00UN | Message Only | 365 | 23 | $5,016.53 | $13.74 | $0.00 | 1.00 | 6.93 |
| 3 | CEFTRIAXONE SODIUM | GERIATRIC MAX DLY = 2.00UN | Message Only | 304 | 89 | $9,852.23 | $32.41 | $0.00 | 1.00 | 226.37 |
| 4 | MIDAZOLAM HCL | GERIATRIC MAX DLY = 3.50UN | Message Only | 245 | 4 | $557.79 | $2.28 | $0.00 | 1.00 | 6.15 |
| 5 | MONTELUKAST SODIUM | PEDIATRIC MAX DLY = .50UN | Message Only | 242 | 19 | $3,343.17 | $13.81 | $0.00 | 36.69 | 36.69 |
| 6 | HYDROCODONE/ ACETAMINOPHEN | ADULT MAX DLY = 6.00 UN | Message Only | 238 | 17 | $7,183.00 | $30.18 | $0.00 | 17.26 | 142.96 |
| 7 | GRANISETRON HCL | GERIATRIC MAX DLY = .85UN | Message Only | 208 | 11 | $2,715.44 | $13.06 | $0.00 | 1.00 | 1.48 |
| 8 | BETAMETHASONE SODIUM PHOS | GERIATRIC MAX DLY = 1.50UN | Message Only | 205 | 5 | $6,269.42 | $30.58 | $0.00 | 1.00 | 5.01 |
| 9 | IBUPROFEN | ADULT MAX DLY = 4.00 UN | Message Only | 187 | 15 | $2,035.29 | $10.88 | $0.00 | 8.24 | 37.74 |
| 9 | INVEGA SUSTENNA | ADULT MAX DLY = .05 UN | Message Only | 187 | 130 | $420,510.87 | $2,248.72 | $0.00 | 26.73 | 1.51 |
| All Others | | | | 14,949 | 3,164 | $8,147,932.71 | $545.05 | $0.00 | 16.29 | 161.30 |
| **HD** | | | | **17,515** | **3,499** | **$8,606,064.07** | **$491.35** | **$0.00** | **15.75** | **145.42** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## ID

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | PROVENTIL HFA | PROVENTIL AER HFA | Message Only | 399 | 18 | $39,306.29 | $98.51 | $0.00 | 28.54 | 8.23 |
| 2 | GABAPENTIN | GABAPENTIN CAP 300MG | Message Only | 286 | 15 | $3,857.94 | $13.49 | $0.00 | 38.00 | 118.81 |
| 3 | TRAZODONE HCL | TRAZODONE TAB 100MG | Message Only | 198 | 9 | $2,338.06 | $11.81 | $0.00 | 35.47 | 49.25 |
| 4 | MONTELUKAST SODIUM | MONTELUKAST TAB 10MG | Message Only | 193 | 8 | $2,556.08 | $13.24 | $0.00 | 44.06 | 44.37 |
| 5 | SERTRALINE HCL | SERTRALINE TAB 100MG | Message Only | 183 | 9 | $2,175.73 | $11.89 | $0.00 | 36.26 | 45.91 |
| 6 | TRAZODONE HCL | TRAZODONE TAB 50MG | Message Only | 179 | 10 | $1,812.46 | $10.13 | $0.00 | 32.14 | 40.22 |
| 7 | CLONIDINE HCL | CLONIDINE TAB 0.1MG | Message Only | 176 | 12 | $2,244.46 | $12.75 | $0.00 | 76.28 | 126.71 |
| 8 | AMLODIPINE BESYLATE | AMLODIPINE TAB 10MG | Message Only | 162 | 7 | $1,715.23 | $10.59 | $0.00 | 76.27 | 75.73 |
| 9 | IBUPROFEN | IBUPROFEN TAB 800MG | Message Only | 156 | 5 | $1,945.93 | $12.47 | $0.00 | 28.80 | 75.37 |
| 10 | LANTUS SOLOSTAR | LANTUS INJ SOLOSTAR | Message Only | 145 | 8 | $110,671.94 | $763.25 | $0.00 | 79.92 | 32.67 |
| 10 | METFORMIN HCL | METFORMIN TAB 500MG | Message Only | 145 | 7 | $1,432.13 | $9.88 | $0.00 | 68.88 | 126.36 |
| All Others | | | | 19,661 | 57,125 | $3,335,330.11 | $169.64 | $0.00 | 37.99 | 98.90 |
| **ID** | | | | **21,883** | **57,233** | **$3,505,386.36** | **$160.19** | **$0.00** | **38.79** | **95.28** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## LD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ONDANSETRON ODT | GERIATRIC MIN DLY = 2.00UN | Message Only | 1,188 | 19 | $466.69 | $0.39 | $0.00 | 1.17 | 1.13 |
| 2 | HEPARIN SODIUM | GERIATRIC MIN DLY = 20.00UN | Message Only | 1,124 | 1,634 | $4,425.75 | $3.94 | $0.00 | 1.00 | 3.12 |
| 3 | IPRATROPIUM BROMIDE/ ALBUT | GERIATRIC MIN DLY = 9.00UN | Message Only | 858 | 21 | $734.87 | $0.86 | $0.00 | 2.08 | 8.80 |
| 4 | HEPARIN SODIUM | GERIATRIC MIN DLY = 4.00UN | Message Only | 845 | 9 | $1,690.94 | $2.00 | $0.00 | 1.21 | 1.96 |
| 5 | METOPROLOL TARTRATE | GERIATRIC MIN DLY = 2.00UN | Message Only | 550 | 33 | $592.19 | $1.08 | $0.00 | 14.70 | 14.26 |
| 6 | ALBUTEROL SULFATE | GERIATRIC MIN DLY = 9.00UN | Message Only | 486 | 11 | $1,065.36 | $2.19 | $0.00 | 5.22 | 27.17 |
| 7 | ONDANSETRON HCL | GERIATRIC MIN DLY = 2.00UN | Message Only | 484 | 61 | $196.62 | $0.41 | $0.00 | 1.84 | 1.84 |
| 8 | METFORMIN HCL | ADULT MIN DLY = 1.70 UN | Message Only | 372 | 104 | $3,122.68 | $8.39 | $0.00 | 62.35 | 61.68 |
| 9 | GABAPENTIN | ADULT MIN DLY = 3.00 UN | Message Only | 371 | 55 | $3,790.15 | $10.22 | $0.00 | 33.40 | 54.89 |
| 10 | VITAMIN D | ADULT MIN DLY = .14 UN | Message Only | 343 | 46 | $3,509.14 | $10.23 | $0.00 | 40.12 | 4.39 |
| All Others | | | | 24,695 | 3,974 | $4,020,295.49 | $162.80 | $0.00 | 28.08 | 49.61 |
| **LD** | | | | **31,316** | **5,967** | **$4,039,889.88** | **$129.00** | **$0.00** | **24.25** | **41.70** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## LR

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | GABAPENTIN | 7 DAYS LATE REFILLING | Message Only | 69 | 4 | $911.27 | $13.21 | $0.00 | 29.06 | 91.39 |
| 2 | LEVOTHYROXINE SODIUM | 7 DAYS LATE REFILLING | Message Only | 64 | 5 | $781.26 | $12.21 | $0.00 | 30.03 | 30.06 |
| 2 | ATORVASTATIN CALCIUM | 7 DAYS LATE REFILLING | Message Only | 64 | 5 | $641.44 | $10.02 | $0.00 | 30.30 | 31.70 |
| 4 | PROVENTIL HFA | 8 DAYS LATE REFILLING | Message Only | 57 | 1 | $4,488.00 | $78.74 | $0.00 | 22.11 | 6.94 |
| 5 | GABAPENTIN | 9 DAYS LATE REFILLING | Message Only | 52 | 3 | $676.63 | $13.01 | $0.00 | 28.60 | 88.67 |
| 5 | GABAPENTIN | 8 DAYS LATE REFILLING | Message Only | 52 | 2 | $653.57 | $12.57 | $0.00 | 28.67 | 91.50 |
| 7 | PROVENTIL HFA | 7 DAYS LATE REFILLING | Message Only | 49 | 2 | $4,261.60 | $86.97 | $0.00 | 22.88 | 7.25 |
| 8 | MONTELUKAST SODIUM | 7 DAYS LATE REFILLING | Message Only | 48 | 2 | $892.80 | $18.60 | $0.00 | 30.00 | 30.00 |
| 8 | PROVENTIL HFA | 12 DAYS LATE REFILLING | Message Only | 48 | 2 | $4,179.00 | $87.06 | $0.00 | 21.27 | 7.12 |
| 10 | QUETIAPINE FUMARATE | 7 DAYS LATE REFILLING | Message Only | 45 | 23 | $542.19 | $12.05 | $0.00 | 28.33 | 44.91 |
| All Others | | | | 52,630 | 6,985 | $6,932,733.57 | $131.73 | $0.00 | 32.20 | 60.64 |
| **LR** | | | | **53,178** | **7,034** | **$6,950,761.33** | **$130.71** | **$0.00** | **32.15** | **60.47** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## MN

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | IPRATROPIUM BROMIDE/ALBUT | MIN. DAYS THERAPY = 30 | Message Only | 1,697 | 237 | $13,325.00 | $7.85 | $0.00 | 5.29 | 66.46 |
| 2 | LISINOPRIL | MIN. DAYS THERAPY = 7 | Message Only | 1,005 | 25 | $98.36 | $0.10 | $0.00 | 1.02 | 1.39 |
| 3 | PANTOPRAZOLE SODIUM | MIN. DAYS THERAPY = 7 | Message Only | 846 | 11 | $146.96 | $0.17 | $0.00 | 1.03 | 1.07 |
| 4 | AMLODIPINE BESYLATE | MIN. DAYS THERAPY = 7 | Message Only | 769 | 15 | $49.33 | $0.06 | $0.00 | 1.02 | 1.22 |
| 5 | METOPROLOL TARTRATE | MIN. DAYS THERAPY = 7 | Message Only | 744 | 9 | $81.04 | $0.11 | $0.00 | 1.04 | 1.42 |
| 6 | LEVETIRACETAM | MIN. DAYS THERAPY = 14 | Message Only | 676 | 30 | $3,487.71 | $5.16 | $0.00 | 2.79 | 32.87 |
| 7 | ATORVASTATIN CALCIUM | MIN. DAYS THERAPY = 7 | Message Only | 633 | 10 | $211.00 | $0.33 | $0.00 | 1.04 | 1.22 |
| 8 | QUETIAPINE FUMARATE | MIN. DAYS THERAPY = 7 | Message Only | 566 | 40 | $486.56 | $0.86 | $0.00 | 1.16 | 2.82 |
| 9 | CLONIDINE HCL | MIN. DAYS THERAPY = 7 | Message Only | 489 | 23 | $739.65 | $1.51 | $0.00 | 1.36 | 3.04 |
| 10 | CARVEDILOL | MIN. DAYS THERAPY = 7 | Message Only | 465 | 13 | $45.20 | $0.10 | $0.00 | 1.01 | 1.87 |
| All Others | | | | 16,822 | 876 | $2,094,422.42 | $124.50 | $0.00 | 1.82 | 17.13 |
| **MN** | | | | **24,712** | **1,289** | **$2,113,093.23** | **$85.51** | **$0.00** | **1.92** | **17.49** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## MX

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 2,429 | 1,712 | $25,275.91 | $10.41 | $0.00 | 31.88 | 67.98 |
| 2 | CYCLOBENZAPRINE HCL | MAX DAYS THERAPY = 21 | Message Only | 1,398 | 0 | $14,898.77 | $10.66 | $0.00 | 32.35 | 72.19 |
| 3 | FLUCONAZOLE | MAX DAYS THERAPY = 1 | Message Only | 501 | 155 | $6,249.20 | $12.47 | $0.00 | 6.86 | 3.00 |
| 4 | EPIPEN 2-PAK | MAX DAYS THERAPY = 1 | Message Only | 389 | 26 | $257,552.67 | $662.09 | $0.00 | 11.24 | 2.34 |
| 5 | AZITHROMYCIN | MAX DAYS THERAPY = 5 | Message Only | 213 | 52 | $5,176.36 | $24.30 | $0.00 | 13.92 | 24.47 |
| 5 | EPINEPHRINE | MAX DAYS THERAPY = 1 | Message Only | 213 | 10 | $64,457.39 | $302.62 | $0.00 | 11.06 | 2.37 |
| 7 | MAPAP | MAX DAYS THERAPY = 10 | Message Only | 202 | 11 | $1,927.49 | $9.54 | $0.00 | 26.63 | 123.24 |
| 8 | SENEXON-S | MAX DAYS THERAPY = 14 | Message Only | 183 | 18 | $1,664.60 | $9.10 | $0.00 | 31.20 | 62.50 |
| 9 | DIPHENOXYLATE/ ATROPINE | MAX DAYS THERAPY = 14 | Message Only | 179 | 14 | $6,144.23 | $34.33 | $0.00 | 28.40 | 110.73 |
| 10 | PHENAZOPYRIDINE HCL | MAX DAYS THERAPY = 2 | Message Only | 178 | 3 | $5,255.89 | $29.53 | $0.00 | 5.53 | 16.15 |
| All Others | | | | 2,930 | 470 | $759,476.51 | $259.21 | $0.00 | 30.72 | 64.81 |
| **MX** | | | | **8,815** | **2,471** | **$1,148,079.02** | **$130.24** | **$0.00** | **27.56** | **59.34** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## PA

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ACETAMINOPHEN/ CODEINE | AGE LESS THAN 10 | Message Only | 52 | 1 | $491.97 | $9.46 | $0.00 | 6.31 | 93.98 |
| 2 | ACETAMINOPHEN/ CODEINE | AGE LESS THAN 4 | Message Only | 18 | 3 | $120.16 | $6.68 | $0.00 | 4.72 | 53.36 |
| 3 | NITROFURANTOIN | AGE LESS THAN 4 | Message Only | 11 | 3 | $1,867.66 | $169.79 | $0.00 | 23.82 | 146.36 |
| 4 | PROMETHAZINE HCL | AGE LESS THAN 4 | Message Only | 5 | 0 | $55.21 | $11.04 | $0.00 | 12.00 | 66.00 |
| 5 | ACETAMINOPHEN/ CODEINE PHO | AGE LESS THAN 10 | Message Only | 4 | 0 | $39.26 | $9.82 | $0.00 | 3.25 | 10.00 |
| 6 | PROMETHAZINE-DM | AGE LESS THAN 4 | Message Only | 3 | 0 | $32.11 | $10.70 | $0.00 | 14.33 | 120.00 |
| 7 | PHENYLEPHRINE HCL | AGE LESS THAN 4 | Message Only | 2 | 0 | $200.34 | $100.17 | $0.00 | 30.00 | 15.00 |
| 8 | PROMETHAZINE/ DEXTROMETHOR | AGE LESS THAN 4 | Message Only | 1 | 0 | $8.40 | $8.40 | $0.00 | 12.00 | 120.00 |
| 8 | INFANRIX | AGE GREATER THAN 64 | Message Only | 1 | 0 | $22.44 | $22.44 | $0.00 | 1.00 | 0.50 |
| 8 | ACETAMINOPHEN/ CODEINE PHO | AGE LESS THAN 4 | Message Only | 1 | 0 | $18.16 | $18.16 | $0.00 | 7.00 | 70.00 |
| 8 | TRAMADOL HCL | AGE LESS THAN 10 | Message Only | 1 | 0 | $10.49 | $10.49 | $0.00 | 5.00 | 15.00 |
| 8 | PROMETHAZINE HCL PLAIN | AGE LESS THAN 4 | Message Only | 1 | 0 | $5.99 | $5.99 | $0.00 | 8.00 | 60.00 |
| **PA** | | | | **100** | **7** | **$2,872.19** | **$28.72** | **$0.00** | **8.84** | **84.83** |

## SX

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx | Quantity Per Rx |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | BICALUTAMIDE | GENERAL CONTRAINDICATION | Message Only | 1 | 0 | $16.47 | $16.47 | $0.00 | 30.00 | 30.00 |
| **SX** | | | | **1** | **0** | **$16.47** | **$16.47** | **$0.00** | **30.00** | **30.00** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## TD

| Curr Rank | Top Drug | Therapy / Reason | DUR Response | Paid Rxs | Rejected Rxs | Plan Paid | Plan Paid Per Rx | Member Paid Per Rx | Days Supply Per Rx |
|---|---|---|---|---|---|---|---|---|---|
| 1 | QUETIAPINE FUMARATE | ORAL ANTIPSYCHOTICS | Message Only | 2,583 | 0 | $39,355.48 | $15.24 | $0.00 | 30.54 |
| 2 | RISPERIDONE | ORAL ANTIPSYCHOTICS | Message Only | 1,624 | 0 | $20,515.52 | $12.63 | $0.00 | 29.86 |
| 3 | MORPHINE SULFATE | SHORT ACTING NARCOTIC ANALGESI | Message Only | 1,476 | 88 | $3,983.41 | $2.70 | $0.00 | 1.00 |
| 4 | GABAPENTIN | GABAPENTIN AND RELATED | Message Only | 1,141 | 0 | $18,655.22 | $16.35 | $0.00 | 35.37 |
| 5 | ARIPIPRAZOLE | ORAL ANTIPSYCHOTICS | Message Only | 1,098 | 0 | $45,268.68 | $41.23 | $0.00 | 30.62 |
| 6 | LISINOPRIL | ANGIOTENSIN BLOCKERS | Message Only | 1,013 | 0 | $10,308.88 | $10.18 | $0.00 | 70.76 |
| 7 | HYDROMORPHONE HCL | SHORT ACTING NARCOTIC ANALGESI | Message Only | 908 | 58 | $3,731.08 | $4.11 | $0.00 | 1.00 |
| 8 | LEVOTHYROXINE SODIUM | THYROID HORMONES | Message Only | 907 | 0 | $16,085.27 | $17.73 | $0.00 | 48.20 |
| 9 | SERTRALINE HCL | SSRIS AND SNRIS | Message Only | 875 | 0 | $11,367.68 | $12.99 | $0.00 | 34.85 |
| 10 | OLANZAPINE | ORAL ANTIPSYCHOTICS | Message Only | 840 | 0 | $13,103.28 | $15.60 | $0.00 | 31.15 |
| All Others | | | | 81,323 | 110,068 | $13,350,757.17 | $164.17 | $0.00 | 28.58 |
| **TD** | | | | **93,788** | **110,214** | **$13,533,131.67** | **$144.29** | **$0.00** | **28.79** |

## TD

| Quantity Per Rx |
|---|
| 44.02 |
| 50.66 |
| 1.74 |
| 113.19 |
| 34.36 |
| 76.56 |
| 2.09 |
| 46.19 |
| 42.54 |
| 39.01 |
| 69.14 |
| **65.89** |

# RXT6050D - Summarized DUR Activity Report

Between 2017-07-01 and 2017-09-30



## Selected Filters

**Client(s): Nevada Medicaid - HPES**

**Carrier(s): NVM-NEVADA MEDICAID**

**Account(s): ALL**

**Group(s): ALL**

| | |
|---|---|
| **Date Type:** | Date Filled Submitted |
| **Start Date:** | 2017-07-01 |
| **End Date:** | 2017-09-30 |
| **Relative Description:** | Select Date Range |
| **Display Report Description:** | No |
| **Top Values to Display:** | 10 |

November 27, 2017

State of Nevada
Department of Health and Human Services
Division of Health Care Financing and Policy
1100 E. William Street, Suite 101
Carson City, Nevada 98701

Dear Sirs/Madams,

Thank you for your letter written on November 2017 regarding your Drug Use Review Board findings. Your review labeled my nurse practitioner, , as the top narcotic prescriber in the state. The sum of members was 2,119 for the period of October 1, 2016 thru September 30, 2017. You stated that the letter was sent to as a means of self-evaluation.

I would like to enumerate our self-evaluation findings.

1. We had a total of three providers for a number of years. It was our decision to treat all patients equally. While most practices limit the amount of Medicaid patients to 10-20%, we felt it was our duty to provide care to all patients regardless of their economic disposition. Hence, we have a much higher percentage of Medicaid patients than most practices.

2. The physicians typically see all the new patients leaving the nurse practitioner to see follow up patients.

3. Our other physician left our practice over a year ago and it has been difficult to replace him. Our individual loads have increased as a result.

4. Our practice provides a holistic approach to pain medicine. While most pain practices focus on interventional procedures, they send their difficult patients to for narcotic management. At we prescribe physical therapy, psychological intervention, alternative treatments, and other similar interventions. In summary, "injection oriented" pain practices send their difficult patients to for maintenance of medications.

5. Despite our patient population encompassing the "worst of the worst", we are persistent and diligent in our efforts to reduce the total amount of narcotic medications for each of our patients. We strive to get most of our patients down to the "recommended dose of 90-120 meq of morphine

per day. We are successful in a good number of our patients, but for some patients, it is nearly impossible to do so.

6. We constantly look for diversion and abuse in all our patients. We perform random and systematic urine toxicology screens. Patients who show inconsistencies are dealt with. We frequently discharge patients from our practice due to non-compliance.

7. Lastly, in the past few years we have been visited by CMS, Board of Pharmacy, and the Nevada Medical State Board of Medicine. They have reviewed voluminous amounts of charts and have found our documentation to be well in compliance with the National Standards. For your review, we have enclosed a copy of our policy and procedures regarding our pain practice.

We hope this sheds a little light into our practice. We welcome any further comments or concerns. Please do not hesitate to call us if you have any questions regarding the above.

Respectfully submitted,