BRIAN SANDOVAL
Governor

RICHARD WHITLEY, MS
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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

AGENDA

Date of Posting:	**April 6, 2018**
Date of Meeting:	**Thursday, April 26, 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 Board (DUR)**
Place of Meeting:	**Hyatt Place Reno-Tahoe Airport** **1790 E. Plumb Lane** **Reno, Nevada 89502** **Phone: (775) 826-2500**
Webinar Registration	https://optum.webex.com/optum/onstage/g.php?MTID=e70c72e9d5524fee86c7c1ef4c0da3cdb **Or go to www.webex.com and enter the Event Number listed below.** **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:	**642 377 688** **Click "Join Now"**

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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 January 25, 2018.

i. Status Update by the DHCFP.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for hydroxyprogesterone caproate (Makena®).

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 updated prior authorization criteria and/or quantity limits for the monoclonal antibody agent class.

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 updated prior authorization criteria and/or quantity limits for GnRH Analogs.

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 for High Dollar Claims.

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. Acetaminophen Utilization.

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

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

c. Opioid utilization – Members under age 18 years.

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

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

e. Opioid utilization – Top prescriber and member, including more than four concurrent opioids.

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

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

g. Diabetic patients with hospital admissions.

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

h. **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 Q2 2011, Q3 2017 and Q4 2017 (by Payment and by Claims).
ii. Top 50 Drugs of Q2 2011, Q3 2017 and Q4 2017 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q1 2018.
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.

This notice and agenda have been posted at http://dhcfp.nv.gov and http://notice.nv.gov. The agenda posting of this meeting can be viewed at the following locations: Carson City Central office, Las Vegas District Office, Reno District Office, Elko District Office, Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a copy of the meeting materials will be mailed to you. Requests and/or written comments may be sent to Colleen McLachlan at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701, at least three 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 cmlachlan@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, January 25, 2018 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

ATTENDEES

Board Members Present
Paul Oesterman, Pharm.D.
James Marx, MD
Michael Owens, MD
Jennifer Wheeler, Pharm.D.
David England, Pharm.D.

Board Members Absent
Marta Bunuel, MD
Yvette Kaunismaki, MD

DHCFP
Darrell Faircloth, Deputy Attorney General
Holly Long, Social Services Program Specialist
Shannon Sprout, Deputy Administrator
Cody Phinney
Theresa Carsten

DXC

Beth Slamowitz, Pharm.D.

OptumRx
Carl Jeffery, Pharm.D.

Public
Rupa Shah, Purdue
Tom Beranek, SilverSummit
Robin Reedy, NAMI
Laura Hill, Abbvie
Yvonne Lun, Teva
Sandy Sierawski, Pfizer
Mark Rueckert, Pfizer
Mark Schwartz, GSK
Ann Nelson, Vertex
Tom O'Connor, Novartis
Ryan Bitton, HPN
Jeannine Murray, Anthem

Teleconference
Jennifer Lauper, BMS

AGENDA

1. Call to Order and Roll Call

Paul Oesterman, Chair: The Department of Health and Human Services, Division of Healthcare Finance and Policy Recommendation Review Board Meeting. We'll start off with a roll call and we will start at the far left side:

Shannon Sprout: I'm Shannon Sprout Deputy Administrator for the health policy for additional healthcare financial costs.

Cody Phinney: I'm Cody Phinney, I'm the Deputy Administrator for Healthcare financing and policy for MCOs and finance.

Beth Slamowitz: I'm Beth Slamowitz with DXC Technology.

Holly Long: I'm Holly Long, Pharmacy Specialist with DHCFP.
Carl Jeffery: I'm Carl Jeffery with OptumRx.

Darrell Faircloth: Senior Deputy Attorney General, Darrell Faircloth.

Paul Oesterman: Paul Oesterman, Pharmacist here in Reno.

James Marx: James Marx, Physician, Las Vegas.

Jennifer Wheeler: Jennifer Wheeler, Pharmacist in Reno.

Michael Owens: Michael Owens, family practice physician in Reno.

2. Public Comment on Any Matter on the Agenda

Paul Oesterman, Chair: For our public, the audience and online, we will ask for public comment.

Carl Jeffery: We have Dave on the line.

Paul Oesterman, Chair: Dave, do you want to tell us you're here?

Dave England: This is Dave England, Pharmacist for Las Vegas.

Paul Oesterman, Chair: For anybody in the audience, either in person or online, we will ask for public comments at each section and also in general for public comments, but we do ask that you limit your comments to 5 minutes and if you wish to address the Board, please notify us and we will be happy to recognize this. We will start off by seeing if there is any public comment on anything in general, if there's an agenda item and you want to address that item; hold your comments to that in general. Is there anybody who wishes to address the Board before we get into our full agenda? Hearing none and seeing none, we'll go into the administrative part of the meeting. I'm going to ask a little bit to digress for a moment because it's kind of with mixed feelings and mixed emotions that I

get to say so long to somebody who has been on my side of the Board Meetings, I think we've been together for about 10 years now.

Darrel Faircloth: This isn't on the agenda.

Paul Oesterman, Chair: I know, you have to stand up because on behalf of the State Drug Utilization Review Board, for your outstanding dedication, leadership and guidance, as District Attorney General to the Drug Use Review Board and the supervision and preservation of the health and lives of citizens of the state of Nevada, we wish to thank you.

Darrel Faircloth: Thank you very much.

Paul Oesterman, Chair: Thank you for everything you've done. Good luck.

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from October 19, 2017.

Carl Jeffery: I think the next item. We actually the meeting minutes on the next agenda.

Paul Oesterman, Chair: Let's take a look at the minutes from our last meeting which was October 19, 2017. Take a moment to review those and see if there are any revisions to get a motion and a second to approve them.

James Marx: Motion for approval.

Paul Oesterman, Chair: So we have a motion to approve the minutes. Do I have a second?

Jennifer Wheeler: Second.

Paul Oesterman, Chair: Any discussion? Hearing none and seeing none, I'll call for a question. All those in favor of the approval of the minutes as presented, please indicate so by saying "Aye."

Multiple Speakers: "Aye."

Paul Oesterman, Chair: All opposed say "nay." Minutes are approved.

b. Status Update by DHCFP

Paul Oesterman, Chair: Our next item is the status update from the Department and I believe we also will be looking at review and approving the updated DUR by-laws.

Shannon Sprout: Thank you everyone. I just would like to announce and not totally do the rest of the updates, but Duane Young with Behavioral Health and Pharmacy Unit, with much excitement, I would like to announce that he will be taking a promotional position with the Division of Quality and Behavioral Health. His last day was Friday. He was hoping to have actually been here for the Board but this is a week that he had an opportunity to start early so he took that opportunity. We will be recruiting for a new Chief of that position. I hope to get that

recruitment out here in the next week so we will now announce when we do have a new Chief of the Departments. Holly will be the go-to of all considered.

Holly Long, Pharmacy Specialist: For the DHCFP update, Podiatry Services have been extended as offered in the 2017 legislative session to include all Medicaid-eligible recipients who are using the services were only provided to children and participants dually enrolled with Medicare. Next, the coverage for gender reassignment services was added to the Medicaid recipients with the diagnosis of gender dysphoria and services will expand to include genital reconstruction surgical procedures based on the necessity. Registered dieticians were added as a recognized provider to support medical and nutrition therapy, physician services, medical nutrition therapy (or MNT), is going to be provider-type 15. These services may only be provided by a licensed registered dietician and must be part of a coordinated multidisciplinary team. The items went into effect on January 1, 2018, and Medicaid is just waiting for CMS approval on this.

c. **For Possible Action**: Review and Approve updated Drug Utilization Committee By-laws

Paul Oesterman, Chair: Do we have any by-laws?

Holly Long, Pharmacy Specialist: So the DUR By-Laws have just been updated, as well, and I believe each of the members have a copy of those? The first change is on page 3 under #5, we're still on that same one. All of the language was removed there under the #5 and it now reads, the director sell point one member recommended by each Managed Care Organization or MCO contracted with the DHCFP. This member shall not be an employee or contractor of any MCO. The next change is on the next page which is page 4 under section…go ahead.

Speaker: (indiscernible).

Carl Jeffery: It's not in your binder, broken down, it was sent separately.

Speaker: (indiscernible).

Holly Long, Pharmacy Specialist: If you have questions about the first one, just let me know. The second change is on page 4 under section 4 under Assistance, letter B. Just a couple of words were added here so that the language reads, the DHCFPs,, PVTM and MCOs shall provide the DUR Board with relevant clinical information, see appendix A, and would support that includes but is not limited to accepting and summarizing submissions by MCOs, Pharmaceutical Management Groups and Special Interest Groups. The next change is further down the page, page 4, under section 2, Agenda Meeting Preparation and Meeting Structure, under letter B. On the second sentence, there was additional information added so that now it reads, this shall include all pertinent information from each MCO, Manufacturers and Special Interest Groups, will be given a deadline for submission of information at time of this posting, and I think it was on the same page.

Paul Oesterman, Chair: Holly, on the last one that you mentioned, article 4 section 2, this shall include all pertinent information from each MCO, there is an s on the end of that. I don't think it needs to be there.

Holly Long, Pharmacy Specialist: Okay, thank you.

Paul Oesterman, Chair: Do we have a motion and a second to approve the revised by-laws for the DUR Board?

Jennifer Wheeler: Yes.

James Marx: Second.

Paul Oesterman, Chair: Any additional discussion? Hearing and seeing none, I will call for a question, all those in favor of the approval of the updated and revised by-laws of the DUR Board, please indicate so by saying "Aye."

Multiple Speakers: "Aye."

Paul Oesterman, Chair: All opposed, say "nay." Motion carried.

4. Clinical Presentations

Paul Oesterman, Chair: Now we are going to go into our clinical presentations. Next we will go into discussion and possible adoption of prior authorization criteria and/or quantity limits for deutetrabenazine (Austedo brand name). Is there anybody here who wishes to address the DUR Board in this regard?

Yvonne Lun: (indiscernible)

Paul Oesterman, Chair: You just step to the podium and give us your name and who you're representing. You have 5 minutes.

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

Yvonne Lun: Oh okay. I'm Yvonne Lun, Teva Pharmaceuticals. Thank you for inviting us to come. We are Teva Pharmaceuticals. We are talking about Austedo in that it is a vesicular monoamine transporter 2 indicated for the treatment of tardive dyskinesia, also abbreviated TD and also in the treatment of chorea associated with Huntington's disease. There is a boxed warning in patients with Huntington's disease, not tardive dyskinesia. Please refer to the prescribing information. Covers studies showing efficacy, side effects and dosing. Due to the lack of FDA-approved treatment for the treatment of tardive dyskinesia and significantly burden for those patients with schizophrenia, schizoaffective disorder, or movement disorder achieved, I would ask members of the committee consider the data presented for tardive dyskinesia patients to have access to Austedo.

Carl Jeffery: We have discussed this at the last meeting. We talked about Huntington's chorea last time. We approved some criteria; the criteria is updated in the binder. It is not in chapter 1200 yet, but that is the criteria that we put in for last time. This time, we brought it back because the diagnosis for the tardive dyskinesia was added later so now we've got some proposed criteria for the tardive dyskinesia. Basically what I did, we modified some of the criteria for the, we had a drug Ingrezza last time which was actually indicated for tardive dyskinesia. We made some modifications to it, combined some of the criteria for that based on some of the input from the MCOs and created that.

So, I copied that criteria for the tardive dyskinesia here. So, that's basically the criteria from that. On this particular one, we didn't have any input from any of the other MCOs so this has just been our criteria basically of what the DUR Board created last time so it just reinstates that the recipient is 18, they have a diagnosis and this is one that we had to modify a little bit from Optum proposed criteria in that we use basically a DSM-5 criteria and they are saying at least 60 days is a stable dose neuroleptic medication first or second generation antipsychotic, presence of involuntary athetoid or chorea movements lasting 30 days prescribed by or in consultation with a neurologist or psychiatrist and having one of the following: If the patient has persistent symptoms of tardive dyskinesia despite a trial dose reduction, tapering or discontinuation of the offending agent or the patient is not a candidate for a dose reduction. So, that's the reauthorization criteria which is the documentation of the positive clinical response.

Paul Oesterman, Chair: The only thing I'm not seeing there is the initial authorization of the 3 months again like we did for the Huntington's.

Carl Jeffery: Yeah, I proposed that 3-month and then probably 12-month with the reauthorization.

Paul Oesterman, Chair: Out of curiosity, we have had some utilization of the Austedo product. Was that for Huntington's or do we know?

Carl Jeffery: I don't know. Well, we didn't have a prior physician on it yet so I can't even pull the PA data on that as this PA isn't in place yet so I'm not sure what it's used for. But, if it's just one patient, then we would taper it up, so I think it's the same basis it's on every time.

Paul Oesterman, Chair: We'll need a motion and a second to approve the revised criteria that includes the diagnosis of tardive dyskinesia for this Austedo product.

James Marx: I move we adopt the proposed criteria.

Jennifer Wheeler: Second.

Paul Oesterman, Chair: We have a motion and second to approve the revised criteria as presented with the addition of the 3-month initial authorization. Any further discussion? Hearing none, I'll call for the question. All those in favor of the revised criteria, please include so by saying "Aye."

Multiple Speakers: "Aye."

Paul Oesterman, Chair: All opposed say "nay." Motion carried.

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

Paul Oesterman, Chair: Our next clinical presentation and possible action is the discussion of the possible adoption of prior authorization criteria and/or quantity limits for betrixaban (Bevyxxa ®). Is there anybody in the audience who wishes to speak before the Board? Hearing none and seeing none, we will go ahead, you can present the information, Carl.

Carl Jeffery: Sure, this is a new medication. It's in the same class as some of the other anti-Xa like the Eliquis and the Pradaxa and the Xarelto and Coumadin, too, so it's all kind of there but this one has a very unique indication. It is actually made by the same company that is making the anti-Xa so it's the reversal agent, but this one is only indicated for being treated in hospital. That is why I brought it before the Board because it's very unique. Indicated for the treatment and prophylaxis of venous thrombosis, 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. So you can, I've got the utilization pulled up on the screen. You can see how we're trending with the Eliquis and the Xarelto and we're just bumping along, and I think a pretty good adoption of these newer NOACS here that are driving down the utilization of the Warfarin therapy like the other ones so we don't have any claims for the Bevyxxa yet so we haven't seen that one come through. Here's kind of our utilization, so I think it's to be expected for a new class of medications. The criteria put together was pretty simple. It was basically just following the FDA indications as being used for prophylaxis event, the VTE, the patient is currently hospitalized for an acute medical illness, and the patient is at risk for thromboembolic complications due to moderate or severe restricted mobility or other risk factors. Something to keep in mind is that patients who are in a hospital don't need to have a prior authorization. So, any criteria for them here is going to apply to the hospital so they'll still be able to get open access to it without any restriction or waiting for something they need to start right away. It is just when they're released from the hospital, then they would need a prior authorization if they are going to fill that at the local Walgreens or something.

Paul Oesterman, Chair: Could we include in the criteria if they are going to be getting filled as an outpatient, then it's a continuation of therapy.

Carl Jeffery: Yeah so it would start it, so to say something like it was started in the hospital.

Holly Long: We actually have that from another state; they have that included. Member has received an extended hospitalization and will be continuing therapy following discharge from the hospital.

Paul Oesterman, Chair: I like that wording better.

Carl Jeffery: Okay, so I've updated the criteria there.

Paul Oesterman, Chair: It's my experience the vast majority of patients are usually treated with low molecular weight like enoxaparin.

Carl Jeffery: Yeah, I honestly don't see a real big pick-up of this one and so I don't think this is going to be a huge, huge thing. I think from my perspective, my fear is always to have the prescriber that's in a hurry, they want to start a NOAC and will open the book and say, oh, here's Bevyxxa okay and write it even though it's not appropriate for the indication.

Holly Long: There was an age younger than 18 on here (indiscernible).

Carl Jeffery: It's probably indicated over 18 because that's all it's studied for. We can certainly add that to the criteria, as well.

Paul Oesterman, Chair: I think that would be a wise thing to do.

Holly Long: Two other things that I saw from another state where the member has not received up to 42 days of Bevyxxa therapy, which (indiscernible).

Carl Jeffery: Well, that's what is studied, but I think that's all its indicated for, just prophylaxis so after an event so I think that's a good dependent on duration, so would that would be like the duration of approval, so it would be a duration of 48 weeks.

Holly Long: 42 days.

Carl Jeffery: 42 days of (indiscernible).

Holly Long: Lastly, the dose does not exceed 80 mg per day or 1 capsule per day.

Carl Jeffery: One capsule per day.

Paul Oesterman, Chair: Loading doses, too.

Jennifer Wheeler: All over 40 PA okay.

Carl Jeffery: But they would get the loading dose in the hospital.

Paul Oesterman, Chair: So, I would say we could include something of a cumulative duration of 42 days; you would have to know how many days they were on it in the hospital and if they were on it for 20 days in the hospital, then our max should be 22.

Beth Slamowitz: How would the Call Center going to be able to qualify that? Because they're not going to have access to their hospital medical records unless (indiscernible)

Carl Jeffery: Right, how that's going to be…

Paul Oesterman, Chair: Whoever orders it…

Speaker: I guess you could do a checkbox for the provider to qualify it, but there's not going to be any way to actually confirm it.

Carl Jeffery: Right, not the way they are, because I know we can put a cumulative dose in there but because of the way the hospital claims would come through, well if they're inpatient, then we won't see it at all, but if they're in a clinic or something or outpatient treatment, then they may not come in for 6 weeks so they're going to be done with therapy by that time…

Beth Slamowitz: If it's okay that the understanding is it's just going to be a checkbox by the provider who is prescribing it to say that this is a duration of therapy that they're receiving.

Paul Oesterman, Chair: Or completion of therapy.

Beth Slamowitz: Right, there's just going to be no (indiscernible).

Dave England: I have a question. As I read through the indications here, it goes through the first few sentences and the last sentence, for moderate or severe restriction of mobility, is there some way it has to be documented what's considered "moderate to severe," if the patient for some reason does not have that restricted mobility after whatever treatment they've gone through, is it still appropriate to be on this medication. I don't recall any anticoagulant having that little description on it of moderate or severe restriction of mobility.

Carl Jeffery: I don't know how they would quantify that.

Holly Long: It's not quantified on what I have, either. (indiscernible)

Dave England: So if you have somebody that comes in like a 20-year-old who has had an injury or something like that but does not have moderate to severe restricted mobility because of whatever accident that may have caused the hospitalization and increased risk of DVT, would they qualify for the use of this because they don't have moderate or restricted mobility? How would we limit or define or categorize that moderate to severe mobility?

Carl Jeffery: Well, we don't actually have that in our criteria so that's from the manufacturer. That was a previous report from the manufacturer so that is not actually in our criteria. No it is, I apologize; you're right, it is in the criteria. So, we would just have to take the word from the prescriber who is filling it in that that's what they're using it for. I don't think there is any way we can verify that.

Paul Oesterman, Chair: We have the criteria for Bevyxxa coverage as on the screen right there. Is there a motion to approve the inclusion of this criteria for prior authorization? Do we have a motion?

Jennifer Wheeler: So moved.

James Marx: Second.

Paul Oesterman, Chair: And the motion and the second. Any further discussion? Hearing none, I'll call for the question, all those in favor of approval of the criteria for Bevyxxa, please indicate so by saying "Aye."

Multiple Speakers: "Aye."

Paul Oesterman, Chair: All opposed say "nay." Motion carried.

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

Paul Oesterman, Chair: Our next clinical presentation is for discussion and possible adoption of prior authorization criteria and/or quantity limits for belimumab (Benlysta). Is there anybody in the audience who wishes to present any information to the DUR Board? Okay, hearing none and seeing none, we will get the utilization and clinical information.

Carl Jeffery: We have another new medication. This one's kind of exciting because I don't think there's too many options to treat SLE, systemic lupus erythematosus, so it is a new medication to treat this. I don't have a whole lot of experience with SLE and I don't know if some of our other providers here do, but I think it's pretty nebulous disease where it's hard to treat and pin down symptoms. It's an autoimmune disease so it kind of fluctuates in its symptoms and similar to some other drugs, some other diseases, and good days and bad days and it kind of comes and goes. So, this medication has been indicated to treat the SLE for that, but it would be active auto antibody positive systemic lupus who are receiving standard therapy. Limitations of use of the efficacy of the Benlysta have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. It has not been studied in combination with other biologics or intravenous cyclophosphamide and it has not been recommended in these situations. We have on page 62 of the binder has the criteria, just kind of the combined criteria. This incorporates some of the other input that we received from Amerigroup and Health Plan of Nevada. They have consolidated the criteria here so they have a diagnosis of SLE, the drugs prescribed by or in consultation with the rheumatologist, and documentation confirms that the recipient is positive for antinuclear antibody, ANA, and/or anti-double stranded DNA, and the recipient is currently receiving at least one standard of care treatment for SLE including one or more of the following: Corticosteroids, glucocorticosteroids, antimalarials, or immunosuppressant and the recipient must not have active CNS lupus.

Holly Long: And this also includes SilverSummit.

Carl Jeffery: Ok, SilverSummit is in here too, they just didn't send me separate criteria.

Holly Long: Just to clarify. The way that I organized it, all of the MCOs criteria, if they all have the same theme, then that's how it put it in the initial prior authorization criteria. They were all in agreement on the same criteria. The other suggestions possibly include maybe one MCO had to give theirs, so that's why it's different, it's separated like that.

James Marx: I have a quick question, when a patient switches MCOs or over to receives a service medications, what's the procedure for continuing the prior authorization?

Cody Phinney: Yes, when they switch between MCOs, they have a transfer of care arrangement to address that. It's slightly more challenging with the Fee for Service population in getting that information to the new MCO.

James Marx: So is it supposed to be seamless then, or what we've encountered is many times we'll do a prior authorization in December, the patient came to us in January, and we have to go through the same prior authorization again 3 weeks later. It's very time consuming.

Cody Phinney: It's clearly a place that we have opportunities to improve and we've been working with the MCOs on how we might particularly improve in that transition between Fee for Service and MCOs so that the MCO gets more information.

James Marx: Well, even from MCO to MCO, is what we see more frequently (indiscernible).

Cody Phinney: I'll take that back to our other committee.

James Marx: It's just really frustrating.

Paul Oesterman, Chair: In the recommendations, here it refers to the patient not having the evidence of severe renal disease. Do we need to have that quantified? Like the creatinine greater than 2.5 or…

Beth Slamowitz: Asking the providers to provide the lab value, like on a CA Form, again it would have to be (indiscernible).

Dave England: Also, I've got another question. I'm looking at the criteria on the page we're looking at here right now, if I filled out the continuance criteria, the documentation of the clinical response to Benlysta, now I seen above that in the other description to possibly include SLE acted by (indiscernible), I'm just looking that up on Google right now, and so the question is, would there have to be this score taken for a baseline given again before you can start this medication if we're "seeing improvement" with the change in the numbers; what percent change would we have to be looking at to see if there is improvement, 5%, 1%, 10%, 25%; what would be (indiscernible) and criteria if we are going to be using it.

Carl Jeffery: Dave what's, I'm not familiar with this SELENA-SLEDAI scoring; they did a scoring of….

Michael Owens: I mean, I've got it right here; I've never heard of it. It's a systemic lupus erythematosus disease activity index, that's SLEDAI, I've never heard of SELENA score, but it gives about 20-seizure, psychosis, organic brain syndrome, cranial nerve, kind of different criteria that you score off of and then you take that score and it gives you an idea of where the disease activity is.

Dave England: If (indiscernible) continue, it has to be a positive clinical response, but this score which we have to have this initially, to see if there's been any improvement to have a baseline to compare it with. I was thinking about the usual prior authorization criteria would have to say, an additional SELENA-SLEDAI score was given and while we're continuing this, there was a positive clinical response, and what sort of change in that would be if the top score was 150 and then next score was 120, does that mean it's getting better or worse. If (indiscernible) something to document it with.

Carl Jeffery: Yeah, so on page 63, so description of the Amerigroup criteria, so their initial approval criteria the Amerigroup has listed in here that the SLE is active as documented by the SELENA-SLEDAI score greater than or equal to 6 while on concurrent treatment regimen but then for the continuation therapy, there's no indication that that would be reviewed for renewal criteria.

Dave England: That's what I'm (indiscernible), not going to be a positive clinical response, I would think that documentation would be based on this form, so would we want to keep the criteria or raise values on that?

Carl Jeffery: What we've done with our other medications we've approved with this kind of criteria is we just take the word from the prescriber saying yes, they're having clinical improvement. There's a lot of these that we're not going to have the ability unless they submit

all their chart notes and everything, we're not going to know for sure if they're seeing clinical improvement, so we're just looking for confirmation from the prescriber that, yes, this is providing benefits for patients and they should continue it.

Dave England: Is it to specific asking for the score to be taken, but we're not doing anything with it, why bother?

Carl Jeffery: Well, I think it's a good measure for, and I'm not familiar with this so I'm learning something here, too, but I think it's-

Dave England: - I'm not saying we have the discrepancy. I'm saying like the rheumatologist or (indiscernible), here's what I think the baseline is this, I consider improvement to be on the baseline of this or underneath that would be something like this, I'm not saying we would have to say, well we're go from this we weren't allowed, but the criteria for that indication based on what they're seeing out there, but think that we could have a value and certainly consistent with asking for a value to be increased.

Beth Slamowitz: If the score is kind of subjective anyway and you're looking at improvement from a subjective standard, then I don't know that it matters either way. The checkbox again prevents that…

Michael Owens: The same amount of objective they wanted the score. I mean, when you're looking at what they want, the points that they get to score, and the scale is a change from baseline rather than giving just straight-out scores so if you've got somebody that's got, you look at all these things and they've got a score of 7. You rescore them because you think there's something that you've got a flare-up. It's not the 6, at least on the scale I'm looking at, it's mild or moderate flares a change from the baseline greater than 3 and severe is greater than 12, so I'm not sure what the-

Beth Slamowitz: -but is it just a flare-up or is it actual improvement in the condition?

Michael Owens: Well, they're calling this a flare, or at least that's the SELENA-SLEDAI score, it's a change of numbers based on these parameters of greater than 3 would be mild to moderate and greater than 12 is severe, proves that's all going in there, so I'm not sure what; this says for greater than or equal to 6 while on current treatment regimens, so they may have gotten that 6 in some other place at least on the scale I'm looking at, the numbers are 3 and 12. I don't know if that's (indiscernible).

Darrel Faircloth: It's your thought that you may want to actually deny a PA on this basis that there isn't adequate improvement shown or is this more a matter of you giving guidance in that it's most appropriate continue utilization when at least there's some improvement over time, perhaps to some extended guided by the statistics? This is just a generalization, in other words.

Beth Slamowitz: Yeah, at least that's where I was getting at, is that you don't have a way to actually validate the score or to compare scores or something and you're just basically… If they're conducting the score and you're relying on their medical knowledge to say they started here and they ended here and there was improvement and therefore would get it, and that's all really we should be asking for unless we have some way of validating that score or associating it

with improvement. I guess, we're out of time, we're just going with that. Kind of going back to what Dave said, that if we don't start with it, don't end with it. Don't include it if you're not going to use it as a marker.

Holly Long: Yeah, (indiscernable) and it was only used by one MCO where he disregarded other and get the other criteria suggesting (indiscernible).

Paul Oesterman, Chair: So let's break this down and take a look at it piece by piece. I think right now we have initially the initial prior authorization criteria, the five bullet points.

Holly Long: I'm looking to be pretty consistent with what I saw with other states as far as the other suggestions to possibly include the one that I saw that was pretty consistent in other states was the recipient is not currently receiving treatment for chronic infection and must not have evidence of severe renal disease with those two.

Paul Oesterman, Chair: I think with the studies and the recipient must be over the age of 18, also.

Holly Long: Okay.

Paul Oesterman, Chair: So, I can see where we would possibly include in the initial prior authorization criteria, those 5 bullet points that are there; they include the recipient must be 18 years of age or older, not currently receiving treatment for chronic infection, and must not have evidence of severe renal disease. (indiscernible) That goes back to the first bullet point. Do we want to add that word, the recipient has a diagnosis of active SLE?

Holly Long: It was in other states.

Paul Oesterman, Chair: It was or was not?

Holly Long: It was. It does say active in other states. Do you want to add the word active?

Paul Oesterman, Chair: Active.

Holly Long: Okay.

Paul Oesterman, Chair: Anybody have anything else they wish to add for the initial prior authorization criteria? So, we will vote on this all as one and extending down to continuing therapy criteria. Like Beth said, documentation of a positive clinical response, we will base that upon the practitioner. If they say, the patient is doing better, he is. I think we've already covered the other suggestions about severe renal disease and we already have in there the patient must not have active CNS lupus with the approval duration initially 6 months or 12 months and then continuing authorization for 12 months. Since this is relatively new, my gut feeling is leaning towards 6 months.

Carl Jeffery: For the initial authorization?

Paul Oesterman, Chair: For the initial authorization. This is not an inexpensive utilization.

Carl Jeffery: Yeah, there is some utilization in there, too. Page 75, so we've got quite a few patients that are on this already and it's not as bad as some of the other newer ones; it's not cheap. It's funny to see the spike there around June or July and it seems to be tapering off so I don't know if we don't have any criteria on it, then it's just, I wonder if there's some kind of feedback provided in the community that is actually using this medication…

James Marx: It looks like most of this is just for one or two days.

Carl Jeffery: Yeah, the day supply is, yeah, I don't see…So, it's given, it's an IV injection or subQ once weekly so it's probably given in the doctor's office to start, and so it comes in as a PAD claim, so it always come in, there's a one-day supply. The subQ injection can be given at home by the patient once they're trained on it.

Holly Long: This is the continuation that I saw for authorization in other states. They did an initial 6 months and they did a continuance in 6 months, as well.

Paul Oesterman, Chair: So, to recap what we're proposing is the initial prior authorization criteria to include more active in the first bullet point and we're also adding the recipient must be 18 years of age or older, recipient is not currently receiving treatment for chronic infection, and must not have evidence of severe renal disease.

Carl Jeffery: I've got highlighted on the screen; did I capture everything?

Paul Oesterman, Chair: Oh, yes.

Carl Jeffery: For the continuation, I think you were getting that one, too, but…

Paul Oesterman, Chair: If we were good with accepting the words from the prescriber that the patient is having positive clinical response, (indiscernible). We have this proposed criteria for the addition of this Benlysta for SLE and the motion and second to approve the criteria.

James Marx: I move we accept the criteria as edited.

Jennifer Wheeler: Second.

Paul Oesterman, Chair: We have a motion and a second. Any further discussion? Hearing none, seeing all, I'll call for the question, all of those in favor of the approval of the new Benlysta prior authorization criteria for initial and continuing therapy, please indicate so by saying "Aye."

Multiple Speakers: "Aye."

Paul Oesterman, Chair: All opposed, say "nay." Motion carries.

d. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Hepatitis C Direct-Acting Antiviral agents.

Paul Oesterman, Chair: Our next action item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Hepatitis C Direct-Acting Antiviral agents. We have

some new medications that go on the market. Is there anybody in the audience who wishes to address the Board? Hearing none and seeing none, we will move quickly then.. Carl.

Carl Jeffery: Kind of surprised there's no comments on this one but alright, so we have 2 new medications, Vosevi and Mavyret, they are all pan-genotypic so they hit all the genotypes. The Vosevi is indicated only for those who have failed previous therapies and the Mavyret is indicated for both naive and treatment experienced patients but they are a little bit more restrictive on which previous therapies that they could be on, so depending on the genotype; it gets really complex and this is where criteria gets a little bit crazy about what we need to include and they're based on what their genotype is and what the previous exposure has been and so especially for the Mavyret, it gets really complex with that criteria. Vosevi is a little bit more simpler because they have all the genotypes covered and it's only for treatment experienced so we don't have to worry about the treatment naive patients, and despite the base regimens and for 12-week approval or if they've had it without an NS5 for approval for 1a and 3 genotypes. We didn't get a combined criteria for the Mavyret on here so we've got the combined criteria for the Vosevi. I've got the Chapter 1200 criteria on here and it starts on page 96 of your binder. The criteria in here, and I think we've redone this a couple of times, and it gets confusing because I think we first tried to organize it by genotype and then if they had like previous exposure or what kind of treatment they've been on before or anything so it gets really confusing for not only for the providers who are trying to reference it to figure out, but really confusing for the call center who is constantly calling me saying, this doesn't make any sense, so that's why I've put the criteria together such that it's separate criteria so when we get a caller calling in, because they know what they want usually; they aren't calling in to say, hey I want to start something for hep-C, they say, I want to start Vosevi, what's the criteria for that. So, I think it's best to identify it by drug, so that's the basis of the criteria there. So, as we're working through these, I think we may update the criteria a little bit but it's mostly identified through drugs but I think we'll try to get the chapter cleaned up a little bit. We have some utilization in here from, this is just the Fee for Service. It starts on page 93 of the Utilization and see where we are with that. We have some claims for the Vosevi; no claims for the Mavyret yet. Also, just to let you know, the P&T Committee reviewed this class. They made Mavyret preferred and the Vosevi non-preferred and that's only because Vosevi only had the indication for prior therapy so just by default if they want Vosevi, they should meet that already, so that's the only reason to try to push people that way. On page 96, you can see the graph of utilization and kind of seeing a downward trend. Let me pull up a screen here quick, but it seems like there has been kind of a downward trend anyway with the utilization of these recently, so I don't know if that means we have treated the majority of the patients that need to be treated and I kind of hope that's where we are, but I don't know that for sure; it's hard to speculate on that, but you can see the Epclusa and Harvoni are still in the favorites.

Paul Oesterman, Chair: That's a general trend and the number meds used are definitely decreasing.

Carl Jeffery: Yeah, and, we have seen some patients already who are either they are coming up from retreatment, whether or not previous therapy has failed and they just have a reinfection from the same virus or if they're getting actually reinfected so it's hard to tell, and we don't have any criteria to specify that differentiate those.

Holly Long: I think, Carl, we have already stated that just to clarify, we do have combined criteria that was provided by Silver Summit and then by Optum which is the Vosevi. We didn't have anything for the Mavyret.

Shannon Sprout: I just want to take a moment and clarify the data that you are collecting that is combined data now, correct, with Optum?

Carl Jeffery: That's just fee for service.
Shannon Sprout: Okay, so we just wanted to make sure that we make that statement instead of…are we getting the data on it, therefore?

Carl Jeffery: Some of the classes.

Holly Long: Sometimes they don't have any yet. Okay, so that would be the reason, is that they just don't have it yet.

Shannon Sprout: They don't have the data yet.

Holly Long: They don't have the data yet or the data doesn't (indiscernible).

Shannon Sprout: Okay, so I think the report said that they are going to be able to make their decisions but we make sure that we footnote that on each one of these going forward so that we can just clarify that data and make sure that that information is there for the Board to make a decision with. And with that data, they can contact for future reference.

Paul Oesterman, Chair: I'm just going to throw something wild out there. Out of all of the prescriptions that are submitted for prior authorization, how many do not get approved?

Carl Jeffery: For, are you talking about hep-C specific?

Paul Oesterman, Chair: Mmm-hmm, yeah.

Carl Jeffery: I don't have the numbers at my fingertips. I can get those.

Paul Oesterman, Chair: I bet it's real small number; are we making this a lot more difficult than we need to, prior authorization criteria?

Carl Jeffery: Um, yeah, I mean, what we're doing is, I guess the denials that I've seen and the ones that have come out, so I just, I think we've had a couple. We've had one or two HPMs recently where people are disputing our decisions to deny their prior authorization requests. Most of them are because, one of them was, they are requesting a medication for somebody who had already been treated with something; the doctor didn't have any record. I think they either changed physicians or there were inaccurate records, but we showed that they were being treated with something with one regimen, but the doctor had something else, so it didn't match and then just some of the other criteria wasn't being met because they don't…. most of it's just missing documentation so I think it's just, you're right, some of it's just, we are adding a hoop to get through so not everybody can…

Beth Slamowitz: I think initially when we started all this, it was what 2 drugs? You know, and they were very expensive in that nature, but it was being appropriate and just like with all the other classes and more and more drugs out, at some point, you take a step back and you go, okay we will need to leave it on the provider to make the appropriate decisions, give the appropriate drug, and leave it at that.

Paul Oesterman, Chair: That's kind of the direction I'm leaning for this whole class. It shouldn't have to break the call center's heart.

Beth Slamowitz: And, I think we will be seeing utilization drop-off but that be more of an appropriate decision and we may want to give it some time before, we make that decision just to make sure that's where we're at, especially with these new drugs coming in, we kind of see where they go.

Carl Jeffery: Another thing you can do, and maybe, and I see the direction you're going, and maybe to taper them off a little bit rather than just completely do away with any kind of prior authorization criteria so maybe we want to start with; you know, there's supposed to be a criteria where they have to have a diagnosis and it is prescribed by a GI doc or some specialist in the field or something; we're still limited so not just wide open access but there are still some checks in here to make sure that it…

Paul Oesterman, Chair: So at this point in time, we have checks and balances for all of them except for these 2 new ones?

Carl Jeffery: Right.

Paul Oesterman, Chair: The usage on these two new ones is 0 for one of them at this point, so I would almost like to see us not vote on this at this point and come back next meeting with a simplified criteria because we are making this way more difficult than it needs to be. That's just my…

Beth Slamowitz: Like an overall criteria for hep-C.

Paul Oesterman, Chair: Yes.

James Marx: It's true, the prior authorization in general like maybe 3 times, I mean, 1 time in 10 years I've had prior authorization dispute and it's just what you had to deal with.

Paul Oesterman, Chair: Let's try to make life a little bit easier for our providers.

Beth Slamowitz: For something that's like, you know, kind of improving care, this is something where you're not sure how much volume of drug to be studied in 2 people and it costs thousands of dollars and not many people are appropriate to kind of limit that utilization, but we're getting to the point very quickly and that's not the issue.

Holly Long: Do you want us to draft something simple like that for next time or do you want to wait? Okay for next time.

Paul Oesterman, Chair: Yes, please. Because it's on the agenda, do we have to vote on it?

Darrell Faircloth: No, you do not.

Paul Oesterman, Chair: I think we have a Board, do we all need to vote on these or in agreement that we defer until next meeting for simplified criteria?

James Marx: It will cover all these.

Paul Oesterman, Chair: Something that will cover….

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

Paul Oesterman, Chair: Okay, our next agenda item for possible action is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for the Immunomodulator agents. Is there anybody in the audience who wishes to address the Board? Sandy.

Sandy Sierawski, Pfizer: Hi, good evening. I'm Sandy Sierawski, I'm a pharmacist here in Nevada and I've worked with Pfizer as a Medical Outcomes Specialist. I'm here just to make a couple comments about Xeljanz and Xeljanz-XR. In looking at your Optum review document, one indication that Xeljanz or Xeljanz-XR now has for the treatment of adult patients with active psoriatic arthritis who have had inadequate response or intolerance to methotrexate or other DMARDs, so this new medication was FDA approved in December so it's new in that area. I don't want to address the other indications with RA because we have already talked about that at previous meetings, but I just wanted you to be aware of the psoriatic arthritis indication. Limitations, it is not recommended for the use in combination with biologic DMARD and potent immunosuppressants such as azathioprine and cyclosporine. As far as dosing goes, Xeljanz is to be given for 5 mg twice daily in combination with nonbiologic DMARD and the Xeljanz-XR is 11 mg once daily in combination with nonbiologic DMARD. So, the drug does have a boxed warning on it so for safety update on the psoriatic arthritis indications, the safety profile observed in patients with active psoriatic arthritis treated with Xeljanz was consistent with the safety profile observed in patients with RA and the most common serious effort ramifications with active psoriatic arthritis was serious infections and in the patient's with RA, malignancies have been observed in clinical trials of patients with active psoriatic arthritis. I'm not going to go into a lot more data and stuff. I can supply a package insert if you'd like more data of give you the website, but what I do want to spend more time on is to address the actual criteria that you have and looking at the criteria, Section 1C under Psoriatic Arthritis, number 4, it states that the recipient had an inadequate response to any one nonsteroidal anti-inflammatory drug or contraindications for treatment with an NSAID and then it states for any of the following DMARDs. So, I'm wondering if that should be reworded to include an inadequate response to the DMARDs; kind of wounds like it's a run-in and it's a contraindication for DMARDs and is making an inadequate response for DMARDs for contraindication. So, maybe to clarify that for me as a system set up for an inadequate response; am I reading that correctly or incorrectly to clarify the regular use…

Carl Jeffery: It would be a question from the call center that would ask and I would have to go with the language that they have for their scripting but I can't, I don't know that…

Sandy Sierawski, Pfizer: But as with the other indications, with the intent to say inadequate response to NSAID or DMARD and then, or contraindication. You know what I'm saying?

Carl Jeffery: Right.

Sandy Sierawski, Pfizer: So how this is supposed to say contraindication for DMARD. Part of the indication for the dosing on Xeljanz is it can be in combination with it; it's supposed to be used in combination with the nonbiologic DMARD so it doesn't say that inadequate response and we couldn't use that indication. Does that make sense what I'm asking? Any questions or comments?

James Marx: I had a question and we've said this before, apparently we don't allow trial of samples or voucher-type supplies to be considered an adequate trial.

Beth Slamowitz: We don't have any way to document those trials.

James Marx: Why would anybody lie about that, to say that they had samples and..

Carl Jeffery: Well, I would think they would accept that as really an adequate trial, but samples are usually to get people started so I don't know. Are these people on like samples for an extended period of time; do you think they really got an adequate trial of samples?

Beth Slamowitz: But, how would you document that, how would document the sample?

Carl Jeffery: Well, it would come from the doctor's notes. They have to document that they got the sample.

James Marx: They have to chart they gave samples and then they had a response, adverse consequences. I don't see why I would have to exclude that as a trial.

Carl Jeffery: From the payer perspective, it wouldn't be any different than if the patient came from another payer and we ended up having claims data for any, having the doctors word for it, but they've been on it through another payer, so from that perspective, it's the same. There's really no difference.

Ryan Bitton, HPN: Ryan Bitton with the Health Plan of Nevada, Senior Director of Pharmacy, and some of the criteria I don't know, it's logical, some of the criteria of the Health Plan of Nevada Pharmacy on the commercial side. Sometimes we say no to taking samples because it's a way to get a new product without trying a preferred agent or trying to lower the cost of an efficacious product for that. The samples sometimes skirt the benefit we put in place around drug A being used first.

James Marx: You guys try and skirt that all the time, I don't see why that would be a…

Ryan Bitton, HPN: I was just explaining why that criteria…

James Marx: We go through this struggle all the time and skirting around it seems to be the (indiscernible).

Ryan Bitton, HPN: That's why it kind of exists is because it's not so much clinical over a cost issue, started on a sample and then go on that therapy long-term.

Carl Jeffery: I can see how it created hardship for patient because if they do start on a sample and they are stabilized on it and maybe doing well but then you go and visit the PA and say, no, they don't

meet the criteria. Now you've got a patient who can't get their medication and they've got to try something else. So, I think it would be to Ryan's point, I think it's almost a detriment to the patient to get a sample for those medications where maybe there's a risk of them not being able to continue it.

James Marx: In reality, when we encounter situations like that, we can usually get an override and it's easier to get an override in that situation than it is to say well we're just not to going to try because you might not get it. We spent a lot of time on prior authorizations and I have to say that we are almost universally successful in getting them.

Ryan Bitton, HPN: I think we clinically have a chance to review it. But that's why we put that criteria there.

Jeannine Murray: This is Jeannine, and I'm the Pharmacy Director with Amerigroup (indiscernible). I don't think that we addressed samples in our PA criteria, but to what Carl was saying earlier, generally I think in Medicaid we don't talk about using samples just because that kind of history might not be there, but with our PA, it's different because it's an application that they've been on it regardless of what (indiscernible).

Paul Oesterman, Chair: So we actually have a couple of things in front of us here. One is being the addition of Kevzara due to formality and then the point that Sandy has brought up for Xeljanz. So, let's take these separately. I think we have existing criteria for the Immunomodulators of the verbiage that the committee agrees to change to include…

Carl Jeffery: Kevzara is a new medication for rheumatoid arthritis and the way I worded the Optum criteria that's in there on page 133 I've got pulled up here, I basically copied and pasted from chapter 1200 the way it currently is and what we've done with the other one so can you see even the Siliq in our ears was the one that we added last, it was just updated, so I would propose that we just add Kevzara to the list of products and in that way, our criteria has everything else, just makes everything meet the current criteria that's already been approved. In that way, when they do as evidence from Sandy and Xeljanz that have new indications, we don't need to go back through here and update, except for the errors in it, but we don't need to update the criteria every time a new medication comes out and that's why we've got it this way.

Paul Oesterman, Chair: So, looking at approving the Optum proposed criteria is that correct?

Carl Jeffery: Yeah, and that's just the criteria that's right out of chapter 1200, so that would essentially just add the drug name to the list of medications in chapter 1200.

Paul Oesterman, Chair: So, let's take the first step here and that would be to see if we can get a motion to approve the Kevzara to the list of Immunomodulating agents and prior authorization criteria as presented here by Optum.

Carl Jeffery: On page 143, so I'll just have chapter 1200, so it's chapter 1200 (indiscernible) on there, so we just added to the list, Kevzara would be just added to the list of Immunomodulators.

Paul Oesterman, Chair: So, a motion to approve the addition of the Kevzara prior authorization criteria to the list of Immunomodulators. Do we have a motion and second?

James Marx: So moved.

Jennifer Wheeler: Second.

Paul Oesterman, Chair: Motion and a second, any further discussion? Hearing none, seeing none, and no further discussion, all those in favor please indicate so by saying "Aye."

Multiple Speakers: Aye.

Paul Oesterman, Chair: All opposed say "nay." The motion carries. We have the second issue within this for the psoriatic arthritis where we want to update our verbiage to include the inadequate response or contraindication under Section C #4.

James Marx: I move for the addition of inadequate response verbiage.

Paul Oesterman, Chair So, we have a motion to add the verbiage of an inadequate response to contraindication C4. Do we have a second?

Jennifer Wheeler: Second.

Paul Oesterman, Chair: We have a motion and a second. Any further discussion? Hearing none and seeing none, no further questions, everybody in favor of the addition of verbiage of an inadequate response to the contraindication and treatment, please indicate so by saying "Aye."

Multiple Speakers: Aye.

Paul Oesterman, Chair: All opposed say "nay." The motion carries.

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

Paul Oesterman, Chair: Next agenda item is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Opioid-Induced Constipation Agents. We do have somebody in the audience to address this.

Rupa Shah: My name is Rupa Shah, I'm the clinical pharmacist and medical science liaison with Purdue Pharma. I'm here to review the prior authorization criteria for the Opioid-Induced Constipation Drugs. I'm available to address any specific questions you have regarding the Symproic tablets. Thank you.

Carl Jeffery: The criteria that I put there, the Optum criteria that's on page 204 is basically just again, I put the chapter 1200 criteria and adopted it into our criteria just to include the other one, so basically has for recipients 18 it's being used for FDA-approved indication which would be the OIC which could be morph depending on what else they get approved, and then there's the application that they had an inadequate response to at least one agent from the three of the four traditional laxatives, so bulk-forming, osmotic, saline and stimulant laxatives. That's what we've got approved from chapter 1200 already for the opioid-induced constipation. We also have some criteria for and I just threw it in there just for the Board's reference, irritable bowel syndrome which has similar medications, which

some of them cross over which we have indications for both, so I just threw that in there for the Board's records just in case you wanted that in there.

Paul Oesterman, Chair: The existing products, do we have an initial quantity duration?

Carl Jeffery: Yeah, in chapter 1200, no, the prior authorization is for one year; we didn't differentiate between initial or continuation.

Paul Oesterman, Chair: Has P&T looked at preferred?

Carl Jeffery: We did, yeah. They have the class a little bit different because they only have a single class for both the OIC and the chronic idiopathic constipation all lumped into a single class, so it's a little bit different, mostly Amitiza is also the other preferred. Amitiza and Linzess, so the P&T has the GI agents, functional gastrointestinal disorder drugs, all lumped into one category, so Amitiza and Linzess are preferred and Movantik, Relistor, Symproic, and Trulance are the non-preferred.

James Marx: I see a lot of opioid-induced constipation obviously, and I would say that we report that some patients don't respond and have pretty much everybody on lactulose and I have to say that have higher satisfaction with lactulose than I do with the peripheral opioid antagonists and the patient will see withdrawal symptoms, massive explosive sort of diarrhea, and I have it all, I sample it all, and I can tell you that most all the patients on lactulose after sampling, maybe a couple percent that don't like the lactulose. So, it's an expensive alternative like lactulose, they get like a 6-month supply for 10 dollars a pill.

Carl Jeffery: Yeah, I think that's the reason behind their criteria there, too. Try 3 of the 4 classes to make sure that at least doing their due diligence before getting one of these.

James Marx: I realize that's the criteria, but I seriously doubt most of these patients actually get 3 of the 4 before someone asks for something they saw on advertising and they ask for something they say, and that's my concern. Lactulose is incredibly expensive.

Jennifer Wheeler: Yeah, I'm assuming most of them probably aren't covered at all. Are you taking the physician's word for it?

Carl Jeffery: No, these would all be. Medicaid pays for over-the-counter. They need to have a prescription for it, but Medicaid does pay for over-the-counter.

James Marx: I would like to see a little bit more aggressive use of… nobody wants a sample Lactulose.

Paul Oesterman, Chair: Do we want to possibly bullet point and go through this documentation of medical record of an inadequate response for a certain period of time and try?

James Marx: If it works, if it works in only 2 days. I mean, it doesn't take 6 months of trial to determine if it will work or not, at least maybe a week at the most recorded for one product. You can give an injection of Relistor and have a bowel movement within an hour.

Carl Jeffery: You can see some of our utilization here. I don't think we have a tremendous amount of utilization, and this is just for Fee for Service, population here, but Movantik and the Amitiza are definitely in a class here but so anywhere up to 90 claims a month for the Movantik so this is for all of the Medicaid population.

James Marx: That's about right, that's a nice percentage.

Carl Jeffery: Yeah, we're not seeing a huge utilization of this stuff anyways.

Paul Oesterman, Chair: Are we looking to try to keep it as a class prior authorization?

Carl Jeffery: Right, and that's how I've got it worded. So, it would essentially just add that name to the criteria; that's how I have it worded in chapter 1200.

Speaker: There are two different criteria in the binder.

Carl Jeffery: Just because there's some drugs in this category that have crossed over.

Speaker: Okay, do they both need to be updated?

Carl Jeffery: No, because this one only, Symproic only has an indication for opioid-induced constipation, not irritable bowel. Some of the other ones that do have an indication for both of them.

Paul Oesterman, Chair: Do we have a motion to approve the inclusion of Symproic to the opioid-induced constipation agents with the criteria that are proposed to match the existing criteria for the other agents for the same indication?

James Marx: I move we adopt the criteria.

Paul Oesterman, Chair: We have a motion. Do we have a second?

Michael Owens: I'll second.

Paul Oesterman, Chair: So we have a motion and a second. Any further discussion? Hearing none and seeing none, and no further questions, all those in favor of the approval of the addition of Symproic to the opioid-induced constipation agents, please indicate so by saying "Aye."

Speaker: Aye.

Paul Oesterman, Chair: Any opposed say "nay." Motion carries.

5. Public Comment on any DUR Board Requested Report

Paul Oesterman, Chair: With that being said, we now will move on to DUR Board Requested Report and ask if there is anything that has any public comment on anything at this point in time? Hearing none, we'll go into the first Board Requested Report which pertains to the Utilization of Medications with the Orphan Designation or Indication.

6. DUR Board Requested Reports

a. Utilization of medications with Orphan Designation.

Carl Jeffery: Alright, so at our pre meeting, I was telling Paul all I learned about Orphan Indications and it was interesting to find that all sorts of medications even like Abilify and Lipitor or Crestor have orphan drug indications, so they're included in here because you pull down the list of all the drugs that have orphan indications from the FDAs website, all these are included. I ran the report of all the drugs that have been orphaned indications and put them all in here and sorted them by how much money to some of the pharmacy, what we've paid pharmacies for these. Again, this will only Fee for service data, but you can see the top here and there's only a single page of these because I think this is just to break the Board in a little bit to see what they want to do with this class or with medications with an orphan disease status but the top ones on here are definitely what we would expect to see, the hemophilia drugs are always up there, hep-C, we've got Harvoni. I really don't see anything that's too out of place on here that we haven't really addressed but I think this is a good report for the Board to see something and maybe from the provider's standpoint, too, you've heard colleagues or somebody say that we always use this medication off-label, it's not indicated for it but it works really well or they think it's works well but if there's any kind of input from the provider community you've heard for those, I think those would be ones that are worthwhile addressing. Something else we've kind of been tossing around, too, is just kind of a blanket P.A. status for medications with an orphan drug, because I think more and more of these orphan medications are coming out with these orphan diseases, we may not even have anybody in Nevada with this disease, so it seems silly to bring every one of these really rare medications to the DUR Board that we will never use the criteria for because we don't have anybody in Nevada for it. If there's some kind of blanket criteria that we may try to come up with for the Board to talk about and approve that would just say, any medication with an orphan disease status that maybe there's a dollar limit, too, it costs so much per therapy that they need to have updated approved indications by a specialist or something like that, but I think it just starts the conversation.

Paul Oesterman, Chair: It seems like the vast majorities are injectable or parental products? Perhaps would could start off on looking at those and the oral products.

Carl Jeffery: Sure.

Dave England: I had a question. On some of these medications, aren't some of these also only available through specialty pharmacies, and what would be the process the patient is not Medicaid and qualifies for one of these medications or being able to work with and provide to those specialty pharmacies?

Carl Jeffery: Yeah, the specialty pharmacies all have contracts with Medicaid to provide these medications and with provider enrollment, it gets kind of complex, too, because even within the specialty pharmacy chains, maybe only one pharmacy in New Jersey is able to dispense that one medication so that one pharmacy in New Jersey has to be licensed with Nevada and then register with Medicaid as being a provider. It gets kind of hectic with some of these new medications that are coming out.

Dave England: Even though someone may be on Medicaid, if the medications are provided by the manufacturer that has a free medicine program or drug-assistance program. Would they even qualify or would they work with us on that sort of thing or is that just something because the patient was told by the insurance they wouldn't be available to do that assistance program?

Carl Jeffery: My experience with patient assistance programs for patients who have Medicaid is that the manufacturers are really reluctant to pay for any medication because they do have Medicaid. They do everything they can to get Medicaid to pay for it first.

Beth Slamowitz: And, usually with the vouchers or something similar, there is a disclaimer that says if they receive government assistance, they won't pay for it.

Dave England: Sometimes the manufactures are more willing to work with you for the patient's situation.

Carl Jeffery: Is there anything else the Board would like to see as far as the orphan diseases or like to see any other reporting for the future and see what I can pull together. This is my first stab; I think at the last meeting we just had a real quick discussion about orphan diseases and this is my first stab of report.

James Marx: How does the Call Center deal with these situations?

Carl Jeffery: If there's no PA criteria, the Call Center doesn't get called.

Holly Long: So what we're going to propose for next time that we talked about is that we would do almost similar to what we were talking about with the hep-C list, like Carl said, some kind of general policy that we could draft up for you at the next DUR meeting that we cover, orphan drugs, new-to-market drugs, fast-track drugs from FDA since they are all kind of falling into that category. That seems to be what other states are doing, in particular and take a look at it next time.

Paul Oesterman, Chair: I think that makes sense.

b. Opioid utilization – Members under age 18 years

Paul Oesterman, Chair: Our next report is opioid Utilization for members under the age of 18.

Carl Jeffery: This one is a response from Dr. Marx. We last time talked about, added a criteria for the Tramadol and codeine the last time we talked about that. So, Dr. Marx said, well we should probably look at all the opioids for kids so that's what this is. We looked at, and again this would be just Fee for service data here, but we looked at just the opioids for children under 18 so on page 228 has it broken down by class, by all kids, and then we broke it down on page 229 to 0-5, 6-11 year olds, and 12 to 17 and this is very timely, too, because the FDA just released some information saying that probably no kid under 18 should be getting opioids. They said, there's very few exceptions of when it's probably okay but for the most part, they shouldn't be getting.

James Marx: I believe I said that.

Paul Oesterman, Chair: One thing that is fairly apparent to me when I looked at this was a lot of these are cough syrups with opioids in them and, for example, promethazine with codeine, we had 15 members under the age of 5, 74 members between 6 and 11 and it is contraindicated in patients under the age of 12.

Holly Long: We just added that FDA criteria that supports that just recently so we do have the criteria that supports that; this is probably before…

Carl Jeffery: Yeah, and this data was through October 31st.

Holly Long: We still have the tail-end of that.

Paul Oesterman, Chair: With the new FDA guidelines for being very restrictive for opioid use in children under the age of 18. I think what they're trying to get at is pretty much all of the cough and maybe the only indication would be acute pain of some kind, facture, something like that and that would be just a very short course. I think we need to revisit the prior authorization criteria for all of the patients under the age of 18 and the use of opioids and I don't want to get to the point of being ultra-restrictive when there is an appropriate indication that…

Dave England: I have a question, too, starting with our national opioid epidemic that we're having and the DEA has required a 25% reduction in community tax shares in 2017 and they required a 20% in reduction in 2018. Have we as DUR submitted to Medicaid, have we implemented the sort of reduction in the use of opioids to our clientele?

James Marx: No.

Dave England: I think the DEA is taking the wrong approach that we can just kind of cut down the use of the amount of opioids available without a case-by-case review, but at the same time, with all the emphasis being put on hospitals and health department and things like that, do we want to consider implementing the reduction in opioid use because of the epidemic going on and supply us with what the hospitals and clinics are being put on to decrease their opioid use.

James Marx: I'm totally opposed to that. I mean, we can't treat an epidemic by killing the patients before they get the disease.

Dave England: I agree. That's why I think it's ridiculous, but at the same time, are we taking it to review or are they going to look at our criteria for opioid use to see if we can possibly reduce but at the same time, not be distracted with what the DEA proposed.

James Marx: Dave, I think if there really is over-utilization, then we need to look at our prior authorization criteria and if they are properly imposed, then a decrease will occur. If there's not an over-utilization, then we won't see anything, but I don't think we should say, well we should just arbitrarily cut down everybody by 25%.

Dave England: Well that's what I was thinking, the comment and the fact that that's what society is being exposed to, but at the same time, do we feel, I think we have these numbers now, take a look at these numbers and they decreased 6 months from now after seeing a change, has it stabilized, has it increased or decreased, maybe determine if we need to take a look at our criteria again to be sure

that we're making medication available, but at the same time, are we truly taking care of our patients by not having accessibility, as well.

James Marx: I still would like, let's say, let's stop the ice cream manufacturer's from making ice cream to cut down on obesity. I mean, it has not relevance to actually how it plays out.

Dave England: I would have to agree with you. It's kind of like, we're kind of preaching to the choir here, but I think we are doing our part to show that we are showing we are interested, I think this is good to take a look a report every 6 months to see if there has been any change and if another client would have use of medication are up or down, would have to review the utilization spike up or down in that period of time to see if we are doing our part in keeping it in check being able to monitor it so that we're not allowing it to go unencumbered.

James Marx: Dave, the problem is your assumption that there's already over-utilization occurring and if that's not correct, you're not going to see a decrease so, I mean, I think we're doing a pretty good job. Maybe we can see a little bit more rigid, unless we want to authorize every single prescription for every single patient. I mean, do you really want to do that, well you really need to have more criteria like the patient's age, what's the extent of the disease, how much do they weigh. I mean, we're not doing all that and I'm not sure that it would make any difference.

Dave England: And I really don't think that's where we need to put the thumb screws on it, in order to do our due diligence, we have to continue our monitors like we're doing out there now or are you watching it, you can say yes, we have been and see what we found. Our population has increased, our utilization has increased, it is pretty much maintaining, we don't feel that we have a problem with our process.

Paul Oesterman, Chair: Well Dave, actually on the next page, there is a trend chart and I think that's very telling and it's very good news that our both member and claim count for opioid utilization and the sum of the day's supply is both trending down. If we can take the credit for it, I'd be more than happy to.

Carl Jeffery: I think the Board should take the credit for it because I think most of it is due to the 7-day quantity limit we put in place and the 60 mg equivalents we put in and the PA criteria that I don't think are overly strict but I think the need for the population.

Holly Long: And, isn't that when the trend started down is after the implementation…

Carl Jeffery: Yeah, so May is when we implemented that so you kind of see still like before it went in in May, it's bumping around here pretty steady. The trend line is down because it's dropped off pretty significantly but May 2017 is when this went in and that's really when it started to go down.

Dave England: I think we keep monitoring this and look at it at least every six months the trend isn't starting to go up again, I think if we do that, I think we are doing our due diligence in response to this issue.

Carl Jeffery: Yeah, and I think we can bring this back next time with some criteria for the children getting opioids. We don't have a huge number of kids that are on here, but there's 500 members

who are on hydrocodone and acetaminophen under 11 years old that probably shouldn't be on there. Not sure why they're getting hydrocodone with acetaminophen.

James Marx: What about the 19 under 5 that are on methadone. That's really…

Carl Jeffery: I would almost guarantee that's detox.

Paul Oesterman, Chair: That's what I was thinking. Newborn…

Multiple Speakers indiscernible.

Paul Oesterman, Chair: Good information and keep going the direction we're going and bring that information next meeting.

Carl Jeffery: So, on page 232, in the opioid information here containing…

James Marx: I just had one more thing. I think if you're going to really address Dave's concern, I think we really need to look at the number of opioid overdoses amongst our Medicaid population, and I would bet that the instances are lower in the managed Medicaid population than it is in the general population, because those patients are actually in the process of receiving medical supervision.

Holly Long: See if it's possible to get that information.

Carl Jeffery: I know it's not in our data, but… It might be in the claim's data.

Holly Long: Okay, I'll see what I can do.

Carl Jeffery: So then on page 232, I've got the top 10 opioids by quantity. I don't know if this has been much use. It gives you a breakdown of which opioids are being used for the Nevada population. It's not surprising to see hydrocodone, acetaminophen, oxycodone, and oxy/acetaminophen is the top one here.

Paul Oesterman, Chair: Can we take a look next time at the acetaminophen components…

Carl Jeffery: We have a 2.8-gram limit on all the acetaminophen already, so they shouldn't be exceeding that.

Paul Oesterman, Chair: Can we check to make sure that we are not exceeding that?

Carl Jeffery: Anything else stick out on that chart?

Paul Oesterman, Chair: It would be interesting again to take a look at the number of members who are receiving more than 4 different opiates.

Carl Jeffery: And those would be the out-layers, I would think, I would think any more than, for your chronic pain patient, any more than 2 are going to be the exception to the… I could see the

standard therapy of long-acting or short-acting for breakthrough. I think it's kind of the standard but then you get the complex patients Dr. Marx maybe sees that…

James Marx: How about somebody with a Fentanyl patch and given some morphine with that, oxycodone. It happens occasionally.

Paul Oesterman, Chair: Four is going to really…

James Marx: Four is really way outside.

c. Opioid Utilization – Top prescriber and member

Paul Oesterman, Chair: Top ten prescribers.

Carl Jeffery: And then we've got the top ten prescribers. All the IDs match so we've got prescriber IDs so that would match and see where they are. They're all sorted by so the top ones by member count and then by claim count and then day supply so it's all sorted a little bit differently. Then, there's two more on the following page so some of quantity and then by the pharmacy amount paid.

James Marx: Is there any indication of type of prescriber like the dental, veterinary…

Carl Jeffery: So, I've got the same chart that's on page 235. I put that same chart that we've been tracking on here so it's just been updated. So, that's the one you're probably looking at. So, that's the top 10 prescribers by sum of the quantity. You can see that same nurse practitioner, he always shows up there at the top, the Las Vegas, he's prescriber W if you want to go back and try to track down where he is, he's top prescriber on a couple different fields in here. But, we really don't have too much turnover on who we're seeing over here, so it's the same kind of docs and nurse practitioners that we're seeing time after time so they really don't rotate through here very much. We did do a retro-DUR and the letter is actually I think the very last page in your binder. We sent retro-DUR out because the Board requested me sending these top 10 prescribers just a letter showing where they stand and where they are compared to their peers and so the letter said, here you're number one among your peers for Medicaid and it's a self-evaluation, we'd just like you to take a look at this and see if the data we have makes sense to what you see. We had one response and it's in the very back one; it's actually the M.D. of the practice for the nurse practitioner that responded and said, yeah, we just have a lot of Medicaid patients and outlined very clearly about which practice and you can see the nurse practitioner does see most of the Medicaid patients; they're working on this. So, it was nice to get some feedback from the prescriber's office.

Paul Oesterman, Chair: Can we get next time, first quarter, just to see if the names are still the same of the top 10 prescriber list?

Carl Jeffery: It's going to be interesting to compare it to the last one because the one we had in October meeting so..

Paul Oesterman, Chair: Top 10 usual reports.

Carl Jeffery: Yeah, and these are just kind of the standard stuff; nothing outstanding to see on these. I know we've got some new members on the Board, too, so if there's anything on here you think you'd like to see that would make these more useful or maybe different, then certainly speak up. We have a lot of data and trying to mush it into something that's worthwhile and see something that's going to be worthwhile.

Paul Oesterman, Chair: ProDUR, you were going to something with the new format?

Carl Jeffery: Well, I think that will be next time. Actually, our company has an initiative to actually redo that one chart so I'm kind of waiting for them to get their act together to redo that chart, so unfortunately you get the same old ProDUR report this time. I'm hoping for next time we'll have a new updated ProDUR report and maybe it's a little bit more clear. I'm at least able to pull all the raw data and I kind of played with it a little bit and I couldn't make it any more clear than what that current report had.

James Marx: I don't see how you got this done in 3 months.

Paul Oesterman, Chair: I think it's been a while since we've looked at. Next time, we can take look at our diabetic patients and see where we're… Again, I always ask the same question, when is it going be possible to merge the medical data with pharmacy data to make sure that diabetic patients are getting their eye exams, their foot exams.

Beth Slamowitz: Well, and it may be helpful, too, because I know our medical steering committee is actually doing a presentation of diabetes and they asked what they even get pulling the medical information so if that presentation's put together, possibly put that on the agenda for use of the population.

James Marx: Hospital admissions too.

Beth Slamowitz: Yeah, and that's all part of that presentation that they're working on.
Paul Oesterman, Chair: Anything else on the Board which is requesting for yourself for next time?

Paul Oesterman, Chair: Any public comments on any subject? No going over the hill tonight?

Carl Jeffery: Yeah, Dave, it's a good thing you didn't drive over and I'm not sure you'd get back.

Paul Oesterman, Chair: Date and location of the next meeting?

Carl Jeffery: So, April 26 and the same room again, I like this place.

a. Adjournment.

Paul Oesterman, Chair: With that being said, we'll go ahead and adjourn and wish Darrell all the best.

Nevada Medicaid

Makena (Hydroxyprogesterone Caproate))

Pharmacy Coverage Guideline

Brand Name	Generic Name
Makena	Hydroxyprogesterone Caproate

CRITERIA FOR COVERAGE/NONCOVERAGE

Indications

Pregnancy indications: Preterm birth (Makena): Pregnant females ≥16 years of age: **Note:** Treatment may begin between 16 weeks 0 days and 20 weeks 6 days of gestation. Continue weekly administration until 37 weeks (through 36 weeks, 6 days) gestation or until delivery, whichever comes first.

Proposed to remove PA restriction.

Clinical Policy: Hydroxyprogesterone Caproate (Makena/compound)

Reference Number: CP.PHAR.14
Effective Date: 08/06
Last Review Date: 04/17

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® medical policy for hydroxyprogesterone caproate intramuscular injection (Makena®/compound).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that hydroxyprogesterone caproate is **medically necessary** for members meeting the following criteria:

A. Prevention of preterm birth (meets all):
1. Current singleton pregnancy;
2. History of singleton spontaneous preterm birth (delivery at < 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes);
3. Therapy to begin between 16 weeks, 0 days and 27 weeks, 6 days of gestation;
4. Request is for Makena unless there is a contraindication or documented reason to use an alternative formulation;
5. Prescribed dose does not exceed 250mg (1ml), once weekly (every 7 days);
6. Member has none of the following contraindications:
   a. Current or history of thrombosis or thromboembolic disorder;
   b. Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions;
   c. Undiagnosed abnormal vaginal bleeding unrelated to pregnancy;
   d. Cholestatic jaundice of pregnancy;
   e. Liver tumor, benign or malignant, or active liver disease;
   f. Uncontrolled hypertension.

Approval duration: Up to a total of 21 doses to reach week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Background

Description/Mechanism of Action:
Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

Formulations:
Makena is supplied as
- 1 mL of a sterile solution in a single dose glass vial.

  - Each 1 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).
  - Single unit carton: Contains one 1 mL single dose vial of Makena containing 250 mg of hydroxyprogesterone caproate.
- 5 mL of a sterile solution in a multidose glass vial.
  - Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v).
    - Includes the preservative benzyl alcohol NF (2% v/v).
  - Single unit carton: Contains one 5 mL multidose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

FDA Approved Indications:
Makena is a progestin/intramuscular formulation indicated:

- To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.
  Limitation of use:
  - While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1725	Injection, hydroxyprogesterone caproate, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Converted criteria to algorithm table	07/13	10/13
Added multiple gestation question to algorithm	12/13	01/14
Renamed to Makena Changed references in policy from 17P to Makena Added FDA approved indications and contraindications Updated background information Added safety information Updated references to include additional information section Updated algorithm to include only Makena	01/15	01/15
Policy converted to new template.	12/15	01/16

Reviews, Revisions, and Approvals	Date	Approval Date
Criteria: age requirement added; criteria added asking for dose, frequency; question regarding major fetal anomalies detected by ultrasound removed		
Added language to prefer Makena formulation Allowed start of therapy up to 27 wks 6 days and continuation through 36 wk 6 days Removed age limit	04/16	05/16
No criteria changes. Added compound to the title. Background section reformatted.	03/17	04/17

References

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3. Mason MV, Poole-Yaeger A, Lucas B, Krueger C, et al. Effects of a pregnancy management program on birth outcomes in managed Medicaid. Manag Care. April 2011; 20(4): 39-46.
4. Mason MV, Poole-Yaeger A, Krueger C, et al. Impact of 17P usage on NICU admissions in a managed Medicaid population – a five-year review. Manag Care. February 2010; 19(2): 46-52.
5. Romero R, Stanczyk FZ. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. June 2013; 208(6): 421-426.

Important reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective

date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

Makena (hydroxyprogesterone caproate injection)

CG-DRUG-19

Override(s)	Approval Duration
Prior Authorization	6 months

Medications	Quantity Limit
Makena (hydroxyprogesterone caproate injection)	N/A

APPROVAL CRITERIA

Requests for Makena (hydroxyprogesterone caproate injection) may be approved if the individual meets the following criteria:

I. Weekly injections of 17 alpha-hydroxyprogesterone caproate between 16 and 36 weeks of gestation **may be approved** in pregnant women who meet the following criteria:

a. A singleton pregnancy; **AND**

b. Absence of preterm labor within the current pregnancy; **AND**

c. A prior history of a preterm delivery before 37 weeks gestation due to either of the following:

i. Spontaneous preterm labor; **OR**

ii. Premature rupture of membranes.

May NOT be approved:

- Progesterone therapy as a technique to prevent preterm labor **may not be approved** in other pregnant women who do not meet the above criteria, or those with other risk factors for preterm delivery, including, but not limited, to: multiple gestations, prior cervical cerclage, a uterine anomaly, positive tests for cervicovaginal fetal fibronectin, or preterm labor within the current pregnancy.

- Injections of 17 alpha-hydroxyprogesterone caproate in a home setting by or through a licensed home health agency **may not be approved**, except when criteria for home health services are met. (See CG-MED-23 - Home Health.)

State Specific Mandates		
State name	Date effective	Mandate details (including specific bill if applicable)
Louisiana		**This policy does not apply.** 6.13.1.2 Provision of injectable or vaginal progesterone for every eligible pregnant woman with a history of pre-term labor or a short cervix found in the current pregnancy. The MCO shall not require prior authorization of progesterone.

Key References:

1. Additional press release information about the FDA new approval of Makena. February 4, 2011. Available at: http://www.prnewswire.com/news-releases/fda-approves-makena-the-first-and-only-treatment-to-reduce-the-risk-of-preterm-birth-in-women-with-a-singleton-pregnancy-who-have-a-history-of-singleton-spontaneous-preterm-birth-115271964.html. Accessed on September 15, 2015.
2. United States Food and Drug Administration (FDA). Additional information about approval of Makena. February 4, 2011. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm242234.htm. Accessed on September 24, 2015

Makena Proposed PA Guideline

Health Plan of Nevada

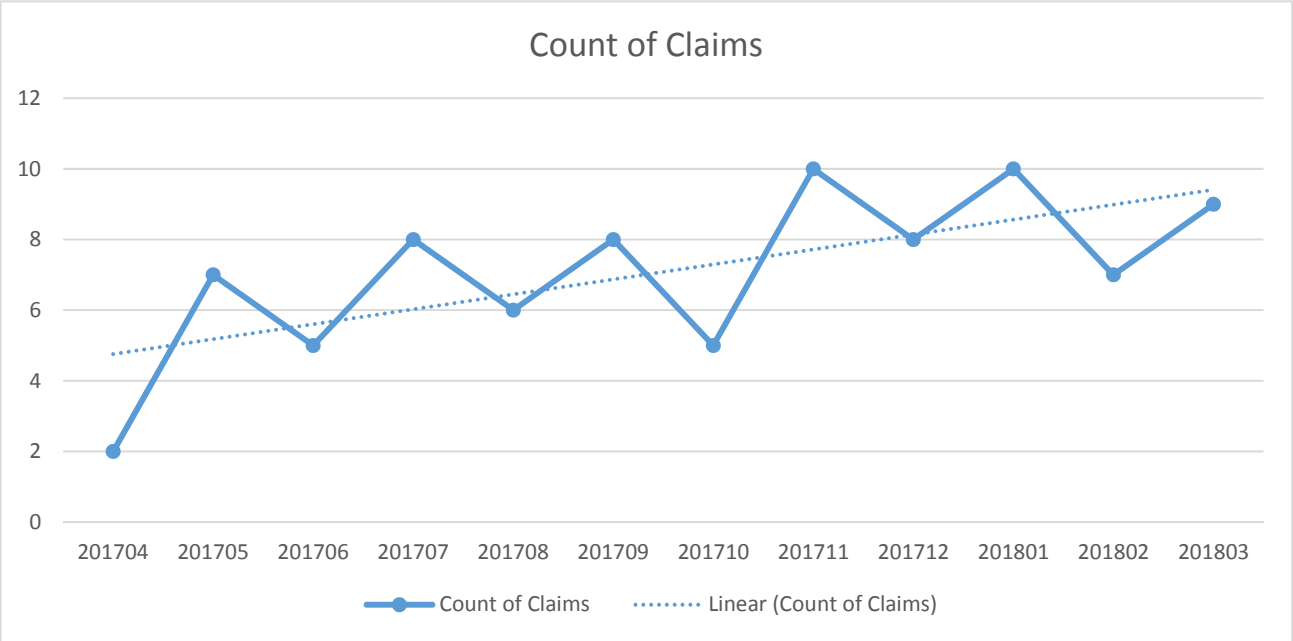
No proposed changes submitted.

Makena (Hydroxyprogesterone Caproate) Utilization

April 1, 2017 - March 31, 2018

Fee for Service Medicaid

Year Month Filled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201704	MAKENA	INJ 250MG/ML	2	2	63	9	$ 3,686.62
201705	MAKENA	INJ 250MG/ML	6	7	223	33	$ 18,323.00
201706	MAKENA	INJ 250MG/ML	4	5	127	20	$ 14,599.68
201707	MAKENA	INJ 250MG/ML	7	8	217	33	$ 24,060.19
201708	MAKENA	INJ 250MG/ML	6	6	187	27	$ 20,698.47
201709	MAKENA	INJ 250MG/ML	7	8	203	30	$ 23,001.69
201710	MAKENA	INJ 250MG/ML	5	5	119	18	$ 13,784.63
201711	MAKENA	INJ 250MG/ML	7	10	280	40	$ 30,675.70
201712	MAKENA	INJ 250MG/ML	8	8	224	32	$ 24,540.56
201801	MAKENA	INJ 250MG/ML	9	10	280	40	$ 31,757.90
201802	MAKENA	INJ 250MG/ML	7	7	198	28	$ 22,555.19
201803	MAKENA	INJ 250MG/ML	9	9	252	36	$ 28,999.53



Makena Utilization

SilverSummit Health

Year Month Filled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201712	MAKENA	INJ 250MG/ML	2	2	56	8	$ 6,163.72
201801	MAKENA	INJ 250MG/ML	4	4	112	16	$ 12,950.80
201802	MAKENA	INJ 250MG/ML	1	1	28	4	$ 3,237.70
201803	MAKENA	INJ 250MG/ML	3	3	84	12	$ 9,713.10
201817	MAKENA	INJ 250MG/ML	1	1	28	4	$ 3,081.86
Grand Total			11	11	308	44	$ 35,147.18

Makena Utilization
March 1, 2017 - February 28, 2018
Anthem Nevada Medicaid

Row Labels	Sum of Net Rxs	Sum of Total Plan Cost	Unique Mbr Count
Mar-2017	15	$ 45,825.93	14
Apr-2017	15	$ 46,577.18	15
May-2017	19	$ 59,348.34	18
Jun-2017	19	$ 56,726.52	18
Jul-2017	10	$ 30,224.78	10
Aug-2017	24	$ 74,398.14	22
Sep-2017	22	$ 68,087.66	22
Oct-2017	23	$ 73,359.33	21
Nov-2017	21	$ 67,837.66	20
Dec-2017	17	$ 53,639.08	17
Jan-2018	11	$ 34,805.19	11
Feb-2018	11	$ 36,462.58	11
MAKENA Grand	**207**	**$ 647,292.39**	199

Health Plan of Nevada

Makena Utilization

March 1, 2017 - February 28, 2018

Year/Month Filled/Paid	Drug Name	Count of Members	Count of Claims	Sum of Qty
2017/03	MAKENA INJ 250MG/ML	10	12	49
2017/03	MAKENA INJ 250MG/ML (medical)	3	3	12
2017/04	MAKENA INJ 250MG/ML	8	8	33
2017/05	MAKENA INJ 250MG/ML	14	15	60
2017/06	MAKENA INJ 250MG/ML	13	14	56
2017/06	MAKENA INJ 250MG/ML (medical)	16	17	68
2017/07	MAKENA INJ 250MG/ML	9	9	37
2017/07	MAKENA INJ 250MG/ML (medical)	14	14	56
2017/08	MAKENA INJ 250MG/ML	7	8	32
2017/08	MAKENA INJ 250MG/ML (medical)	8	8	32
2017/09	MAKENA INJ 250MG/ML	4	4	16
2017/10	MAKENA INJ 250MG/ML	11	11	44
2017/11	MAKENA INJ 250MG/ML	11	13	52
2017/12	MAKENA INJ 250MG/ML	8	8	32
2017/12	MAKENA INJ 250MG/ML (medical)	18	18	72
2018/01	MAKENA INJ 250MG/ML	11	11	44
2018/01	MAKENA INJ 250MG/ML (medical)	2	2	8
2018/02	MAKENA INJ 250MG/ML	13	14	56

PLEASE NOTE: Utilization comes from standard claims as well as capitated encounters where the amount paid is $0. Utilization also comes from medical claims (listed as medical) and pharmacy claims.

GG. Makena™ (Criteria for Physician Administered Drug)

Therapeutic Class: Progestational Agents
Last Reviewed by the DUR Board: April 28, 2011

Makena™ is 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

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

   a. Treatment with Makena™ is ordered by or recommended by a physician specializing in Obstetrics/Gynecology, Perinatology or Maternal/Fetal Medicine; and

   b. The recipient is female, 16 years of age or older and pregnant with a singleton pregnancy; and

   c. The recipient's pregnancy is between 16 weeks, 0 days and 20 weeks, six days of gestation when therapy begins; and

   d. The recipient has a history of singleton spontaneous preterm birth (prior to 37 weeks gestation); and

   e. The recipient does not have other risk factors for preterm birth; and

   f. There is no known major fetal anomaly or fetal demise; and

   g. The recipient has not been treated with heparin therapy during the current pregnancy; and

   h. The recipient has no history of thromboembolic disease; and

   i. The recipient has no maternal/obstetrical complication (e.g. current or planned cerclage, hypertension requiring medication or seizure disorder).

2. Length of approval:

   Makena™ will be approved for use until the recipient's pregnancy is 36 weeks, six days of gestation or delivery, whichever occurs first.

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

New Drug Overview
Makena (hydroxyprogesterone caproate)

INTRODUCTION

- Preterm birth is defined as delivery between 20 and 37 weeks of gestation and preterm delivery is the leading cause of perinatal morbidity and mortality. Preterm labor is the most common reason for antenatal hospitalization. The diagnosis is generally based on criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of ≥ 2 cm. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation (*Iams 2014, Fuchs et al 2004, American College of Obstetricians and Gynecologists [ACOG] 2016).*
- In the United States (US), the annual rate of preterm births was estimated at 11.7% in 2011, which was nearly twice the rate in European nations. Preterm birth in the US accounts for 35% of deaths in the first year of life (*Iams 2014).* Premature infants have a higher risk of mortality in their first year of life, and those that survive have a higher risk of hospital readmissions and long-term impairment (*Dodd et al 2013, Manuck et al 2016, Norwitz et al 2017*).
- The strongest risk factor for preterm birth is a prior history of preterm birth. Other major risk factors for spontaneous preterm birth in cases of singleton pregnancies include Black maternal race, previous pregnancy with an adverse outcome, genitourinary infection, smoking, extremes of body weight, and social disadvantage. Maternal depression, pre-pregnancy stress, poor diet, assisted fertility, and periodontal disease are also associated with preterm birth (*Iams 2014, Manuck et al 2016, Norwitz et al 2017*).
- Progesterone is an important natural hormone in the process of labor. Progesterone is naturally produced by the corpus luteum and is critical in early pregnancy and labor begins when the ratio of progesterone activity to estrogen activity is reversed or when progesterone activity is blocked, resulting in cervical ripening and uterine contractility (*Iams 2014, Meis et al 2003, Norwitz et al 2017*).
- Hydroxyprogesterone caproate (or 17-alpha [α]-hydroxyprogesterone caproate, HPC, or 17P) is a natural metabolite of progesterone that was first approved by the Food and Drug Administration (FDA) in 1956 as Delalutin for several indications. Delalutin was withdrawn from the market in 2000 for reasons unrelated to efficacy or safety. After market withdrawal, hydroxyprogesterone caproate was compounded by pharmacies into an injectable formulation. In February 2011, Makena was FDA-approved as an orphan drug under the FDA's accelerated approval process (*Clinical Pharmacology 2017*, *FDA summary review 2011*).
- Progesterone is available in the US in natural and synthetic forms and intramuscular (IM), oral, and vaginal routes of administration. Only hydroxyprogesterone caproate is FDA-approved for the reduction in the risk of preterm birth; however, there is compendia support for the use of progesterone off-label for this indication (*Clinical Pharmacology 2017*). Different routes of administration have different pharmacokinetic and pharmacodynamic effects. Experts concede that more information is needed regarding the appropriate dose, mode of administration, gestation age to initiate therapy, and duration of therapy for treatment (*Caritis et al 2014, Dodd et al 2013, Manuck et al 2016*).
- Medispan class: Progestins; Hydroxyprogesterone

INDICATION

- Hydroxyprogesterone caproate injection is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.
  - Limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth.
- 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

- The approval of Makena was based primarily on a multicenter (MC), randomized, double-blinded (DB), placebo controlled trial conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine

Unit (NICHD-MFMU). The study was published, but not designed or intended for marketing approval (*FDA summary review 2011*).
  - In one cohort (N = 463), hydroxyprogesterone caproate was evaluated at 16 to 20 weeks of gestation in very high-risk women with a documented history of singleton spontaneous preterm delivery. Results demonstrated a significantly reduced risk of delivery at < 37 weeks of gestation for hydroxyprogesterone caproate vs placebo (36.3 vs 54.9%, respectively; relative risk [RR], 0.66; 95% confidence interval [CI], 0.54 to 0.81), at < 35 weeks (20.6 vs 30.7%, respectively; RR, 0.67; 95% CI, 0.48 to 0.93), and at < 32 weeks (11.4 vs 19.6%, respectively; RR, 0.58; 95% CI, 0.37 to 0.91). There was no significant difference in neonatal deaths (2.6 vs. 5.9%, respectively; RR, 0.44; 95% CI, 0.17 to 1.13); however, the study was not powered to assess this endpoint. Infants of women treated with hydroxyprogesterone had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage (any Grade), and need for supplemental oxygen (*Meis et al 2003*, *FDA summary review 2011*).
- In a study in a home nursing program setting (N = 5493), compounded 17-*α*-hydroxyprogesterone was safe and effective, with preterm birth rates similar to those reported in the NICHD-MFMU study. No pregnancy outcome differences were noted based on the gestational age at which 17-*α*-hydroxyprogesterone caproate was initiated, either overall or within the Black and non-Black race groups. Miscarriage, stillbirth, or neonatal death was reported in 0.8% of cases, and there was no difference in these outcomes based on the gestational age at which 17-*α*-hydroxyprogesterone caproate was initiated. In an analysis performed based on race, there was a significant decrease in delivery at 35 weeks to 36 weeks in Black women vs non-Black women, (17.3 vs 21.7%, respectively) and a significant increase in delivery < 35 weeks (19.2 vs 12%, respectively). (*FDA summary review 2011, Meis et al 2003, Sibai et al 2012).*
- One meta-analysis (MA) reviewed 39 randomized trials of progesterone (IM, oral, or vaginal formulations) administration for the prevention of preterm birth in women at increased risk. A total of 11 trials (N = 1899) included women with a history of spontaneous preterm birth, and results demonstrated progesterone supplementation lowered the risks of preterm birth (including birth < 34 to 37 weeks, use of assisted ventilation, necrotizing enterocolitis, and neonatal intensive care unit admission), in addition to neonatal morbidities compared to placebo. Differences in the risks of intraventricular hemorrhage, neonatal sepsis, and retinopathy of prematurity did not differ significantly from placebo (*Dodd et al 2013*).
- Additional studies have supported the use of hydroxyprogesterone caproate for spontaneous preterm birth, although the results the optimal time to administer is highly debated. One study examined the administration of hydroxyprogesterone caproate 250 mg IM weekly starting between weeks 16 and 20 and continuing through week 36 in high-risk women, and demonstrated a decreased incidence of recurrent preterm birth (*Meis et al 2004*). Another study replicated the findings using vaginal progesterone suppositories (100 mg) (*da Fonseca et al 2003).* However, progesterone supplementation in women whose previous preterm birth occurred beyond 34 weeks produced similar rates of preterm delivery compared with placebo based on a secondary analysis of *Meis et al 2003* (*Spong et al 2005*).
- Compared to placebo, prophylactic IM weekly injections of hydroxyprogesterone caproate did not prolong pregnancy until a favorable gestation age or fetal lung maturity (3 vs 8%) or improve perinatal outcomes when given to mothers with singleton pregnancies, gestational age 23 to 30 weeks, with spontaneous preterm rupture of membranes. The randomized study (N = 152) was terminated early. There were no significant between-group differences observed in the days from randomization to delivery, gestational age at delivery, or any neonatal outcome (eg, neonatal death, respiratory distress syndrome, stage 2 or 3 necrotizing enterocolitis). A numerical increase in cesarean deliveries with hydroxyprogesterone caproate was observed (60 vs 44%); however, this was not statistically significant (*Combs et al 2015*).
- Very few studies have been conducted head-to-head comparing IM formulations to other formulations of progesterone therapy. The following summarizes current outcomes:
  - One prospective, randomized, open-label (OL) trial compared progesterone IM 250 mg once weekly (manufactured as Proluton Depot, manufactured by Bayer Schering Pharma AG, Germany; not available in the US) to vaginal progesterone 90 mg once daily gel in 518 women with a history of preterm birth and a current singleton pregnancy. Patients receiving vaginal progesterone experienced a significantly lower rate of preterm birth at < 34 weeks vs those treated with progesterone IM (16.6 vs 25.7%; odds ratio [OR], 0.58; 95% CI, 0.37 to 0.89; p = 0.02) (*Maher et al 2013*).
  - Another prospective RCT compared hydroxyprogesterone caproate IM 250 mg once weekly to vaginal progesterone suppositories 400 mg daily as prevention of preterm birth in 304 women with a sonographically short cervix. The women were between 16 and 24 gestational weeks with a cervical length of < 25 mm. The rates of preterm birth were

not statistically significantly different between groups (10.4% in the progesterone suppository group vs 14% in the hydroxyprogesterone caproate IM group; p = 0.416) (*Pirjani et al 2017*).
  - *Eliminian et al* compared hydroxyprogesterone caproate IM 250 mg once weekly to vaginal progesterone suppositories 100 mg daily in 145 women with singleton pregnancies ranging from 16 to 20 weeks of gestation and a history of spontaneous preterm birth. Results demonstrated similar efficacy in reducing the rate of recurrent preterm birth between agents (37.9% in the progesterone suppository group vs 43.9% in the hydroxyprogesterone caproate IM group; p = 0.50) (*Eliminian et al 2016*).
- One MA of 3 RCTs comprising 680 women assessed the benefit of vaginal progesterone to hydroxyprogesterone caproate IM for the prevention of recurrent spontaneous preterm birth in singleton gestations. Studies included vaginal progesterone in doses ranging from 90 mg to 200 mg daily vs hydroxyprogesterone caproate IM 250 mg once weekly. In women with a previous spontaneous preterm birth, vaginal progesterone demonstrated lower rates of spontaneous preterm birth < 34 weeks vs hydroxyprogesterone caproate IM (17.5 vs 25.0%; RR, 0.71; 95% CI, 0.53 to 0.95). Additionally, lower rates of adverse events were reported in the vaginal progesterone group vs hydroxyprogesterone caproate IM (7.1 vs 13.2%; RR, 0.53; 95% CI, 0.31 to 0.91). Although daily vaginal progesterone starting at 16 weeks of gestation appeared to be better than hydroxyprogesterone caproate IM, conclusions were based mainly on low quality evidence. More large comparative trials are needed to validate superiority of one formulation over the other for all pregnancies at high risk for preterm birth (*Saccone et al 2017*).
- Progesterone may not be effective in unselected multiple gestations, which may in part be due to the lack of influence progesterone changes impart on multiple gestations compared to singleton (*Norwitz et al 2017*). In a 2017 MA of unselected twin gestations, neither IM nor vaginal progesterone improved preterm or neonatal outcomes. Other publications have supported that hydroxyprogesterone caproate IM may not have benefit in women with twin pregnancies and a short cervix or in asymptomatic women with triplet pregnancies, and some publications concluded that IM formulations may increase adverse perinatal outcomes in twin pregnancies (*Combs et al 2016, Dodd et al 2017, Schuit et al 2015, Senat et al 2013*).
  - Two trials in which women with singleton gestations and a short cervical length were randomly assigned to weekly hydroxyprogesterone caproate IM 250 mg or 500 mg vs placebo through 36 weeks reported that treatment with hydroxyprogesterone caproate did not reduce the risk of preterm birth in women with a short cervix and other risk factors for preterm delivery, such as previous preterm birth, cervical surgery, uterine anomalies, or prenatal diethylstilbestrol (DES) exposure. The frequency of preterm birth at < 37 weeks did not differ from placebo (25.1 vs 24.2%; RR, 1.03; 95% CI, 0.79 to 1.35) (*Grobman et al 2012*). In *Winer et al 2015*, after enrolling 105 patients an interim analysis demonstrated a lack of efficacy for hydroxyprogesterone caproate IM in prolonging pregnancy. There may have been methodological issues that influenced outcomes. Both trials were stopped before completion because of lack of efficacy at the scheduled interim analysis. Also *Grobman et al 2012* was limited to nulliparous women with a short cervix while *Winer et al 2015* included women with both a short cervix and risk factors for preterm birth (*Grobman et al 2012, Winer et al 2015*).

CLINICAL GUIDELINES

- **Note**: Makena (hydroxyprogesterone caproate) was FDA-approved in February 2011. Prior to the approval, compounding pharmacies were supplying hydroxyprogesterone caproate for this use. The FDA has recommended that when an FDA-approved drug is commercially available, the commercially available product be used instead of a compounded form. However, the FDA is not aware of any scientifically reliable evidence demonstrating that compounding 17P without a preservative or in an oil base different than the one used in Makena produces a significant difference for an identifiable group of patients (aside from the rare patient who is known to be allergic to either the preservative or the oil base). Trials have evaluated compounded drug use. Although compounded hydroxyprogesterone caproate preparations may be tailored to an individual patient's particular medical needs, practitioners should be aware of regulation and quality concerns related to this practice. (*FDA 2012*).

- **American College of Obstetricians and Gynecologists** (*ACOG 2012*, *ACOG 2016*)
  - Women with a prior spontaneous preterm birth should be evaluated by obtaining a detailed medical history, reviewing comprehensively aspects of all previous pregnancies, reviewing risk factors, and determining their candidacy for prophylactic interventions, such as progesterone supplementation, cervical cerclage, or both.

- ACOG recommends that progesterone supplementation be limited to women with a singleton pregnancy and a previous history of spontaneous preterm birth, starting at 16 to 24 weeks of gestation, to reduce the risk of recurrent spontaneous preterm birth (Level A).
- Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations (Level A).
- Insufficient evidence exists to assess if progesterone and cerclage together have an additive effect in reducing the risk of preterm birth in women at high risk for preterm birth (Level B).
- ACOG does not specify what type of progesterone formulation is preferred.
- The 2012 Practice Bulletin was reaffirmed in 2016.
- See Appendix for definitions of the levels of evidence.

- **Society for Maternal-Fetal Medicine** (*SMFM 2017*)
  - In women with a singleton gestation and a history of prior spontaneous preterm birth between 20 and 36 6/7 weeks of gestation, hydroxyprogesterone caproate is recommended at 250 mg IM weekly, starting at 16 to 20 weeks of gestation until 36 weeks of gestation or delivery.
  - Few studies directly compare hydroxyprogesterone caproate and vaginal progesterone in women with a history of a prior spontaneous preterm birth.
  - Vaginal progesterone has not been adequately proven to decrease recurrent preterm birth in women with a history of a prior spontaneous preterm birth. SMFM stipulates that vaginal progesterone should not be considered a substitute for hydroxyprogesterone caproate in these patients.
  - However, SMFM recommends the use of vaginal progesterone to prevent preterm birth in women with a sonographically short cervix of ≤ 20 mm without a history of a prior spontaneous preterm birth.
  - In women with a prior spontaneous preterm birth who start hydroxyprogesterone caproate therapy and then develop cervical shortening, it is not clear if there is any benefit to changing the progestogen choice to vaginal progesterone (with or without cervical cerclage placement).

SAFETY SUMMARY

- **Contraindications**
  - Makena should not be used in women with current or history of thrombosis or thromboembolic disorders; known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions; undiagnosed abnormal vaginal bleeding unrelated to pregnancy; cholestatic jaundice of pregnancy; liver tumors, benign or malignant, or active liver disease; or uncontrolled hypertension.
- **Key Warnings/Precautions**
  - Thromboembolic disorders: Should an arterial or deep vein thrombosis or thromboembolic event occur, therapy should be discontinued.
  - Allergic reactions: As with other products that contain castor oil, reactions including urticaria, pruritus, and angioedema have been reported. Therapy should be discontinued should such reactions occur.
  - Decreased glucose tolerance: A lowering of glucose tolerance has been observed. Prediabetic and diabetic women should be monitored closely.
  - Fluid retention: May occur with progestational drugs; therefore, conditions affected by this should be monitored (eg, preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).
  - Depression: Women who have a history of clinical depression should be monitored and treatment discontinued if clinical depression recurs.
  - Jaundice: Women who develop jaundice should be monitored and benefits/risks of continued therapy considered.
  - Hypertension: Women who develop hypertension should be monitored and benefits/risks of continued therapy considered.
- **Adverse effects**
  - Common adverse events (incidence ≥ 2% and at a higher rate compared to the control group) with hydroxyprogesterone caproate IM were injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%).

- Certain pregnancy-related fetal and maternal complications or events were numerically increased in hydroxyprogesterone caproate-treated patients as compared to control patients, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios.
  - Miscarriage (< 20 weeks) occurred in 5 out of 209 hydroxyprogesterone caproate-treated patients compared to 0 out of 107 control patients measured.
  - Stillbirth (≥ 20 weeks) occurred in 6 out of 305 hydroxyprogesterone caproate-treated patients compared to 2 out of 153 control patients measured.
  - Pregnancy complications include preeclampsia or gestational hypertension (4.2% more with hydroxyprogesterone caproate), oligohydramnios or a deficiency of amniotic fluid (2.3% more with hydroxyprogesterone caproate), admission for preterm labor (2.2% more with hydroxyprogesterone caproate), and gestational diabetes (1.0% more with hydroxyprogesterone caproate).

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulation	Usual Recommended Frequency	Comments
Makena (hydroxyprogesterone caproate)	Injection for IM use	Once weekly	• Begin treatment between 16 weeks and 20 weeks + 6 days of gestation. • Continue until week 37 of gestation or delivery, whichever occurs first.

See the current prescribing information for full details

CONCLUSION

- Makena (hydroxyprogesterone caproate) was FDA-approved in February 2011. Prior to the approval, compounding pharmacies were supplying hydroxyprogesterone caproate for use. The FDA does recommend commercially-available manufacturer products above compounded products due to the standardization and oversight associated with good manufacturing practices (*FDA 2012*).
- Hydroxyprogesterone caproate is administered via IM injection and is indicated to reduce the risk of preterm birth in women with a singleton pregnancy and a history of singleton spontaneous preterm birth. Risks are reduced in approximately one-third of women. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Improvement in neonatal mortality and morbidity have not been demonstrated in clinical studies.
  - Based on clinical studies, hydroxyprogesterone caproate has demonstrated an ability to prolong pregnancy, and in high risk women, hydroxyprogesterone caproate demonstrated a reduced rate of recurrent preterm delivery at less than 32, 35, and 37 weeks. Other studies have demonstrated that if preterm birth does occur, babies who survive have fewer complications if their mothers received hydroxyprogesterone caproate before the birth. Observed benefits of hydroxyprogesterone caproate have not been strongly correlated to improvements in infant mortality. Additionally, it is not clear how hydroxyprogesterone caproate compares to other routes of administration or to other formulations, such as vaginal progesterone (*Combs et al 2015, Dodd et al 2013*, *FDA summary review 2011, Meis et al 2003*, *Meis et al 2004*, *Norwitz et al 2017, Sibai et al 2012*).
  - Evidence suggests there could be differences in the pharmacologic action of progesterone formulations. Comparative effectiveness data have methodological limitations and evidence are often of lower quality. Vaginal progesterone may be associated with similar or reduced rates of recurrent spontaneous preterm birth vs hydroxyprogesterone caproate; however, more robust studies are required to validate conclusions (*Eliminian et al 2016, Maher et al 2013, Pirjani et al 2017, Saccone et al 2017*).
- The ACOG recommends progesterone supplementation in women with a singleton gestation and a prior spontaneous preterm singleton birth starting at 16 to 24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth. ACOG does not specify what type of progesterone formulation is preferred. The SMFM takes a stronger stance, rejecting certain evidence, recommending the use of hydroxyprogesterone caproate IM, and concluding that vaginal progesterone has not been adequately proven to decrease recurrent preterm birth in women with a history of a prior spontaneous preterm birth (*ACOG 2012, ACOG 2016, SMFM 2017*).

- Hydroxyprogesterone caproate is contraindicated in patients with current or prior thromboembolic disease, known or suspected breast or hormone-mediated cancer, undiagnosed abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, hepatic tumors, liver disease, or uncontrolled hypertension. Patients with a history of or at risk for depression, fluid retention, or diabetes should be monitored. Allergic reactions have been reported with hydroxyprogesterone caproate and other products containing castor oil.
- Hydroxyprogesterone caproate is correlated with numerically increased fetal and maternal complications or events compared to placebo. Events include miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios. Common adverse events are mostly related to injection-site reactions; however, others include urticaria, pruritus, nausea, and diarrhea.

APPENDIX

ACOG Levels of Evidence

- Level A: Based on good and consistent scientific evidence
- Level B: Based on limited or inconsistent scientific evidence
- Level C: Based primarily on consensus and expert opinion

REFERENCES

- ACOG Practice Bulletin No. 130, October 2012 (replaces Committee Opinion No. 419, October 2008 and Practice Bulletin No. 31, October 2001). Use of progesterone to reduce preterm birth. *Obstet Gynecol.* 2012;120:964–73.
- ACOG Practice Bulletin No. 171, October 2016 (replaces No. 159, January 2016). Management of preterm labor. *Obstet Gynecol.* 2016;128(4):e155-64.
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Publication Date: December 1, 2017

- The following chart includes the suggested criteria from OptumRx then each of the MCO's criteria where **differences** are seen.

	OptumRx	Anthem	HPN	SSH
Fasenra				
Initial Auth Criteria	1. Diagnosis of **severe** asthma 2. Patient is 12 years of age or older 3. The recipient will not use the requested antiasthmatic monocolonal antibody in combination with other antiasthmatic monoclonal antibodies 4. Asthma is an eosinophilic phenotype as defined by a baseline blood eosinophil level greater than or equal to 150 cells per microliter 5. And one of the following: a. Patient has had at least two or more asthma exacerbations requiring systemic corticosteroids within the past 12 months b. Any prior intubation for an asthma exacerbation c. Prior asthma-related hospitalization within the past 12 months 6. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications: a. Both of the following: i. High-dose inhaled corticosteroid (ICS) [e.g., greater than 500 mcg fluticasone propionate equivalent/day] ii. Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline] b. Or one maximally-dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formaoterol] 7. Prescribed by or in consultation with one of the following: a. Pulmonologist b. Allergy/Immunology Specialist	1. Diagnosis of severe **eosinophilic** asthma Individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, **including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection)** greater than or equal to **300** cells/microliter at initiation of therapy Or temporary increase in the individual's usual maintenance dosage of oral corticosteroids Symptoms are inadequately controlled with use of either combination therapy: fluticasone at a medium- or high-dosage of 250 micrograms or greater [or equivalent] or high dosage of greater than or equal to 500 micrograms [or equivalent] given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist, or leukotriene receptor antagonist Evidence of asthma is demonstrated by all of the following: a. A pretreatment forced	Asthma is an eosinophilic phenotype as defined by a baseline (pre-benralizumab treatment) peripheral blood eosinophil level ≥ 150 cells/mL within the past **6 weeks** Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following; a. poor symptom control (e.g., Asthma Control Questionnaire (ACQ) score consistently greater than 1.5 or Asthma Control Test (ACT) score consistently less than 2.0, or b. two or more burst of systemic corticosteroids for at least 3 days each in the previous 12 months, or c. Airflow limitation (e.g., after appropriate bronchodilator withhold forces expiratory volume in 1 second (FEV_1) less than 80% predicted (in the face of reduced	1. Diagnosis of asthma Asthma with absolute blood eosinophil count ≥ 150 cells/mcL within the past **3 months**

		expiratory volume in 1 second (FEV_1) less than 80% predicted; and b. FEV_1 reversibility of at least 12% and 200 milliliters (ml) after albuterol (salbutamol) administration; and c. A baseline Asthma Control Questionnaire-6 score of greater than or equal to 1.5	FEV_1/forced vital capacity [FVC] defined as less than the lower limit of normal)	Dose does not exceed 30 mg every 4 weeks for the first 3 doses, then 30 mg every 8 weeks thereafter
ReAuth	1. There is documentation of a positive clinical response (e.g. reduction in exacerbation) 2. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications: a. Both of the following: i. Inhaled corticosteroid (ICS) [5, E] ii. Additional asthma controller medication [e.g. leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline] b. Or a combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera mometasone/formoterol], Symbicort [budesonide/formaoterol] 3. Prescribed by or in consultation with one of the following: a. Pulmonologist b. Allergy/Immunology Specialist			Demonstrated adherence to asthma controller therapy that includes an ICS plus either a LABA or leukotriene modifier (LTRA) If request is for a new dose increase, new dose does not exceed 30 mg every 8 weeks
Approval Duration	Approval length: 12 months for initial And for reauthorization	Approval Length: : 12 months for initial And for reauthorization	Approval Length: Initial authorization **6** months	Approval length: **6** months for initial And 12 months for reauthorization

Nevada Medicaid
Fasenra (benralizumab)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Fasenra	benralizumab

CRITERIA FOR COVERAGE/NONCOVERAGE

Indications

Severe Eosinophilic Asthma Indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Limitation of use: Fasenra is not indicated for treatment of other eosinophilic conditions. Fasenra is not indicated for the relief of acute bronchospasm or status asthmaticus.

Initial Authorization:

Approval Length: 12 Months

1. Diagnosis of severe asthma
2. Patient is 12 years of age or older
3. The recipient will not use the requested antiasthmatic monocolonal antibody in combination with other antiasthmatic monoclonal antibodies
4. Asthma is an eosinophilic phenotype as defined by a baseline blood eosinophil level greater than or equal to 150 cells per microliter
5. And one of the following:
    a. Patient has had at least two or more asthma exacerbations requiring systemic corticosteroids within the past 12 months
    b. Any prior intubation for an asthma exacerbation
    c. Prior asthma-related hospitalization within the past 12 months
6. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:
    a. Both of the following:
        i. High-dose inhaled corticosteroid (ICS) [e.g., greater than 500 mcg fluticasone propionate equivalent/day]
        ii. Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]

   b. Or One maximally-dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

7. Prescribed by or in consultation with one of the following:
   a. Pulmonologist
   b. Allergy/Immunology specialist

Reauthorization:

Approval Length: 12 Months

1. There is documentation of a positive clinical response (e.g. reduction in exacerbation)
2. Patient is currently being treated with one of the following unless there is a contraindication or intolerance to these medications:
   a. Both of the following:
      i. Inhaled corticosteroid (ICS) [5, E]
      ii. Additional asthma controller medication [e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline]
   b. Or a combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])
3. Prescribed by or in consultation with one of the following:
   a. Pulmonologist
   b. Allergy/Immunology specialist

Clinical Policy: Benralizumab (Fasenra)

Reference Number: CP.PHAR.373
Last Review Date: 05.18
Line of Business: Commercial, Health Insurance Marketplace, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Benralizumab (Fasenra™) is an interleukin (IL)-5 receptor alpha-directed cytolytic monoclonal antibody.

FDA Approved Indication(s)

Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitation(s) of use:

- Fasenra is not indicated for treatment of other eosinophilic conditions.
- Fasenra is not indicated for the relief of acute bronchospasm or status asthmaticus.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Fasenra is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Severe Asthma (must meet all)**:**

1. Diagnosis of asthma with absolute blood eosinophil count ≥ 150 cells/mcL within the past 3 months;
2. Prescribed by or in consultation with a pulmonologist or allergist;
3. Age ≥ 12 years;
4. Member has experienced ≥ 2 exacerbations within the last 12 months, requiring any of the following despite adherent use of controller therapy (i.e., high-dose inhaled corticosteroid (ICS) plus either a long-acting beta$_2$ agonist (LABA) or leukotriene modifier (LTRA) if LABA contraindication/intolerance):
   a. Oral/systemic corticosteroid treatment (or increase in dose if already on oral corticosteroid);
   b. Urgent care visit or hospital admission;
   c. Intubation;
5. Fasenra is prescribed concomitantly with an ICS plus either a LABA or LTRA;
6. Dose does not exceed 30 mg every 4 weeks for the first 3 doses, then 30 mg every 8 weeks thereafter.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Severe Asthma (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Demonstrated adherence to asthma controller therapy that includes an ICS plus either a LABA or LTRA;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 30 mg every 8 weeks.

Approval duration:
Medicaid/Health Insurance Marketplace – 12 months
Commercial – 6 months or member's renewal period, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Acute bronchospasm or status asthmaticus.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration	IL: interleukin
BEC: blood eosinophil count	LABA: long-acting beta$_2$ agonist
ICS: inhaled corticosteroid	LTRA: leukotriene modifier

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ICS		
Qvar® (beclomethasone)	40 mcg, 80 mcg per actuation 1-4 actuations BID	4 actuations BID
budesonide (Pulmicort®)	90 mcg, 180 mcg per actuation 2-4 actuations BID	2 actuations BID
Alvesco® (ciclesonide)	80 mcg, 160 mcg per actuation 1-2 actuations BID	2 actuations BID
Aerospan® (flunisolide)	80 mcg per actuation 2-4 actuations BID	2 actuations BID
Flovent® (fluticasone propionate)	44-250 mcg per actuation 2-4 actuations BID	2 actuations BID
Arnuity Ellipta® (fluticasone furoate)	100 mcg, 200 mcg per actuation 1 actuation QD	1 actuation QD
Asmanex® (mometasone)	HFA: 100 mcg, 200 mcg per actuation Twisthaler: 110 mcg, 220 mcg per actuation 1-2 actuations QD to BID	2 inhalations BID
LABA		
Serevent® (salmeterol)	50 mcg per dose 1 inhalation BID	1 inhalation BID
Combination products (ICS + LABA)		
Dulera® (mometasone/ formoterol)	100/5 mcg, 200/5 mcg per actuation 2 actuations BID	4 actuations per day
Breo Ellipta® (fluticasone/vilanterol)	100/25 mcg, 200/25 mcg per actuation 1 actuation QD	1 actuation QD
Advair® (fluticasone/ salmeterol)	Diskus: 100/50 mcg, 250/50 mcg, 500/50 mcg per actuation HFA: 45/21 mcg, 115/21 mcg, 230/21 mcg per actuation 1 actuation BID	1 actuation BID
fluticasone/salmeterol (Airduo RespiClick®)	55/13 mcg, 113/14 mcg, 232/14 mcg per actuation 1 actuation BID	1 actuation BID
Symbicort® (budesonide/ formoterol)	80 mcg/4.5 mcg, 160 mcg/4.5 mcg per actuation 2 actuations BID	2 actuations BID
LTRA		
montelukast (Singulair®)	4 to 10 mg PO QD	10 mg per day
zafirlukast (Accolate®)	10 to 20 mg PO BID	40 mg per day
zileuton ER (Zyflo® CR)	1200 mg PO BID	2400 mg per day
Zyflo® (zileuton)	600 mg PO QID	2400 mg per day
Oral corticosteroids		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
dexamethasone (Decadron®)	0.75 to 9 mg/day PO in 2 to 4 divided doses	Varies
methylprednisolone (Medrol®)	40 to 80 mg PO in 1 to 2 divided doses	Varies
prednisolone (Millipred®, Orapred ODT®)	40 to 80 mg PO in 1 to 2 divided doses	Varies
prednisone (Deltasone®)	40 to 80 mg PO in 1 to 2 divided doses	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: General Information

- The pivotal trials defined severe asthma as 2 or more exacerbations of asthma despite regular use of high-dose ICS plus an additional controller (e.g., LABA or LTRA) with or without oral corticosteroids. Although the CALIMA trial included patients receiving medium-dose ICS, Fasenra was not shown to have an effect on annual exacerbation rate, pre-bronchodilator forced expiratory volume in 1 second, or total asthma symptom score in those patients.
- Clinically significant exacerbation was defined as a worsening of asthma (any new or increased symptoms or signs that were concerning) that led to one of the following: (1) use of systemic corticosteroids, (2) emergency department or visit to urgent care center, or (3) inpatient hospital stay.
- Baseline blood eosinophil count (BEC) is a predictor of response to therapy. Although the SIROCCO and CALIMA trials were powered for efficacy analysis in patients with baseline BEC ≥ 300 cells/µL, a pooled analysis which stratified patients by baseline BEC (≥ 0 cells/µL, ≥ 150 cells/µL, ≥ 300 cells/µL, and ≥ 450 cells/µL) found Fasenra to have a statistically significant positive treatment effect on those with baseline BEC ≥ 150 cells/µL. In addition, the ZONDA trial found Fasenra to significantly reduce oral corticosteroid dose in patients with baseline BEC ≥ 150 cells/µL.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Severe asthma	30 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter	See regimen

VI. Product Availability

Single-dose prefilled syringe with solution for injection: 30 mg/mL

VII. References

1. Fasenra Prescribing Information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. Available at: www.fasenra.com. Accessed November 20, 2017.
2. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051). Available at http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed December 7, 2017.

3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology.com. Accessed November 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.16.18	05.18

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

Cinqair (reslizumab)
Fasenra (benralizumab)
Nucala (mepolizumab)

DRUG.00080

Override(s)	Approval Duration
Prior Authorization	Initial Therapy: 1 year Continuation Therapy: 1 year

Medications
Cinqair (reslizumab)
Fasenra (benralizumab)
Nucala (mepolizumab)

APPROVAL CRITERIA

Eosinophilic asthma

Cinqair (reslizumab) may be approved for the treatment of severe eosinophilic asthma when the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Symptoms are inadequately controlled with a minimum of 12 months of maintenance inhaled corticosteroid (for example, daily fluticasone at a dosage of 440 micrograms [or equivalent]), unless the individual is intolerant of, or has a medical contraindication to these agents; **AND**
III. Individual has experienced at least one asthma exacerbation in the prior 12 months requiring uninterrupted oral, intramuscular, or intravenous corticosteroid administration for 3 or more days; **AND**
IV. Individual has blood eosinophil counts (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 400 cells/microliter* in the prior 12 months; **AND**
V. Evidence of asthma is demonstrated by **all** of the following:
    A. A pretreatment FEV_1 less than 80% predicted; **AND**
    B. FEV_1 reversibility of at least 12% and 200 ml after albuterol (salbutamol) administration; **AND**
    C. A baseline Asthma Control Questionnaire-7 score of greater than or equal to 1.5.

Fasenra (benralizumab) may be approved for the treatment of severe eosinophilic asthma when the following criteria are met:

I. Individual is 12 years of age or older; **AND**
II. Symptoms are inadequately controlled with use of **either** combination therapy:
   A. 12 months of medium- or high-dose inhaled corticosteroid (for example, daily fluticasone at a medium dosage of 250 micrograms or greater [or equivalent] **or** high dosage of greater than or equal to 500 micrograms [or equivalent]) given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist, **or** leukotriene receptor antagonist, **or** theophylline), unless the individual is intolerant of, **or** has a medical contraindication to these agents; **OR**
   B. 6 months of inhaled corticosteroid with daily oral glucocorticoids given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist, **or** leukotriene receptor antagonist, **or** theophylline), unless the individual is intolerant of, **or** has a medical contraindication to these agents;

AND

III. Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of a systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids;

AND

IV. Individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection) greater than or equal to 300 cells/microliter* at initiation of therapy;

AND

V. Evidence of asthma is demonstrated by all of the following:
   A. A pretreatment forced expiratory volume in 1 second (FEV_1) less than 80% predicted; **AND**
   B. FEV_1 reversibility of at least 12% and 200 milliliters (ml) after albuterol (salbutamol) administration; **AND**
   C. A baseline Asthma Control Questionnaire-6 score of greater than or equal to 1.5.

Nucala (mepolizumab) may be approved for the treatment of severe eosinophilic asthma when the following criteria are met:

I. Individual is 12 years of age or older; **AND**
II. Symptoms are inadequately controlled with use of **either** combination therapy:
    A. 12 months of high-dose inhaled corticosteroid given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist , **or** leukotriene receptor antagonist , **or** theophylline), unless the individual is intolerant of, **or** has a medical contraindication to these agents; **OR**
    B. 6 months of inhaled corticosteroid with daily oral glucocorticoids given in combination with a minimum of 3 months of controller medication (either a long-acting beta2-agonist, **or** leukotriene receptor antagonist, **or** theophylline), unless the individual is intolerant of, **or** has a medical contraindication to these agents;

AND
III. Individual has **one** of the following blood eosinophil counts (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection):
    A. Greater than or equal to 150 cells/microliter* at initiation of therapy; **OR**
    B. Greater than or equal to 300 cells/microliter* in the prior 12 months;

AND
IV. Evidence of asthma is demonstrated by **both** of the following:
    A. A pretreatment forced expiratory volume in 1 second (FEV_1) less than 80% predicted; **AND**
    B. FEV_1 reversibility of at least 12% and 200 milliliters (ml) after albuterol (salbutamol) administration.

Continuation of therapy with either Cinqair (reslizumab), Fasenra (benralizumab), or Nucala (mepolizumab) or after 12 months may be approved for the treatment of an individual with documented severe eosinophilic asthma when the following criteria are met:

I. Treatment with Cinqair (reslizumab), Fasenra (benralizumab), or Nucala (mepolizumab) has resulted in clinical improvement as documented by **one or more** of the following:
    A. Decreased utilization of rescue medications; **OR**
    B. Decreased frequency of exacerbations (defined as worsening of asthma that requires an increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); **OR**
    C. Increase in predicted FEV_1 from pretreatment baseline; **OR**
    D. Reduction in reported asthma-related symptoms, such as, asthmatic symptoms upon awakening, coughing, fatigue, shortness of breath, sleep disturbance, or wheezing.

Cinqair (reslizumab), Fasenra (benralizumab), or Nucala (mepolizumab) may **not** be approved when criteria are not met and for **all** other conditions, including but not limited to:

I. Aspirin-exacerbated respiratory disease; **OR**
II. Atopic dermatitis; **OR**
III. Eosinophilic esophagitis; **OR**
IV. Eosinophilic granulomatosis with polyangiitis ; **OR**
V. Nasal polyposis; **OR**
VI. Hypereosinophilic syndromes (other than severe eosinophilic asthma).

Eosinophilic granulomatosis with polyangiitis

Nucala (mepolizumab) may be approved for the treatment of severe eosinophilic granulomatosis with polyangiitis when the following criteria are met:

I. Individual is 18 years of age or older; **AND**

II. Individual is diagnosed with eosinophilic granulomatosis with polyangiitis for 6 months or greater, defined as:

   A. A history or presence of asthma; **AND**

   B. A blood eosinophil level of greater than or equal to 10% of leucocytes or an absolute eosinophil count of greater than 1000 cells per cubic millimeter (mm3) (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or suspected parasitic infection); **AND**

   C. The presence of two or more features of eosinophilic granulomatosis with polyangiitis (such as, a biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatosis inflammation; neuropathy, mono or poly [motor deficit or nerve conduction abnormality]; pulmonary infiltrates, non-fixed; sino-nasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura, or antineutrophil cytoplasmic antibody [ANCA] positive status).

Continuation of therapy with Nucala (mepolizumab) after 12 months may be approved for an individual with documented relapsing or refractory eosinophilic granulomatosis with polyangiitis when treatment has resulted in clinical improvement as documented by the achievement of remission at some point during treatment, defined as the following:

   A. Birmingham Vasculitis Activity Score (BVAS), version 3, of 0 (on a scale from 0 to 63); **AND**
   B. Receipt of prednisolone or prednisone at a dose of 4.0 mg or less per day.

Nucala (mepolizumab) may **not** be approved when criteria are not met and for **all** other conditions, including but not limited to:

I. Aspirin-exacerbated respiratory disease; **OR**
II. Atopic dermatitis; **OR**
III. Eosinophilic esophagitis; **OR**
IV. Eosinophilic granulomatosis with polyangiitis ; **OR**
V. Nasal polyposis; **OR**
VI. Hypereosinophilic syndromes (other than severe eosinophilic asthma or eosinophilic granulomatosis with polyangiitis).

****Note*:** 1 microliter (ul) is equal to 1 cubic millimeter (mm^3)

State Specific Mandates		
State name N/A	Date effective N/A	Mandate details (including specific bill if applicable) N/A

Key References:

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3. Cinqair [Product Information], Frazer, PA. Teva Pharmaceuticals, LLC; March 23, 2016. Available at: http://www.cinqair.com/pdf/PrescribingInformation.pdf. Accessed on December 26, 2017.
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RESPIRATORY INTERLEUKINS (CINQAIR®, FASENRA®, AND NUCALA®)

Policy Number: CS2018D0055C **Effective Date**: March 1, 2018

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Commercial Policy

- Respiratory Interleukins (Cinqair®, Fasenra®, and Nucala®)

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced. The terms of the federal, state or contractual requirements for benefit plan coverage may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the contractual requirements for benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the federal, state or contractual requirements for benefit coverage.

COVERAGE RATIONALE

This policy provides information about the use of certain specialty pharmacy medications administered by either the subcutaneous (SC) or intravenous (IV) route for severe asthmatic conditions.

This policy refers to the following drug products:

- Cinqair® (reslizumab)
- Fasenra® (benralizumab)
- Nucala® (mepolizumab)

Proven

I. Cinqair®
   A. **Cinqair for intravenous use is proven and medically necessary when ALL of the following criteria are met**:[2-6]
      1. Diagnosis of severe asthma; **and**

2. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:
   a. Poor symptom control (e.g., ACQ score consistently greater than 1.5 or ACT score consistently less than 20); **or**
   b. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
   c. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
   d. Airflow limitation (e.g., after appropriate bronchodilator withhold FEV1 less than 80% predicted [in the face of reduced FEV1/FVC defined as less than the lower limit of normal]);

   and
3. Asthma is an eosinophilic phenotype as defined by a baseline (pre-reslizumab) peripheral blood eosinophil level of ≥ 400 cells/µL within the past 4 weeks; **and**
4. Used in combination with **one** of the following:
   a. One maximally-dosed (appropriately adjusted for age) combination ICS/LABA product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; **or**
   b. Combination therapy including **both** of the following:
      i. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; **and**
      ii. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®), leukotriene receptor antagonist − montelukast (Singulair®), theophylline];

   and
5. Patient is not receiving Cinqair in combination with **any** of the following:
   a. Fasenra (benralizumab)
   b. Xolair (omalizumab)
   c. Nucala (mepolizumab);

   and
6. Cinqair dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration (U.S. FDA) approved labeling: 3 mg/kg intravenously once every 4 weeks; **and**
7. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
8. Initial authorization will be for no more than 6 months.

II. Fasenra®
   A. **Fasenra for subcutaneous use is proven and medically necessary when ALL of the following criteria are met**: [3, 5, 6, 10-12]
      1. Diagnosis of severe asthma; **and**
      2. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:
         a. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); **or**
         b. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
         c. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
         d. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal]);

         and
      3. Asthma is an eosinophilic phenotype as defined by a baseline (pre- benralizumab treatment) peripheral blood eosinophil level ≥ 150 cells/µL within the past 6 weeks[12]; **and**
      4. Used in combination with **one** of the following:
         a. **One** maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; **or**
         b. Combination therapy including **both** of the following:
            i. **One** high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; **and**
            ii. **One** additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist − montelukast (Singulair®); theophylline];

         and
      5. Patient is not receiving Fasenra in combination with any of the following:
         a. Cinqair (reslizumab)
         b. Nucala (mepolizumab)
         c. Xolair (omalizumab);

         and

6. Fasenra dosing for severe eosinophilic asthma is in accordance with the US FDA approved labeling: 30mg subcutaneously once every 4 weeks for 3 doses, then once every 8 weeks thereafter; **and**
7. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
8. Initial authorization will be for no more than 6 months.

III. Nucala®

A. **Nucala for subcutaneous use is proven and medically necessary when ALL of the following criteria are met**:[1,3-6]

1. Diagnosis of severe asthma; **and**
2. Classification of asthma as uncontrolled or inadequately controlled as defined by at least **one** of the following:
   a. Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); **or**
   b. Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; **or**
   c. Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); **or**
   d. Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal]);

   and
3. Asthma is an eosinophilic phenotype as defined by a baseline (pre-mepolizumab treatment) peripheral blood eosinophil level ≥ 150 cells/µL within the past 6 weeks; **and**
4. Used in combination with **one** of the following:
   a. One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; **or**
   b. Combination therapy including **both** of the following:
      i. One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; **and**
      ii. One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline];

   and
5. Patient is not receiving Nucala in combination with any of the following:
   a. Cinqair (reslizumab)
   b. Fasenra (benralizumab)
   c. Xolair (omalizumab);

   and
6. Nucala dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 100mg subcutaneously once every 4 weeks; **and**
7. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
8. Initial authorization will be for no more than 6 months.

Reauthorization/Continuation of Care Criteria

I. For patients currently on Cinqair, Fasenra, or Nucala for the treatment of severe eosinophilic asthma, authorization for continued use will be approved based on **all** of the following criteria:

A. Documentation of positive clinical response as demonstrated by at least **one** of the following:
   1. Reduction in the frequency of exacerbations
   2. Decreased utilization of rescue medications
   3. Increase in percent predicted FEV1 from pretreatment baseline
   4. Reduction in severity or frequency of asthma-related symptoms (e.g., wheezing, shortness of breath, coughing, etc.);

   and

B. Used in combination with an ICS-containing controller medication; **and**

C. **One** of the following:
   1. Patient is not receiving Nucala in combination with any of the following:
      a. Cinqair (reslizumab)
      b. Fasenra (benralizumab)
      c. Xolair (omalizumab);

      or
   2. Patient is not receiving Cinqair in combination with any of the following:
      a. Fasenra (benralizumab)
      b. Nucala (mepolizumab)

c. Xolair (omalizumab);

or

3. Patient is not receiving Fasenra in combination with any of the following:
   a. Cinqair (reslizumab)
   b. Nucala (mepolizumab)
   c. Xolair (omalizumab);

and

D. **One** of the following:
   1. Nucala dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 100mg subcutaneously once every 4 weeks; **or**
   2. Cinqair dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 3 mg/kg intravenously once every 4 weeks; **or**
   3. Fasenra dosing for severe eosinophilic asthma is in accordance with the U.S. FDA approved labeling: 30 mg subcutaneously once every 8 weeks;

and

E. Prescribed by or in consultation with a pulmonologist or allergist/immunologist; **and**
F. Reauthorization will be for no more than 12 months.

Unproven

Cinqair, Fasenra, and Nucala are unproven and not medically necessary in the following:[1-2,8]

- Other eosinophilic conditions
- Acute bronchospasm
- Status asthmaticus
- Chronic obstructive pulmonary disease (COPD)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Cinqair (Reslizumab)

Cinqair is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, who have an eosinophilic phenotype. Cinqair is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus. Because of the risk of anaphylaxis, healthcare providers administering Cinqair should observe patients closely for an appropriate period of time and be prepared to manage anaphylaxis that can be life-threatening.[2]

Fasenra (benralizumab)

Fasenra is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, who have an eosinophilic phenotype. Fasenra is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus.[10]

Nucala (Mepolizumab)

Nucala is approved by the U.S. Food and Drug Administration (FDA) for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, who have an eosinophilic phenotype. Nucala is not indicated for the treatment of other eosinophilic conditions or for acute bronchospasm or status asthmaticus.[1]

BACKGROUND

Asthma is a common chronic inflammatory disease of the airways that affects an estimated 24 million adults and children. Although the disease is well controlled with inhaled therapy in most patients, approximately 1.2-2.4 million people have severe asthma (i.e., 5-10% of the asthma population) that is associated with substantial morbidity, mortality, and economic effects. Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils. It is estimated that about half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma. Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation. Therapies that decrease IL-5 levels, such as Nucala (mepolizumab) and Cinqair (reslizumab), may decrease eosinophils in lung tissue. Fasenra (benralizumab) directly binds to the human IL-5 receptor on the surface of eosinophils and basophils, leading to the apoptosis of these cells through antibody-dependent cell mediated cytotoxicity.[4,7,9,10]

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 federal, state or contractual

requirements 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 Code	Description
J2182	Injection, mepolizumab, 1 mg
J2786	Injection, reslizumab, 1 mg

ICD-10 Diagnosis Code	Description
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J82	Pulmonary eosinophilia, not elsewhere classified

CLINICAL EVIDENCE

Proven

Severe Eosinophilic Asthma

Benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.[10]

Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.[1]

Reslizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.[2]

Professional Societies

Severe Eosinophilic Asthma

The Global Initiative for Asthma (GINA, 2017) recommends that for Step 5 treatment, adults and adolescents, aged ≥ 12 years old may be treated with mepolizumab or reslizumab as follows (Evidence B: Randomized controlled trials and meta-analyses. Limited body of evidence):[6]

- Step 5: Higher level care and/or add-on treatment. Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma (Evidence D: Panel consensus judgment).
- Treatment options that may be considered at Step 5 (in not already tried) include: add-on anti-interleukin-5 treatment (subcutaneous mepolizumab, intravenous reslizumab: (anti-interleukin-5 treatment) for patients aged ≥ 12 years old with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence B).

On March 14, 2016, the Institute for Clinical and Economic Review (ICER) released a clinical report entitled, "Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks." ICER recommendations are as follows: [4]

- ICER judges the current body of evidence on mepolizumab to be "comparable or better."
- For adult patients with severe eosinophilic asthma, ICER judges there to be moderate certainty of a comparable or better net benefit for mepolizumab 100mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENSA trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in oral corticosteroids dosage, were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. Ongoing post-marketing trials and extension studies evaluating mepolizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunist infection, anaphylaxis).

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines define severe asthma as that which requires treatment with high-dose ICSs plus a second controller (or systemic corticosteroids) to prevent progression to uncontrolled disease status or continuing uncontrolled disease status despite this therapy.[3] The guidelines recommend that, "While the anti-IL5 antibody, mepolizumab, was not beneficial in unselected adult patients with moderate asthma, when studied in severe asthma patients with persistent sputum eosinophilia, two anti-

IL-5 antibodies, mepolizumab and reslizumab, have been shown to decrease exacerbations and oral corticosteroid use, as well as improve symptoms and lung function to varying degrees."

Unproven

Nucala and Cinqair have additional uses listed in the FDA label:[1-2]

- Other eosinophilic conditions
- Acute bronchospasm
- Status asthmaticus
- Chronic obstructive pulmonary disease (COPD)

Statistically robust randomized controlled trials are necessary to establish the safety and efficacy of Nucala and Cinqair to treat these conditions.[1-2,8]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Nucala® (mepolizumab). Local Coverage Determinations (LCDs) do not exist at this time.

Medicare covers 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 http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

Medicare does not have an NCD for Cinqair® (reslizumab). LCDs do not exist at this time.

Medicare covers 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 http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed June 22, 2017)

STATE EXCEPTIONS

State	Note
Iowa	Policy does not apply because the drugs are not a UnitedHealthcare covered benefit
Kansas	State mandated drug policy/criteria applies

REFERENCES

1. Nucala® [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline, LLC; February 2017.
2. Cinqair® [prescribing information]. Frazer, PA; Teva Respiratory, LLC; May 2016.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014 Feb:43(2):343-73.
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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2018	• Changed policy title; previously titled *Respiratory Interleukins (Cinqair® and Nucala®)* • Revised coverage rationale: ○ Updated list of applicable drug products: ▪ Removed language indicating the [listed] drug products are interleukin-5 (IL-5) antagonists ▪ Added Fasenra® (benralizumab) ○ Updated coverage guidelines for Cinqair: ▪ Reformatted/combined content addressing proven and medically necessary indications ▪ Added coverage criterion requiring patient is not receiving Cinqair in combination with Fasenra (benralizumab) ○ Added language to indicate Fasenra for subcutaneous use is proven and medically necessary when all of the following criteria are met: ▪ Diagnosis of severe asthma; and ▪ Classification of asthma as uncontrolled or inadequately controlled as defined by at least one of the following: - Poor symptom control (e.g., Asthma Control Questionnaire [ACQ] score consistently greater than 1.5 or Asthma Control Test [ACT] score consistently less than 20); or - Two or more bursts of systemic corticosteroids for at least 3 days each in the previous 12 months; or - Asthma-related emergency treatment (e.g., emergency room visit, hospital admission, or unscheduled physician's office visit for nebulizer or other urgent treatment); or - Airflow limitation (e.g., after appropriate bronchodilator withhold forced expiratory volume in 1 second [FEV1] less than 80% predicted [in the face of reduced FEV1/forced vital capacity [FVC] defined as less than the lower limit of normal]); and ▪ Asthma is an eosinophilic phenotype as defined by a baseline (pre-benralizumab treatment) peripheral blood eosinophil level ≥ 150 cells/µL within the past 6 weeks12; and ▪ Used in combination with one of the following: - One maximally-dosed (appropriately adjusted for age) combination inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) product [e.g., fluticasone propionate/salmeterol (Advair®), budesonide/formoterol (Symbicort®)]; or - Combination therapy including both of the following: • One high-dose (appropriately adjusted for age) ICS product [e.g., ciclesonide (Alvesco®), mometasone furoate (Asmanex®), beclomethasone dipropionate (QVAR®)]; and • One additional asthma controller medication [e.g., LABA - olodaterol (Striverdi®) or indacaterol (Arcapta®); leukotriene receptor antagonist – montelukast (Singulair®); theophylline]; and ▪ Patient is not receiving Fasenra in combination with any of the following: - Cinqair (reslizumab) - Nucala (mepolizumab) - Xolair (omalizumab); and ▪ Fasenra dosing for severe eosinophilic asthma is in accordance with the US FDA approved labeling: 30mg subcutaneously once every 4 weeks for 3 doses, then once every 8 weeks thereafter; and ▪ Prescribed by or in consultation with a pulmonologist or allergist/immunologist; and

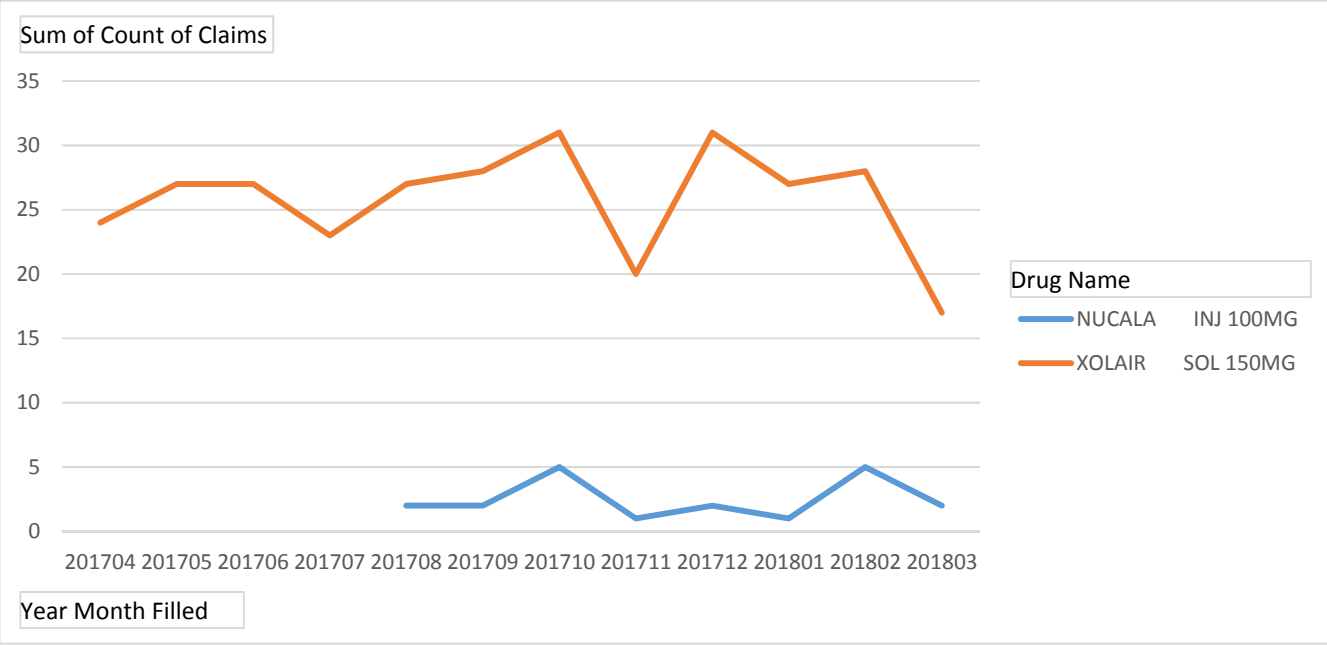
Date	Action/Description
	▪ Initial authorization will be for no more than 6 months ○ Updated coverage guidelines for Nucala: ▪ Reformatted/combined content addressing proven and medically necessary indications ▪ Added criterion requiring patient is not receiving Nucala in combination with Fasenra (benralizumab) ○ Updated reauthorization/continuation of care criteria: ▪ Added language to indicate authorization for continued use of Fasenra for the treatment of severe eosinophilic asthma will be approved based on all of the [listed] criteria ▪ Added criteria requiring: - Patient is not receiving Fasenra in combination with any of the following: • Cinqair (reslizumab) • Nucala (mepolizumab) • Xolair (omalizumab) - Fasenra dosing for severe eosinophilic asthma is in accordance with the United States Food and Drug Administration approved labeling: 30 mg subcutaneously once every 8 weeks ▪ Added language to indicate Fasenra is unproven and not medically necessary for: - Other eosinophilic conditions - Acute bronchospasm - Status asthmaticus - Chronic obstructive pulmonary disease (COPD) • Updated supporting information to reflect the most current background information, clinical evidence, FDA information, and references • Archived previous policy version CS2017D0055B

Antiasthmatic - Monoclonal Antibodies

April 1, 2017 - March 31, 2018

Fee for Service Medicaid

Year Month Filled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201704	XOLAIR	SOL 150MG	22	24	617	54.5	$ 51,359.16
201705	XOLAIR	SOL 150MG	24	27	646	72	$ 73,190.54
201706	XOLAIR	SOL 150MG	22	27	605	66	$ 67,045.43
201707	XOLAIR	SOL 150MG	19	23	454	66	$ 60,176.33
201708	NUCALA	INJ 100MG	2	2	29	2	$ 4,565.79
201708	XOLAIR	SOL 150MG	26	27	648	67	$ 66,013.27
201709	NUCALA	INJ 100MG	2	2	2	101	$ 1,805.50
201709	XOLAIR	SOL 150MG	27	28	689	78.5	$ 78,821.99
201710	NUCALA	INJ 100MG	2	5	59	203	$ 7,431.08
201710	XOLAIR	SOL 150MG	28	31	760	89.5	$ 90,526.06
201711	NUCALA	INJ 100MG	1	1	1	1	$ 1,770.50
201711	XOLAIR	SOL 150MG	20	20	533	55	$ 57,241.40
201712	NUCALA	INJ 100MG	2	2	2	2	$ 3,541.00
201712	XOLAIR	SOL 150MG	29	31	748	83.5	$ 86,544.29
201801	NUCALA	INJ 100MG	1	1	1	1	$ 1,781.50
201801	XOLAIR	SOL 150MG	23	27	539	65.5	$ 61,577.96
201802	NUCALA	INJ 100MG	4	5	59	104	$ 9,355.68
201802	XOLAIR	SOL 150MG	26	28	691	76.5	$ 78,364.33
201803	NUCALA	INJ 100MG	1	2	56	2	$ 5,757.68
201803	XOLAIR	SOL 150MG	17	17	476	53	$ 56,532.56



Fasenra Utilization

SilverSummit Health Plan

No utilization submitted.

Fasenra Utilization
3/1/17 - 2/28/18
Anthem

Drug Name	Month Serviced	Date - Serviced	Total Plan Cost	Net Rxs
FASENRA	Feb-2018	2/15/2018	[redacted]	1
				1

Health Plan of Nevada

Fasenra Utilization

March 1, 2017 - February 28, 2018

Year/Month Filled/Paid	Drug Name	Count of Members	Count of Claims	Sum of Qty

No claims for FASENRA during the requested time period

P. Monoclonal Antibody Agents

Therapeutic Class: Respiratory Monoclonal Antibody Agents
Last Reviewed by the DUR Board: July 28, 2016
Xolair previously reviewed: July 24, 2014 and April 23, 2015

Xolair® (Omalizumab) is 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. Xolair® (Omalizumab)

1. The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies.

2. All of the following criteria must be met and documented for a diagnosis of moderate to severe persistent asthma:

a. The recipient must be 12 years of age or older; and

b. The recipient must have a history of a positive skin test or Radioallergosorbent (RAST) test to a perennial aeroallergen; and

c. The prescriber must be either a pulmonologist or allergist/ immunologist; and

d. The recipient must have had an inadequate response, adverse reaction or contraindication to inhaled, oral corticosteroids; and

e. The recipient must have had an inadequate response, adverse reaction or contraindication to an oral second generation antihistamine; and

f. The recipient must have had an inadequate response, adverse reaction or contraindication to a leukotriene receptor antagonist; and

g. The recipient must have had a pretreatment serum total Immunoglobulin E (IgE) level between 30 IU/mL and 700 IU/mL; and

h. The recipient's current weight must be recorded; and

i. The requested dose is appropriate for the recipient’s pre-treatment serum IgE and body weight (see Table 1).

3. All the following criteria must be met and documented for diagnosis of chronic idiopathic urticaria (CIU); and

   a. The recipient is 12 years of age or older; and

   b. The recipient must have had an inadequate response, adverse reaction or contraindication to two different oral second generation antihistamines; and

   c. The recipient must have had an inadequate response, adverse reaction or contraindication to an oral second generation antihistamine in combination with a leukotriene receptor antagonist; and

   d. The prescriber must be either an allergist/immunologist, dermatologist or a rheumatologist or there is documentation in the recipient's medical record that a consultation was done by an allergist/immunologist, dermatologist or a rheumatologist regarding the diagnosis and treatment recommendations; and

   e. The requested dose is:

      1. Initial therapy: 150 mg every four weeks or 300 mg every four weeks and clinical rationale for starting therapy at 300 mg every four weeks has been provided.

      2. Continuation of therapy: 150 mg or 300 mg every four weeks.

b. Nucala® (mepolizumab), Cinqair® (reslizumab)

   1. All the following criteria must be met and documented:

      a. The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies; and

      b. The recipient must have a diagnosis of severe eosinophilic-phenotype asthma; and

      c. The recipient must be an appropriate age:

         1. Mepolizumab: 12 years of age or older

         2. Reslizumab: 18 years of age or older

d. And, the prescriber must be either a pulmonologist or allergist/ immunologist; and

e. The recipient must be uncontrolled on current therapy including high dose corticosteroid and/or on a secondary asthma inhaler; and

f. There is documentation of the recipient's vaccination status; and

g. The requested dose is appropriate:

1. Mepolizumab: 100 mg subcutaneously every four weeks.

2. Reslizumab: 3 mg/kg via intravenous infusion of 20 to 50 minutes every four weeks.

2. Prior Authorization Guidelines

a. Prior Authorization approval will be for 12 months.

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

Table 1: Dosing for Xolair® (omalizumab)*

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30-60	**>60-70**	**>70-90**	**>90-150**
≥30-100	150 mg	150 mg	150 mg	300 mg
>100-200	300 mg	300 mg	300 mg	225 mg
>200-300	300 mg	225 mg	225 mg	300 mg
>300-400	225 mg	225 mg	300 mg	
>400-500	300 mg	300 mg	375 mg	
>500-600	300 mg	375 mg		
>600-700	375 mg	**DO NOT DOSE**		
Every 2 Weeks Dosing				
Every 4 Weeks Dosing				

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*NHLBI 2014*).
- The goal of asthma management – asthma control – can be described in the following domains (*NHLBI 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (e.g., omalizumab)
    - Leukotriene modulators
    - Long-acting β-agonists (LABAs)
    - Methylxanthines (i.e., theophylline)
  - Quick-relief medications include:
    - Anticholinergics (i.e., ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*).
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2017, Saini 2017*).
- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life.

CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 1 to 5 years (*Saini 2017*).

- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2017, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Schwartz et al 2016).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux 2016*).
- This monograph describes the use of Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists, each approved as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
  - Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2017, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2017*)

INDICATIONS

- Xolair is indicated for:
  - Patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - The treatment of adults and adolescents 12 years of age and older with CIU who remain symptomatic despite H_1-antihistamine treatment.

Limitations of use include the following:
  - Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
  - Xolair is not indicated for treatment of other allergic conditions or other forms of urticaria.

- Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitations of use include the following:
- Fasenra is not indicated for treatment of other eosinophilic conditions.
- Fasenra is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Nucala is indicated for:
  - The add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
  - The treatment of adult patients with EGPA.

Limitations of use include the following:
- Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

Limitations of use include the following:
- Cinqair is not indicated for treatment of other eosinophilic conditions.
- Cinqair is not indicated for the relief of acute bronchospasm or status asthmaticus.

- 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

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a step-wise manner.
  - In the 28-week study by Busse et al (N=525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; P=0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; P<0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; P=0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; P=0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N=546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; P<0.001) and steroid reduction phases (0.36 vs 0.75; P<0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N=246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; P=0.003). The percentages of patients with at least 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Solèr et al 2001, Holgate et al 2004*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (i.e., all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (P=0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies, 3,261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies, 1,889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies, 1,824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N=3,429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk, 1.8; 95% CI, 1.42 to 2.28; P=0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (relative risk, 0.57; 95% CI, 0.48 to 0.66; P=0.0001) and adjustable-steroid phases (relative risk, 0.55; 95% CI, 0.47 to 0.64; P=0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; rate ratio, 0.69; P=0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (P<0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors

concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients was found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0% to 33.6%). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit *(Ledford et al 2017)*.

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo (P≤0.001) (*Saini et al 2014*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1,312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group (P<0.00001) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%, P<0.0001). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2017)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n=80), benralizumab 2 mg (n=81), benralizumab 20 mg (n=81), or benralizumab 100 mg (n=82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n=142) or placebo (n=143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60, P=0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of at least 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; P=0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; P=0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N=1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n=407), benralizumab 30 mg every 4 weeks (n=400), or benralizumab 30 mg every 8 weeks (n=398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (rate ratio, 0.55; 95% CI, 0.42 to 0.71; P<0.0001) or every 8 weeks (rate ratio, 0.49; 95% CI, 0.37 to 0.64; P<0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n=425), benralizumab 30 mg every 8 weeks (n=441) or placebo (n=440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (rate ratio, 0.64; 95% CI, 0.49 to 0.85; P=0.0018) and every 8 weeks (rate ratio, 0.72; 95% CI, 0.54 to 0.95; P=0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N=211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n=106) or placebo (n=105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150, P=0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n=72), benralizumab 30 mg every 8 weeks (n=73), or placebo (n=75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (P<0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; P=0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; P<0.001).

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥150 cells/µL in the peripheral blood at screening or ≥300 cells/µL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication *(Pavord et al 2012, Ortega et al 2014, Bel et al 2014)*.
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N=621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (P<0.0001), 1.46 in the 250 mg mepolizumab group (P=0.0005), and 1.15 in the 750 mg mepolizumab group (P<0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N=576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (P<0.001), and 0.83 per patient per year in the SC mepolizumab group (P<0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (P<0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N=135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; P=0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (P=0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1,192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio, 0.53; 95% CI, 0.44 to 0.62; P<0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (rate ratio, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥150 cells/µL to 70% (rate ratio, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥500 cells/µL. At a baseline count <150 cells/µL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for at least 24 weeks. Four studies (N=1,388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; P=0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; P<0.001) vs placebo. Significant

reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n=68) or placebo (n=68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; P<0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; P<0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; P<0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N=953) in patients with asthma who were required to have a blood eosinophil count ≥400 cells/μL, and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: rate ratio, 0.50; 95% CI, 0.37 to 0.67; Study 3083: rate ratio, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N=315) in patients who were required to have a blood eosinophil count ≥400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; P=0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count <400 cells/μL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils <400 cells/μL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥400 cells/μL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N=1,366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; P<0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; P<0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; P<0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).

COMPARATIVE REVIEWS

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated rate ratios of 0.66 (95% credible interval [CrI], 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CrI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median rate ratio of 0.63 (95% CrI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median rate ratio of 0.58 (95% CrI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with a duration of ≥12 weeks. A total of 18 omalizumab studies (N=4854) and 4 mepolizumab studies (N=1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2017)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N=6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2017, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. For patients with severe asthma uncontrolled on Step 4 treatment (e.g., 2 or more controllers plus as-needed reliever medication), phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma is suggested. Anti-IgE treatment with omalizumab is recommended as the preferred option for the management of patients at Step 5 of treatment. Similarly, add-on anti-IL-5 therapy (i.e., mepolizumab, reslizumab) is recommended for patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (*GINA 2017*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Updated joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab, cyclosporine, or a leukotriene receptor antagonist in patients with symptoms despite treatment with a 4-fold dose of modern second generation antihistamines (*Zuberbier et al 2013*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Schwartz et al 2016*).
  - These guidelines have not been updated to include the place in therapy for mepolizumab; however, the EGPA Consensus Task Force recommendations notes that mepolizumab hold promise for this condition based on the pilot studies available at the time of guideline development (*Groh et al 2015*).

SAFETY SUMMARY

Cinqair:

- Contraindication: History of hypersensitivity to Cinqair or excipients in the formulation.
- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warning and precaution:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
- The most common adverse reaction (≥2%) includes oropharyngeal pain.

Fasenra:

- Contraindication: History of hypersensitivity to Fasenra or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Systemic or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with Fasenra. Corticosteroids should be decreased gradually, if appropriate.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥5%) include headache and pharyngitis.

Nucala:

- Contraindication: History of hypersensitivity to Nucala or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.

- Herpes zoster infections have occurred in patients receiving Nucala. In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with Nucala compared with none in patients treated with placebo.
- The most common adverse reactions (≥5%) include headache, injection site reaction, back pain, and fatigue.

Xolair:

- Contraindication: Severe hypersensitivity reaction to Xolair or any ingredient of Xolair.
- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥12 years of age, the most commonly observed adverse reactions in clinical studies (≥1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients younger than 12 years have not been established.

Drug	Route	Usual Recommended Frequency	Comments
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. • Safety and efficacy in pediatric patients other than those with asthma have not been established.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). • Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2017, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA-approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU generally recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second

generation antihistamines and, in some cases, a leukotriene receptor antagonist (*Bernstein et al 2014, Zuberbier et al 2013, Powell et al 2015*).

- Cinqair, Fasenra , and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, with demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy (*GINA 2017*).
- Nucala is the only IL-5 antagonist approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients aged 18 years and older (12 years and older for Nucala and Fasenra), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis.

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Nevada Medicaid
Lupron Depot (leuprolide acetate)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Lupron Depot Lupron Depot- PED	Leuprolide acetate

CRITERIA FOR COVERAGE/NONCOVERAGE

Indications

Off Label Uses

Gender Identity Disorder. Suppression of pubertal development and gonadal function is accomplished most effectively by gonadotropin suppression with gonadotropin releasing hormone analogues and antagonists. Analogues suppress gonadotropins after a short period of stimulation, whereas antagonists immediately suppress pituitary secretion. Since no long-acting antagonists are available for use as pharmacotherapy, long-acting analogues are the currently preferred treatment option. Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would.

Authorization:

Approval Length: 12 Months

1. Use is for suppression of puberty
2. Demonstrable knowledge of what gonadotropins medically can and cannot do and their social benefits and risks
3. One of the following:
    a. A documented real-life experience (living as the other gender) of at least three months prior to the administration of gonadotropin OR
    b. A period of psychotherapy of a duration specified by the mental health professional after the initial evaluation (usually a minimum of three months)
4. The member must meet the definition of Gender Identity Disorder (see definition below):
    a. Gender Identity Disorder: A disorder characterized by the following diagnostic criteria:
        - A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex)

- Persistent discomfort with his or her sex or sense of inappopriateness in the gender role of that sex
- The disturbance is not concurrent with a physical intersex condition
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The transsexual identity has been present persistently for at least two years
- The disorder is not a symptom of another mental disorder or a chromosomal abnormality

Lupron PA Criteria

SilverSummit Health Plan

Place-holder for SSHP proposed PA criteria.

Gonadotropin Releasing Hormone Analogs (GnRH)

CG-DRUG-60
CG-DRUG-61

Override(s)	Approval Duration
Prior Authorization Quantity Limit	Varies upon diagnosis

Medications	Quantity Limit	Line of Business
Eligard (leuprolide acetate) 7.5mg	1 per 4 weeks	All MCD
Eligard (leuprolide acetate) 22.5mg	1 per 12 weeks	All MCD
Eligard (leuprolide acetate) 30mg	1 per 16 weeks	All MCD
Eligard (leuprolide acetate) 45mg	1 per 24 weeks	All MCD
Firmagon (degarelix) 80mg	1 injection (80 mg) per 28 days	VA MCD and AGP MCD Only
Firmagon (degarelix) 120mg	2 injections (240 mg) per year	VA MCD and AGP MCD Only
Lupaneta Pack (leuprolide acetate and norethindrone acetate)	N/A	VA MCD and AGP MCD Only
Leuprolide acetate (immediate release)	N/A	All MCD
Lupron Depot (1 month) (leuprolide acetate) 3.75mg	1 per 4 weeks	VA MCD and AGP MCD Only
Lupron Depot (1 month) (leuprolide acetate) 7.5 mg	1 per 4 weeks	VA MCD and AGP MCD Only
Lupron Depot (3 months) (leuprolide acetate) 11.25mg and 22.5mg	1 kit per 12 weeks	VA MCD and AGP MCD Only
Lupron Depot (4 month) (leuprolide acetate) 30mg	1 per 16 weeks	VA MCD and AGP MCD Only
Lupron Depot (6 month) (leuprolide acetate) 45mg	1 per 24 weeks	VA MCD and AGP MCD Only
Lupron Depot Ped (leuprolide acetate) 7.5mg	1 per 4 weeks	VA MCD and AGP MCD Only
Lupron Depot Ped (leuprolide acetate) 11.25mg	N/A	VA MCD and AGP MCD Only
Lupron Depot Ped (leuprolide acetate) 15mg	N/A	VA MCD and AGP MCD Only
Lupron Depot Ped (3 month) (leuprolide acetate) 11.25mg and 30mg	N/A	VA MCD and AGP MCD Only
Supprelin LA (histrelin acetate) 50mg	1 implant per year	VA MCD and AGP MCD Only
Synarel Nasal Spray (nafarelin acetate) 2mg/mL (60 sprays/bottle)	5 bottles per 30 days	All MCD

Trelstar (triptorelin pamoate) 22.5mg	1 per 24 weeks	VA MCD and AGP MCD Only
Trelstar Depot (triptorelin pamoate) 3.75mg	1 per 4 weeks	VA MCD and AGP MCD Only
Trelstar LA (triptorelin pamoate) 11.25mg	1 per 12 weeks	VA MCD and AGP MCD Only
Triptodur (triptorelin pamoate extended release) 22.5mg kit	1 kit per 24 weeks	VA MCD and AGP MCD Only
Vantas Implant (histrelin acetate)	N/A	VA MCD and AGP MCD Only
Zoladex (1 month) (goserelin acetate) 3.6mg implant	1 per 4 weeks	VA MCD and AGP MCD Only
Zoladex (3 month) (goserelin acetate) 10.8mg implant	1 per 12 weeks	VA MCD and AGP MCD Only

APPROVAL CRITERIA

I. **Breast Cancer –Goserelin acetate or leuprolide acetate (Lupron Depot 3.75 mg)**

Goserelin acetate or leuprolide acetate (Lupron Depot 3.75 mg) **may be approved** for the treatment of men and pre- or peri- menopausal women with hormone receptor positive breast cancer.

Goserelin acetate or leuprolide acetate **may *NOT* be approved** for the treatment of breast cancer when the criteria above are not met.

II. **Ovarian Cancer (including fallopian tube cancer and primary peritoneal cancer)– Leuprolide acetate (Lupron Depot 3.75 mg, Lupron Depot-3 Month 11.25 mg)**

Leuprolide acetate (Lupron Depot 3.75 mg, Lupron Depot-3 Month 11.25 mg) **may be approved** for ovarian cancer when ***any*** of the following are met:

A. Hormonal therapy for clinical relapse in individuals with stage II-IV granulosa cell tumors; **OR**
B. Hormonal therapy for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer as a single agent for persistent disease or recurrence.

Leuprolide acetate **may *NOT* be approved** for ovarian cancer when the criteria above are not met.

III. **Prostate Cancer- Degarelix; goserelin acetate; histrelin acetate (Vantas); leuprolide acetate (Eligard 7.5 mg [1 Month], 22.5 mg [3 Month], 30 mg [4 month], 45 mg [6 Month]; Lupron Depot 7.5 mg [1 Month], 22.5 mg [3 Month], 30 mg [4 Month], 45 mg [6 Month]), or triptorelin pamoate**

A. Degarelix; goserelin acetate; histrelin acetate (Vantas); leuprolide acetate, **or** (Eligard 7.5 mg [1 Month], 22.5 mg [3 Month], 30 mg [4 Month], 45 mg [6 Month]; Lupron Depot 7.5 mg [1 Month], 22.5 mg [3 Month], 30 mg [4 Month], 45 mg [6 Month]); triptorelin pamoate **may be approved** for the treatment of prostate cancer when ***any*** of the following indications are met:
    1. Used as androgen deprivation therapy as a single agent or in combination with an antiandrogen; **OR**
    2. Used for clinically localized disease***** with intermediate (T2b to T2c cancer, Gleason score of 7/Gleason grade group 2-3, or prostate specific antigen (PSA) value of 10-20 ng/ml) or higher risk of recurrence as neoadjuvant therapy with radiation therapy or cryosurgery; **OR**
    3. Used for progressive castration-naïve disease; **OR**
    4. Used for castration-recurrent disease; **OR**
    5. Other advanced*****, recurrent, or metastatic disease*****.

**Definitions –*

- Clinically localized prostate cancer: Cancer presumed to be confined within the prostate based on pre-treatment findings such as physical exam, imaging, and biopsy findings.
- Locally advanced disease (prostate cancer): Cancer that has spread from where it started to nearby tissue or lymph nodes.
- Metastatic: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Advanced prostate cancer: Disease that has spread beyond the prostate to surrounding tissues or distant organs.

Degarelix, goserelin acetate, histrelin acetate (Vantas), leuprolide acetate, or triptorelin pamoate **may *NOT* be approved for** treatment of prostate cancer when the criteria above are not met.

IV. **Central Precocious Puberty- Leuprolide acetate (Lupron Depot-Ped), nafarelin acetate, histrelin acetate subcutaneous implant (Supprelin LA), Triptodur (triptoerlin pamoate intramuscular extended release)**

Leuprolide acetate (Lupron Depot-Ped), nafarelin acetate, histrelin acetate subcutaneous implant (Supprelin LA), and Troptodur* (triptorelin IM) **may be approved** for the treatment of children known to have central precocious puberty (defined as the beginning of secondary sexual characteristics before age 8 in girls and 9 in boys).

*Triptodur (triptorelin pamoate) is indicated for intramuscular injection every 6 months for pediatric persons 2 years of age or older with central precocious puberty.

Leuprolide acetate (Lupron Depot-Ped), nafarelin acetate, histrelin acetate subcutaneous implant (Supprelin LA) and Triptodur (triptorelin) **may *NOT* be approved** for the treatment of central precocious puberty when the criteria above are not met.

V. **Gynecology Uses- Goserelin acetate, leuprolide acetate, leuprolide acetate for depot suspension and norethindrone (Lupaneta Pack), or nafarelin acetate**

A. Goserelin acetate, leuprolide acetate, or nafarelin acetate **may be approved** when ***any*** of the following indications are met:
    1. Chronic pelvic pain (noncyclical pain lasting 6 or more months that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks, and is of sufficient severity to cause functional disability or lead to medical care [ACOG, 2004])-not to continue beyond 3 months if there is no symptomatic relief; **OR**
    2. To induce amenorrhea in women in certain populations, including menstruating women diagnosed with severe thrombocytopenia or aplastic anemia

B. Goserelin acetate **may be approved** for ***any*** of the following additional indications:
    1. Endometriosis (duration of treatment limited to 6 months); **OR**
    2. Dysfunctional uterine bleeding; **OR**
    3. Endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding (3.6 mg implant only)

C. Leuprolide acetate **may be approved** for ***any*** of the following additional indications:
    1. Initial treatment of endometriosis (duration of treatment limited to 6 months); **OR**
    2. Retreatment of endometriosis (duration of treatment limited to 6 months); **OR**
    3. Preoperative treatment as adjunct to surgical treatment of uterine fibroids (leiomyoma uteri). May be used to reduce size of fibroids to allow for a vaginal procedure; **OR**
    4. Prior to surgical treatment (myomectomy or hysterectomy) in individuals with documented anemia

D. Leuprolide acetate for depot suspension and norethindrone acetate tablets (Lupaneta Pack) **may be approved** for **any** of the following indications:
    1. Initial treatment of endometriosis (duration limited to 6 months); **OR**
    2. Retreatment of endometriosis (duration of treatment limited to 6 months).

E. Nafarelin acetate may be approved for the following additional indication:
    1. Endometriosis (duration of treatment limited to 6 months).

Goserelin acetate, leuprolide acetate, leuprolide acetate for depot suspension and norethindrone acetate tablets, or nafarelin acetate **may *NOT* be approved** for gynecological uses when the criteria above are not met.

VI. **Ovarian Preservation for Fertility during Chemotherapy**

A. GnRH analogs **may be approved** for preservation of fertility in pre-menopausal women that will receive chemotherapy with curative intent.

GnRH analogs **may *NOT* be approved** for preservation of fertility when the criteria above are not met.

VI. **Gender Dysphoria/Incongruence in Adolescents**

A. GnRH analogs **may be approved** for adolescents (greater than or equal to 10 years of age and less than 18 years of age) with gender dysphoria when **all** of the following criteria are met:
    1. Fulfills the DSM V criteria for gender dysphoria; **and**
    2. Has experienced puberty to at least Tanner stage 2; **and**
    3. Has (early) pubertal changes that have resulted in an increase of their gender dysphoria; **and**
    4. Does not suffer from a psychiatric comorbidity that interferes with the diagnostic work-up or treatment; **and**
    5. Has psychological and social support during treatment; **and**
    6. Demonstrates knowledge and understanding of the expected outcomes of GnRH analog treatment.

GnRH analogs **may *NOT* be approved** for adolescents with gender dysphoria when the criteria above are not met.

State Specific Mandates		
State name N/A	Date effective N/A	Mandate details (including specific bill if applicable) N/A

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GONADOTROPIN RELEASING HORMONE ANALOGS

Policy Number: CS2017D0038H **Effective Date**: December 1, 2017

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Related Community Plan Policies

- Gender Dysphoria Treatment
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Commercial Policy

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INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced. The terms of the federal, state or contractual requirements for benefit plan coverage may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the contractual requirements for benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the federal, state or contractual requirements for benefit coverage.

Treatment for gender dysphoria is sometimes referred to as: gender identity disorder treatment, sex transformation surgery, sex change, sex reversal, gender change, transsexual surgery, transgender surgery and sex or gender reassignment. These terms are used interchangeably throughout this document, and, for purposes of this document, are intended to have the same meaning.

COVERAGE RATIONALE

Please refer to the Oncology Medication Clinical Coverage Policy for updated information based on the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®) for oncology indications.

This policy refers to the following gonadotropin releasing hormone analog (GnRH analog) drug products:

- Firmagon (degarelix)
- Lupron Depot (leuprolide acetate)
- Lupron Depot-Ped (leuprolide acetate)
- Supprelin LA (histrelin acetate)
- Trelstar (triptorelin pamoate)
- Triptodur (triptorelin)
- Vantas (histrelin acetate)

- Zoladex (goserelin acetate)

For the coverage criteria below, in absence of specified drug products, the term "GnRH analogs" will be used in this policy where the coverage criteria apply to all products listed above.

Covered Indications

1. Central precocious puberty (Lupron Depot-Ped, Supprelin LA)

   Lupron Depot-Ped, Supprelin LA, and Triptodur are proven for the treatment of central precocious puberty.
   Additional information to support medical necessity review where applicable:
   Lupron Depot-Ped, Supprelin LA, and Triptodur are medically necessary for the treatment of central precocious puberty when ALL of the following criteria are met: [1,12]
   a. Diagnosis of central precocious puberty (idiopathic or neurogenic); **and**
   b. Onset of secondary sexual characteristics in ONE of the following:
      (1) Females ≤ 8 years of age
      (2) Males ≤ 9 years of age;
      and
   c. Confirmation of diagnosis as defined by ONE of the following:
      (1) Pubertal basal level of luteinizing hormone (based on laboratory reference ranges)
      (2) A pubertal luteinizing hormone response to a GnRH stimulation test
      (3) Bone age advanced one year beyond the chronological age.

   Lupron Depot-Ped, Supprelin LA, or Triptodur treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician. Give consideration to discontinuing treatment before 11 years of age in girls and 12 years of age in boys.[13]

2. Endometriosis (Lupron Depot, Zoladex)

   Lupron Depot and Zoladex are proven for the treatment of endometriosis or suspected endometriosis.
   Additional information to support medical necessity review where applicable:
   Lupron Depot and Zoladex are medically necessary for the treatment of endometriosis when ALL of the following criteria are met: [2,10,12,31]
   a. For initial therapy, ALL of the following**:**
      (1) Diagnosis of endometriosis or endometriosis is suspected; **and**
      (2) ONE of the following:
         (a) Contraindication, intolerance, or failure of initial treatment with BOTH of the following:
            i. Oral contraceptives or depot medroxyprogesterone (e.g., Depot Provera)
            ii. Non-steroidal anti-inflammatory drugs (NSAIDs);
            or
         (b) Patient has had surgical ablation to prevent recurrence;
         and
      (3) Initial treatment course is limited to a maximum of 6 months.
   b. For retreatment, ALL of the following (Lupron Depot ONLY):
      (1) Diagnosis of endometriosis or suspected endometriosis; **and**
      (2) Recurrence of symptoms following an initial course of therapy; **and**
      (3) Concurrently to be used with add-back therapy (e.g., progestin, estrogen, or bone sparing agents); **and**
      (4) Duration of both the initial and recurrent course of therapies is no longer than 12 months total.

   Zoladex is not recommended for the retreatment of endometriosis, per FDA labelling.

   The prescribing information for Lupron Depot and Zoladex state that the duration of initial treatment for endometriosis should be limited to 6 months.[2,31]

   For Lupron Depot, for recurrence of symptoms, the prescriber should consider the impact to bone mineral density prior to retreatment. Leuprolide must be used in combination with add back therapy (e.g., norethindrone acetate) for 6 months; greater than one retreatment period is not recommended. Lupron Depot monotherapy is not recommended for retreatment.[13]

   For Zoladex, there is no clinical data on the effect of treatment of benign gynecological conditions with Zoladex for periods in excess of 6 months. Retreatment with Zoladex cannot be recommended for the management of endometriosis.

3. Endometrial thinning/dysfunctional uterine bleeding (Zoladex)

Zoladex is proven for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding.
Additional information to support medical necessity review where applicable:
Zoladex is medically necessary for endometrial thinning when ALL of the following criteria are met:
a. For use prior to endometrial ablation; **and**
b. Other causes of symptoms or bleeding are ruled out; **and**
c. Patient is to receive Zoladex 3.6mg implant; **and**
d. Course of therapy is a maximum of two depots.

4. Fertility preservation

GnRH analogs are proven and medically necessary for the treatment of fertility preservation when ALL of the following criteria are met:
a. BOTH of the following:
   (1) For use in pre-menopausal women; **and**
   (2) Patient is receiving a cytotoxic agent that is associated with causing primary ovarian insufficiency (premature ovarian failure) [e.g., Cytoxan (cyclophosphamide), procarbazine, vinblastine, cisplatin].[25,26]

GnRH therapy should be discontinued upon the completion of cytotoxic treatment.

5. Uterine leiomyomata (fibroids) (Lupron Depot)

Lupron Depot is proven for the treatment of uterine leiomyomata (fibroids).
Additional information to support medical necessity review where applicable:
Lupron Depot is medically necessary for the treatment of uterine leiomyomata when ONE of the following criteria is met:[5-9,11,12]
a. ALL of the following:
   (1) For the treatment of uterine leiomyomata related anemia; **and**
   (2) Patient did not respond to iron therapy of one month duration; **and**
   (3) For use prior to surgery;
   or
b. For use prior to surgery to reduce the size of fibroids to facilitate a surgical procedure (e.g., myomectomy, hysterectomy).

The recommended duration of therapy for the treatment of uterine leiomyomata is ≤ 3 months.[13]

6. Gender dysphoria in adolescents

GnRH analogs may be covered for the treatment of gender dysphoria when ALL of the following criteria are met:
a. Submission of medical records (e.g., chart notes, laboratory values) documenting ALL the following:
   (1) Diagnosis of gender dysphoria, according to the current DSM criteria, by a mental health professional with expertise in child and adolescent psychiatry; **and**
   (2) ONE of the following:
      (a) Medication is prescribed by a pediatric endocrinologist; or
      (b) Medication is prescribed by a physician in consultation with a pediatric endocrinologist;
      and
   (3) Patient has experienced puberty development to at least Tanner stage 2; **and**
   (4) ONE of the following laboratory tests, based upon the laboratory reference range, confirming:
      (a) Pubertal levels of estradiol in females; or
      (b) Pubertal levels of testosterone in males;
   and
b. A letter from the prescriber and/or formal documentation stating ALL of the following:
   (1) Patient has experienced pubertal changes that have resulted in an increase of their gender dysphoria that has significantly impaired psychological or social functioning; **and**
   (2) Coexisting psychiatric and medical comorbidities or social problems that may interfere with the diagnostic procedures or treatment have been addressed or removed; **and**
   (3) BOTH of the following:
      (a) Current enrollment, attendance, and active participation in psychological and social support treatment program; **and**

(b) Patient will continue enrollment, attendance and active participation in psychological and social support throughout the course of treatment;

and

(4) Patient demonstrates knowledge and understanding of the expected outcomes of treatment and related transgender therapies.

Note: Clinical evidence supporting the use of GnRH analogs for the treatment of gender dysphoria is limited and lacks long-term safety data. Statistically robust randomized controlled trials are needed to address the issue of whether the benefits outweigh the clinical risk in its use.

Disclaimer

This Medical Benefit Drug Policy does not constitute medical advice. UnitedHealthcare does not make decisions about the kind of care a member should or should not receive. Health care professionals are solely responsible for the care they deliver.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Firmagon is a gonadotropin releasing hormone (GnRH) receptor antagonist indicated for treatment of patients with advanced prostate cancer.

Lupron Depot-Ped, Supprelin LA, and Triptodur are GnRH agonists indicated for the treatment of children with central precocious puberty (CPP).[1,28]*

Lupron Depot is a GnRH agonist indicated for:[2]

- Management of endometriosis, including pain relief and reduction of endometriotic lesions (3.75 mg for 1-month administration, 11.25mg for 3-month administration) with duration of initial treatment or retreatment not to exceed 6 months
- Initial management of endometriosis and for management of recurrence of symptoms (3.75 mg monthly with norethindrone acetate 5 mg daily) with duration of initial treatment or retreatment not to exceed 6 months
- Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata (3.75 mg concomitantly with iron therapy) with recommended duration of therapy up to 3 months
- Palliative treatment of advanced prostate cancer (22.5 mg for 3-month administration, 30 mg for 4-month administration, and 45 mg for 6-month administration)*

Trelstar and Vantas are GnRH agonists indicated for the palliative treatment of advanced prostate cancer.[29,30]*

Zoladex is a GnRH agonist indication for:[31]

- Use in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.*
- Palliative treatment of advanced carcinoma of the prostate.*
- Management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with Zoladex for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months
- Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding.
- Use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.*

*This statement is provided for information only. Oncology indications for GnRH analogs are listed in the NCCN Drugs & Biologics Compendium.

The prescribing information for the GnRH analogs contain warnings associated with their use:[2]

- Tumor flare – transient worsening of symptoms due to increases of testosterone above baseline during the first weeks of treatment. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first weeks of therapy.
- Convulsions have been reported in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions.
- Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH analog and manage with current practice for treatment of hyperglycemia or diabetes.
- Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Patients receiving a GnRH analog should be monitored for

symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.
- Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected.
- For Lupron Depot: Monitor serum levels of testosterone following injection of LUPRON DEPOT 7.5 mg for 1-month administration, 22.5 mg for 3-month administration, 30 mg for 4-month administration, or 45 mg for 6-month administration. In the majority of patients, testosterone levels increased above baseline, and then declined thereafter to castrate levels (< 50 ng/dL) within four weeks.
- Injection site injury and vascular injury including pain, hematoma, hemorrhage and hemorrhagic shock, requiring blood transfusions and surgical intervention, have been reported with GnRH analogs. Extra care should be taken when administering to patients with a low BMI and/or to patients receiving full anticoagulation

BACKGROUND

Firmagon (degarelix) is a GnRH receptor antagonist. It binds reversibly to the pituitary gonadotropin releasing hormone (GnRH) receptors, thereby reducing the release of gonadotropins and consequently gonadal steroids.[27]

Lupron (leuprolide acetate) is a synthetic nonapeptide analog of naturally occurring GnRH which acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent.[13]

Supprelin LA and Vantas (histrelin acetate) are GnRH agonists and an inhibitor of gonadotropin secretion when given continuously, in turn causes a reduction in ovarian and testicular steroidogenesis.[28,30]

Trelstar (triptorelin pamoate), Triptodur (triptorelin), and Zoladex (goserelin acetate) are synthetic decapeptide analog agonists of GnRH, which inhibit gonadotropin secretion when given continuously in therapeutic doses.[29,31]

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 federal, state or contractual requirements 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 Code	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J3315	Injection, triptorelin pamoate, 3.75 mg
J3490	Unclassified drug – used for Triptodur until a code is assigned
J9155	Injection, degarelix, 1 mg
J9202	Goserelin acetate implant, per 3.6 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
J9225	Histrelin implant (Vantas), 50 mg
J9226	Histrelin implant (Supprelin LA), 50 mg

ICD-10 Diagnosis Code	Description
D25.0	Submucous leiomyoma of uterus
D25.1	Intramural leiomyoma of uterus
D25.2	Subserosal leiomyoma of uterus
D25.9	Leiomyoma of uterus, unspecified
E22.8	Other hyperfunction of pituitary gland
E30.1	Precocious puberty
E30.8	Other disorders of puberty
F64.1	Gender identity disorder in adolescence and adulthood
F64.2	Gender identity disorder of childhood

ICD-10 Diagnosis Code	Description
F64.8	Other gender identity disorders
F64.9	Gender identity disorder, unspecified
N80.0	Endometriosis of uterus
N80.1	Endometriosis of ovary
N80.2	Endometriosis of fallopian tube
N80.3	Endometriosis of pelvic peritoneum
N80.4	Endometriosis of rectovaginal septum and vagina
N80.5	Endometriosis of intestine
N80.6	Endometriosis in cutaneous scar
N80.8	Other endometriosis
N80.9	Endometriosis, unspecified
N93.8	Other specified abnormal uterine and vaginal bleeding
Z31.62	Encounter for fertility preservation counseling
Z31.84	Encounter for fertility preservation procedure

CLINICAL EVIDENCE

Central Precocious Puberty

Lupron Depot-Ped is indicated for the treatment of central precocious puberty (CPP).[1]

A phase III, open-label, multicenter extension study was designed to assess the long term (36 month) hypothalamic-pituitary-gonadal axis suppression and safety of leuprolide acetate 3-month depot 11.25mg and 30mg in children with CPP, for 36 months was performed. Seventy-two patients with CPP who completed the preceding study and showed maintenance of LH suppression were included.[17,18] All eligible subjects had documented LH suppression as evidenced by peak-stimulated LH < 4 mIU/mL after 6 months of treatment and demonstrated suppression of physical signs of puberty (regression or no progression of breast development in girls or of testicular volume and genital staging in boys). Subjects received up to 12 intramuscular injections of the same treatment they were previously assigned in the lead-in study. No dose adjustments were permitted during the treatment period. The main outcome measures were peak-stimulated LH, estradiol, testosterone, growth rate, pubertal progression, and adverse events. Twenty-nine of 34 subjects in the 11.25mg group and 36 of 38 subjects in the 30mg group had LH values < 4 mIU/mL after day 1 at all time points. All seven subjects who escaped LH suppression at any time still maintained sex steroid concentrations at prepubertal levels and showed no signs of pubertal progression. Adverse events were comparable between groups, with injection site pain being the most common (26.4% overall). No adverse event led to discontinuation of study drug. The safety profile over 36 months was comparable to that observed during the 6-month pivotal study.

Endometriosis

Leuprolide acetate is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Leuprolide acetate, concomitantly with norethindrone acetate 5 mg daily, is also indicated for the initial management of endometriosis and management of recurrence of symptoms.[2]

The Pelvic Pain Study Group evaluated and compared the safety and efficacy of leuprolide versus placebo in managing chronic pelvic pain in women with clinically suspected endometriosis.[3] Women ages 18 to 45 years with moderate to severe pelvic pain of at least 6 months' duration underwent extensive, noninvasive diagnostic testing and laboratory evaluation. Those with clinically suspected endometriosis were randomized to double-blind treatment with either depot leuprolide 3.75 mg or placebo IM every 4 weeks for 12 weeks. Of 100 women randomized, 95 completed the study: 49 in the leuprolide group and 46 in the placebo group. Post-treatment laparoscopic examination confirmed endometriosis in 78% of patients in the depot leuprolide group and 87% of the placebo group. Women in the leuprolide group had clinically and statistically significant ($p \leq 0.001$) mean improvements from baseline after 12 weeks of therapy in all pain measures. These mean improvements were significantly greater ($p \leq 0.001$) than those in the placebo group. At 12 weeks, mean decreases in physician-rated scores (on a 4 point scale) for dysmenorrhea, pelvic pain, and pelvic tenderness were 1.7, 1.0, and 0.8 points greater, respectively, in the leuprolide group than in the placebo group. Depot leuprolide was effective and safe for treating patients with chronic pelvic pain and clinically suspected endometriosis, confirming the potential of its empiric use in these patients.

The Lupron Study Group evaluated the safety and efficacy of leuprolide acetate for depot suspension 3.75 mg versus placebo in the treatment of pain associated with endometriosis.[4] In a randomized, double-blind, multicenter study

involving 52 patients, dysmenorrhea, pelvic pain, and pelvic tenderness all responded significantly to leuprolide acetate compared to placebo. Menses were suppressed in all of the subjects in the leuprolide acetate treatment group. Estradiol decreased significantly to menopausal levels in the leuprolide acetate group. Although there were small to moderate changes in a variety of laboratory parameters, these were not clinically significant. The most common adverse event was vasodilatation, occurring significantly more frequently in the leuprolide acetate group.

Uterine Leiomyomata (Fibroids)

Leuprolide acetate, concomitantly with iron therapy, is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.[2] Leuprolide acetate may also be used preoperatively to reduce the size of uterine fibroids to allow for a vaginal procedure (e.g., myomectomy, hysterectomy).[5-9]

Stovall et al. conducted a phase III, stratified, randomized, double-blind, placebo-controlled, parallel-group, 12-week multicenter study to determine the effectiveness of leuprolide acetate depot plus iron compared with iron alone in the preoperative treatment of anemia due to prolonged or excessive bleeding associated with uterine leiomyomas.[6] Study participants had hemoglobin levels of 10.2 g/dL or less and/or hematocrit values of 30% or less. Subjects were entered into one of two strata based on their pre-study hematocrit level: stratum A, hematocrit less than or equal to 28%, and stratum B, hematocrit greater than 28%. Of the 309 patients entered into the study, 265 were evaluated. Patients within each stratum were randomized to one of three treatment arms: leuprolide acetate depot 7.5 mg (n=99), leuprolide acetate depot 3.75 mg (n=89), or placebo (n=77). All patients received iron orally. Response was defined as a hemoglobin level of 12 g/dL or more and a hematocrit value of 36% or greater. A significantly greater number of patients in both leuprolide acetate groups (combined strata) responded to therapy than did those in the placebo group: 74% in each leuprolide acetate group versus 46% in the placebo group ($p<0.001$). Gonadotropin-releasing hormone agonist-treated patients had a significant reduction in uterine and myoma volume when compared with the placebo group ($p<0.01$). Hot flashes and vaginitis were reported significantly more often ($p<0.001$) in the leuprolide acetate-treated groups than in the placebo group. Both dosages of GnRH agonist plus iron were more effective than iron alone in treating the anemia of patients with uterine leiomyomas, in reducing uterine-myoma volume, and in alleviating bleeding and other leiomyoma-related symptoms.

In a randomized, double-blind, placebo-controlled multicenter study involving 13 investigative centers, Friedman et al. evaluated efficacy and safety parameters in women (n=128) with leiomyomata uteri treated with the GnRH agonist leuprolide acetate.[7] Study participants received either leuprolide acetate depot 3.75 mg (n=63) or placebo (n=65) by intramuscular (IM) injection every 4 weeks for 24 weeks. Of the 128 patients enrolled in the study, 124 were eligible for efficacy analysis. Patients were seen every 4 weeks for 24 weeks, and those confirmed by unblinding at the end of the study to have received leuprolide acetate were followed under a separate, no-treatment protocol for one year. While mean uterine volume decreased by 36% at 12 weeks and 45% at 24 weeks of leuprolide therapy, patients treated with placebo had increased in mean uterine volume of 16% at 12 weeks and 5% at 24 weeks. Seventy-seven percent of leuprolide-treated patients had a more than 25% reduction in uterine volume, compared with 9% of placebo-treated controls. Mean uterine volume returned to pre-treatment size 24 weeks after cessation of leuprolide treatment. The majority of patients had resolution or improvement of their fibroid-related symptoms after 24 weeks of leuprolide treatment. Of 38 leuprolide-treated patients presenting with menorrhagia, 37 (97%) had resolution of this symptom at the time of the final visit. Although 95% of women treated with leuprolide acetate experienced some side effects related to hypoestrogenism, only five patients (8%) terminated treatment prematurely. The authors concluded that leuprolide acetate depot treatment of leiomyomata uteri is safe and causes significant but temporary reductions in uterine size and fibroid-related symptoms.

Stovall et al. conducted a randomized trial in 50 premenopausal patients to evaluate leuprolide acetate before hysterectomy as treatment for symptomatic uterine leiomyomas which were the size of 14 to 18 weeks' gestation.[8] Subjects were randomized into two groups to determine whether preoperative gonadotropin-releasing hormone agonist would increase the feasibility of vaginal rather than abdominal hysterectomy. The control group (group A; n=25) did not receive preoperative leuprolide acetate and underwent immediate hysterectomy, but patients in Group B (n=25) received 2 months of leuprolide acetate before undergoing hysterectomy. Patients in the two groups were similar with respect to age, gravidity, parity, pretreatment uterine size, and hemoglobin and hematocrit levels. After GnRH therapy, patients in group B had an increase in hemoglobin levels (10.75 to 12.12 gm/dL, $p<0.05$), a reduction in uterine size from 15.7 to 11.2 weeks' mean gestational size as determined by pelvic examination ($p<0.05$), and a decrease in uterine volume (1086.7 to 723.4 mL, $p<0.05$). Patients in group B also were more likely to undergo vaginal hysterectomy (76.0% vs 16%) and had shorter hospitalizations (5.2 vs 3.8 days, $p<0.05$). The authors concluded that the administration of leuprolide acetate for 2 months followed by vaginal hysterectomy is preferable to abdominal hysterectomy in selected patients with uterine leiomyomas.

Friedman et al. enrolled thirty-eight premenopausal women with uterine leiomyomata in a randomized, double-blind, placebo-controlled study evaluating the efficacy of depot leuprolide acetate (LA) in decreasing uterine volume.[9] Subjects received intramuscular (IM) depot LA 3.75 mg every 4 weeks for 24 weeks (group A, n=18) or IM placebo with the same injection schedule (group B, n=20). The study groups were well-matched for age, weight, and

pretreatment uterine volume. Patients were seen at 4-week intervals during the treatment period and assessed once more at 3 months after cessation of therapy. Group A patients had a mean reduction in pretreatment uterine volume from 505 ± 93 cu cm to 305 ± 57 cu cm after 12 weeks ($p<0.05$ versus pretreatment) and 307 ± 57 cu cm after 24 weeks of therapy ($p<0.05$ versus pretreatment). At 3 months after cessation of therapy, the mean uterine volume in group A had increased to 446± 92 cu cm ($p<0.05$ versus week 24). Group B patients had no significant change in uterine volume over the 24-week treatment period. These results suggest that depot LA therapy may significantly decrease uterine volume in patients with leiomyomata and may be useful as a preoperative adjuvant for hysterectomy and myomectomy.

Fertility Preservation

NCCN oncology guidelines for Breast Cancer (V2.2017) report that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Additionally noted is that smaller historical experiences in women with ER-positive breast cancer have reported conflicting results regarding the protective effect of GnRH agonist on fertility.[19]

The NCCN oncology guidelines for adolescents and young adults (V2.2017) state that fertility preservation should be an essential part in the management of adolescent and young adults with cancer who are at any risk for infertility due to cancer treatments.[20] Providers should discuss with their patients the risks for infertility due to cancer and its therapy, fertility preservation, and contraception prior to the start of therapy. Men are at risk for azoospermia following therapy, which may or may not resolve over time. Women are at risk for premature ovarian failure due to chemotherapy. For men, options include the use of a sperm bank. For females, oocyte or embryo cryopreservation, oophoropexy, and menstrual suppression are possibilities. The guidelines state that menstrual suppression is inconclusive whether this would protect the ovaries. Randomized trials that have evaluated the role of menstrual suppression with gonadotropin-releasing hormone agonists to preserve ovarian function during chemotherapy have provided conflicting reports. Medroxyprogesterone, oral contraceptives, or gonadotropin-releasing hormone agonists may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[20]

Ovarian toxicity of chemotherapy treatments involve the prevention of cell division and adverse effects on DNA function within the ovarian cells.[25,26] Alkylating agents are overall more toxic to the ovaries than platinum-based therapies and antimetabolites. These effects are age dependent, with older individuals being associated with greater impact, probably due to an overall smaller follicular reserve at the beginning of treatment. Different chemotherapy regimens and cytotoxic agents carry different risks for primary ovarian insufficiency. The table below lists the cytotoxic medications that carry a high or intermediate degree of risk of ovarian toxicity when administered.

Cytotoxic Drugs with High or Intermediate Risk of Ovarian Toxicity[25,26]	
High Risk of Ovarian Toxicity	• Busulfan • Carmustine • Cyclophosphamide • Dacarbazine • Ifosfamide • Lomustine • Melphalan • Procarbazine
Intermediate Risk of Ovarian Toxicity	• Cisplatinum • Cytarabine • Etoposide • Vinblastine

A single-center, prospective, randomized study investigated the efficacy of leuprolide acetate in premenopausal patients with breast cancer on ovarian function protection against chemotherapy-induced genotoxicity.[21] Premenopausal women aged 18 to 45 years with stage I−III breast cancer were eligible for this study. All patients received primary surgical therapy, but needed to have no history of prior chemotherapy or hormone therapy, in addition to other criteria. FSH, estradiol, and menstrual activity were measured throughout the trial. Patients were randomly allocated to receive chemotherapy only (n=94) or chemotherapy plus leuprolide acetate (LA, 3.75 mg, n=89). Serum estrogen level was measured 2 weeks after injection. If ovarian suppression was confirmed, patients started to receive chemotherapy, otherwise treatment was not started until ovarian suppression was proved. During chemotherapy, patients were given LA at the same dosage every 4 weeks. All patients received cyclophosphamide-doxorubicin-based chemotherapy with some patients receiving additional adjuvant therapy. For those patients experiencing early menopause, 27 patients (28.7%) in the chemotherapy only group and 15 patients (16.9%) in the chemotherapy plus LA group had early menopause ($p<0.01$). Paclitaxel treatment significantly affected the risk of

developing early menopause (0.01 < P < 0.05). Patients with cyclophosphamide, doxorubicin, and paclitaxel had a significantly lower occurrence of early menopause in chemotherapy plus LA group (0.01 < P < 0.05). Resumption of menses was reported by 39 patients in chemotherapy only group and 53 patients in chemotherapy plus LA group (0.01 < P < 0.05). Premenopausal level of FSH and estrogen without resumption of menses was observed in seven patients in chemotherapy only group and 14 patients in the LA group (p > 0.05). Per the author's definition of effective treatment, ovarian suppression with LA effectively preserved the ovarian function after chemotherapy (P < 0.01) The median time to resume menstruation was 9.2 months in the LA group, while no median time was reached with the chemotherapy only group. The mean estrogen levels were significantly decreased in both groups relatively to the values at study entry. At 12 months, these levels were not significantly different between the two groups. In contrast, mean values of FSH were significantly elevated in both groups relative to the values at study entry, but significantly higher in the chemotherapy only group at 12 months after the end of treatment (P < 0.05). The authors conclude that LA treatment simultaneously with cyclophosphamide-doxorubicin-based chemotherapy reduced the risk of developing premature menopause in premenopausal women with breast cancer.

Somers et al., conducted a cohort study to evaluate the effectiveness of depot leuprolide acetate (LA), a synthetic gonadotropin-releasing hormone analog (GnRH-a), for protection against premature ovarian failure (POF) during cyclophosphamide (CYC) therapy in premenopausal patients diagnosed with systemic lupus erythematosus (SLE).[23] Patients were eligible for this study if they had a diagnosis consistent with lupus or if they satisfied the American College of Rheumatology (ACR) criteria for SLE, were women of reproductive age, and had an exacerbation of disease activity requiring treatment with at least 6 monthly boluses of CYC. Patients were excluded from this analysis if they were age ≥35 years at the beginning of CYC treatment or if they were found at baseline to have symptoms consistent with ovarian failure based on gynecologic evaluation. All study participants underwent a standardized IVCYC protocol for the treatment of severe manifestations of SLE. Participation in the GnRH-a protocol was offered to consecutive female SLE patients in whom CYC treatment was initiated. Depot LA was administered by injection once per month at a dose of 3.75 mg throughout the course of CYC treatment. In patients who did not achieve satisfactory disease control, LA administration was continued throughout CYC therapy. In order to avoid CYC exposure during the initial surge of estrogen, the GnRH-a injection was timed to occur at least 10 days prior to the subsequent monthly bolus of CYC. Controls were randomly selected female SLE patients in the Michigan Lupus Cohort who had participated in the IVCYC protocol and fulfilled the above eligibility criteria, but who had not received GnRH-a. Controls were randomly selected female SLE patients in the Michigan Lupus Cohort who had participated in the IVCYC protocol and fulfilled the above eligibility criteria, but who had not received GnRH-a. The minimum period of follow-up was 3.0 years unless ovarian failure developed sooner. The analysis was based on a total of 287.1 person-years at risk for POF, including 186.9 person-years among controls (median 10.3 years at risk for POF, range 0.8−16.7 years) and 100.2 person-years among GnRH-a−treated patients (median 4.6 years at risk for POF, range 0.6−9.3 years). At follow-up, ovarian failure had developed in 1 of 20 GnRH-a−treated patients (5%) compared with 6 of 20 controls (30%). Based on a matched pairs analysis, the odds of ovarian failure were significantly lower in the GnRH-a−treated group (OR 0.09, P < 0.05). The single GnRH-a−treated patient who developed ovarian failure was older (28.2 years) and received a higher cumulative CYC dose (33.5 gm) than the corresponding mean values for the population (24.4 years and 12.9 gm). Accounting for time at risk for ovarian failure, Kaplan-Meier survival estimates showed greater cumulative preservation of ovarian function in the GnRH-a−treated group than in controls (P = 0.04). The median time to onset of ovarian failure was 4.3 years (interquartile range 1.2−5.7). Based on Cox regression, the hazard of developing ovarian failure within 10 years of CYC initiation in the GnRH-a−treated group was less than one-tenth that in the control group (hazard ratio 0.09, 95% confidence internal 0.01−0.8). Although it is not known how many of the women attempted conception subsequent to CYC therapy, 3 of 20 control patients (15%) and 7 of 20 GnRH-a−treated patients (35%) had successful pregnancies following treatment. There was no statistically significant difference in adverse events potentially attributable to the study protocol, including dysfunctional uterine bleeding, deep venous thrombosis, or new ischemic cardiac events during the treatment period. The authors acknowledged that their study is limited because it was not a randomized controlled trial, however, they matched controls to account for known confounders. The authors concluded that treatment with a depot GnRH-a during CYC therapy was associated with a significant reduction in the future incidence of ovarian failure among women with severe SLE.

A systematic review and meta-analysis of studies assessing the efficacy of GnRH agonists in reducing chemotherapy induced ovarian failure in cancer or systemic lupus erythematosus (SLE) identified sixteen trials, four SLE and twelve cancer. The meta-analysis revealed that GnRH agonists are effective in reducing amenorrhea rates in all patients (RR .26, 95% CI 0.14-0.49). Pregnancy rate was also higher in the GnRH agonist arms. This advantage, however, was shown only in the observational trials, not in randomized trials. The authors concluded that GnRH agonists appear to improve menstruation resumption, but larger, prospective, randomized trials are needed to further evaluate the role of GnRH agonists in preventing chemotherapy induced ovarian failure.[24]

Gender Dysphoria in Adolescents

Costa et al, published the results of a longitudinal study involving 201 adolescents with gender dysphoria (GD), comparing treatment modalities involving psychological support, puberty suppression with GnRH analogs, or both.[35] Patients' global functioning were evaluated every 6 months from the first visit. Patients completed the Utrecht Gender

Dysphoria Scale (UGDS), a self-report measure of GD-related discomfort, and the Children's Global Assessment Scale (CGAS) to assess the psychosocial functioning of adolescents. The authors hypothesized that subjects would have poor general functioning at baseline, an improvement after psychological support, and a further improvement after beginning puberty suppression. The 201 adolescents participating in the study completed the diagnostic procedure (about 6 months) and continued to participate in follow-up evaluations. All patients were eligible for puberty suppression with GnRH analogs per WPATH guidelines, however, some were immediately eligible, and some were delayed eligible, who continued to receive psychological support without medication, until the patient was ready to make a decision to continue therapy. GD adolescents' CGAS at baseline (Time 0, M = 57.7 ± 12.3) revealed a score suggestive of "variable functioning with sporadic difficulties or symptoms in several but not all social areas" (range 50−59). Natal men had a significantly lower functioning than natal women at baseline (P = 0.03). GD adolescents' CGAS scores at baseline were significantly lower (t = 7.4, P < 0.001) than that found in a sample of children/adolescents without observed psychological/psychiatric symptoms (N=169, 67.1 ± 12). GD adolescents' psychosocial functioning was increasingly higher at each of the following evaluations. In particular, CGAS scores were significantly higher after 6 months of psychological support (Time 0 vs. Time 1, P < 0.001). Also there was a further significant improvement 18 months from baseline (Time 1 vs. Time 3, P = 0.02). Delayed eligible GD adolescents, who received only psychological support for the entire duration of the study, had a significantly better psychosocial functioning after six months of psychological support (Time 0 vs. Time 1, P = 0.05). The delayed eligible group, however, continued to score lower than a sample of children/adolescents without observed psychological/psychiatric symptoms, even after 18 months of psychological support (Time 3, t = 2.0, P = 0.04). The immediately eligible group, who at baseline had a higher, but not significantly different psychosocial functioning than the delayed eligible group, did not show any significant improvement after 6 months of psychological support. However, immediately eligible adolescents had a significantly higher psychosocial functioning after 12 months of puberty suppression compared with when they had received only psychological support (Time 1 vs. Time 3 P = 0.001). Also, their CGAS scores after 12 months of puberty suppression (Time 3) coincided with those found in a sample of children/adolescents without observed psychological/psychiatric symptoms (t = 0.01, P = 0.99). The authors concluded that psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescents. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescents.

In 2014, de Vries et al, published the results of a small, longitudinal study, that followed 55 patients with gender dysphoria (GD), to evaluate the psychological functioning, objective and subjective well-being through 3 time points during the patient therapy: 1) Before start of puberty suppression with GnRH analogs (mean age 13.6 years, T0), 2) when cross-sex hormones (CSH) are introduced (mean age 16.7 years, T1), and at least 1 year after gender reassignment surgery (GSR) (mean age 20.7 years, T2). Throughout the course of puberty suppression therapy, GD and body image difficulties persisted (at T0 and T1) and remitted after the administration of CSH and GRS (at T2). Transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. At T2, the patients were slightly more likely to live with parents (67% vs 63%), than the Dutch population, and more likely, when studying, to be pursuing higher education (58% vs 31%). Families of GD patients were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy. None of the participants reported regret during puberty suppression, CSH treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries. The authors concluded that their clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults.

Technology Assessments

Proven

Endometriosis

A 2014 Cochrane review was published as an overview of reports on interventions for pain relief and subfertility in pre-menopausal women with clinically diagnosed endometriosis.[5,15] The objective was to summarize the evidence from Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis. Seventeen systematic reviews published in The Cochrane Library were included. All the reviews were high quality. The quality of the evidence for specific comparisons ranged from very low to moderate. The authors concluded that for women with pain and endometriosis, suppression of menstrual cycles with gonadotropin-releasing hormone (GnRH) analogues, the levonorgestrel-releasing intrauterine system (LNG-IUD) and danazol were beneficial interventions. Laparoscopic treatment of endometriosis and excision of endometriomata were also associated with

improvements in pain. The evidence on NSAIDs was inconclusive. There was no evidence of benefit with post-surgical medical treatment. In women with endometriosis undergoing assisted reproduction, three months of treatment with GnRH agonist improved pregnancy rates. Excisional surgery improved spontaneous pregnancy rates in the nine to 12 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone. There was no evidence that medical treatment improved clinical pregnancy rates. Evidence on harms was scanty, but GnRH analogues, danazol and depot progestogens were associated with higher rates than other interventions.

Uterine Leiomyomata (Fibroids)

A 2011 Cochrane review was published evaluative the efficacy and safety of GnRH analogues given before or in parallel to chemotherapy to prevent chemotherapy-related ovarian damage in premenopausal women with malignant or non-malignant conditions.[16] The authors concluded that the use of GnRH agonists should be considered in women of reproductive age receiving chemotherapy. Intramuscular or subcutaneous GnRH analogues seem to be effective in protecting ovaries during chemotherapy and should be given before or during treatment, although no significant difference in pregnancy rates was seen.

Other

Gender Dysphoria

Hayes compiled a Medical Technology Directory on hormone therapy for the treatment of gender dysphoria dated May 19, 2014.[14] Hayes assigned a rating of D2, no proven benefit and/or not safe, for pubertal suppression therapy in adolescents. This rating was based upon insufficient published evidence to assess safety and/or impact on health outcomes or patient management.

Professional Societies

Proven

Fertility Preservation

In 2013, the American Society of Clinical Oncology (ASCO) released an update to their clinical practice guideline regarding fertility preservation for adults and children with cancer.[22] The following recommendations and conclusions were published:

- Currently, there is insufficient evidence regarding the effectiveness of GnRHa and other means of ovarian suppression in fertility preservation. GnRHa should not be relied upon as a fertility preservation method. However, GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy. This benefit must be weighed against other possible risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers. Women interested in this method should participate in clinical trials, because current data do not support it. In true emergency or rare or extreme circumstances where proven options are not available, providers may consider GnRHa an option, preferably as part of a clinical trial.

Endometriosis

In 2010 (reaffirmed in 2016), the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses the management of endometriosis.[10] The following recommendations and conclusions were published:

- After an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs), empiric therapy with a 3-month course of a GnRH agonist is appropriate.
- When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH agonist-induced bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief.
- Medical suppressive therapy improves pain symptoms; however, recurrence rates are high after the medication is discontinued.
- There is significant short-term improvement in pain after conservative surgical treatment; however, as with medical management, there is also a significant rate of pain recurrence.
- Medical suppressive therapies such as oral contraceptives (OCs) or gonadotropin-releasing hormone (GnRH) agonists for endometriosis-associated infertility are ineffective.
- Surgical management of endometriosis-related infertility does improve pregnancy rates, but the magnitude of improvement is unclear.
- In patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or depot medroxyprogesterone acetate (DMPA) are effective compared with placebo and are equivalent to other more costly regimens.
- Long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence as well as a reduction in the frequency and severity of dysmenorrhea.

- In patients with normal ovaries, a hysterectomy with ovarian conservation and removal of the endometriotic lesions should be considered.

Uterine Leiomyomata (Fibroids)

In 2008, the American College of Obstetricians and Gynecologists (ACOG) released a practice bulletin that discusses alternatives to hysterectomy in the management of leiomyomas.[11] The following recommendations and conclusions are based upon good and consistent scientific evidence (Level A):

- GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and post-operative pain when given for 2-3 months preoperatively.
- The benefits of preoperative use of GnRH agonists should be weighed against their cost and side effects for individual patients.

Other

Gender Dysphoria in Adolescents

In 2009 the Endocrine Society published their clinical practice guidelines for the endocrine treatment of transsexual persons. The guidelines state that adolescents are eligible and ready for GnRH treatment if they meeting the following criteria:[32]

- Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism
- Have experienced puberty to at least Tanner stage 2
- Have (early) pubertal changes that have resulted in an increase of their gender dysphoria
- Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment
- Have adequate psychological and social support during treatment; and
- Demonstrate knowledge and understanding of the expected outcomes of GnRH analog treatment, cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and the social risks and benefits of sex reassignment.

In 2012, the World Professional Association for Transgender Health (WPATH), an advocacy group, published *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th Version.* This publication suggested the following criteria for the use of puberty-suppressing hormones in adolescents with gender dysphoria:[33]

- In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:
  - The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
  - Gender dysphoria emerged or worsened with the onset of puberty;
  - Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
  - The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

WPATH also presented regimens, monitoring and risks for puberty suppression in adolescents with gender dysphoria.[33]

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and progesterone.

During pubertal suppression, an adolescent's physical development should be carefully monitored – preferably by a pediatric endocrinologist – so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density).

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising, the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

In May 2013, the American Psychiatric Association published an update to their Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). The DSM-5 provided updated diagnostic criteria for gender dysphoria for both children and adults. The new criteria are as follows:[34]

- Gender Dysphoria in Adolescents:
  - A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):
    1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
    2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
    3. A strong preference for cross-gender roles in make-believe play or fantasy play.
    4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
    5. A strong preference for playmates of the other gender.
    6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
    7. A strong dislike of one's sexual anatomy.
    8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
  - B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

  Specify if:
  - With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
  - Coding note: Code the disorder of sex development as well as gender dysphoria.

- Gender Dysphoria in Adolescents and Adults:
  - A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:
    1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
    2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
    3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
    4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
    5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
    6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
  - B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

  Specify if:
  - With a disorder of sex development (e.g., a congenital adrenogenital disorder such as 255.2 [E25.0] congenital adrenal hyperplasia or 259.50 [E34.50] androgen insensitivity syndrome).
  - Coding note: Code the disorder of sex development as well as gender dysphoria.

  Specify if:
  - Post-transition: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen—namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Firmagon (degarelix). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers 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 http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

Medicare does not have a National Coverage Determination (NCD) for Leuprolide Acetate, Goserelin Acetate, Triptorelin Acetate or Histrelin Acetate. Local Coverage Determinations (LCDs) exist. Refer to the LCDs for Luteinizing Hormone-Releasing Hormone (LHRH) Analogs.

In general, Medicare covers 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 http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.
(Accessed May 11, 2017)

STATE EXCEPTIONS

State	Note
Kansas	Drug policy not approved for use in this market

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37. Triptodur [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals, LLC; June 2017.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2017	• Revised coverage rationale: ○ Updated list of applicable gonadotropin releasing hormone analog (GnRH

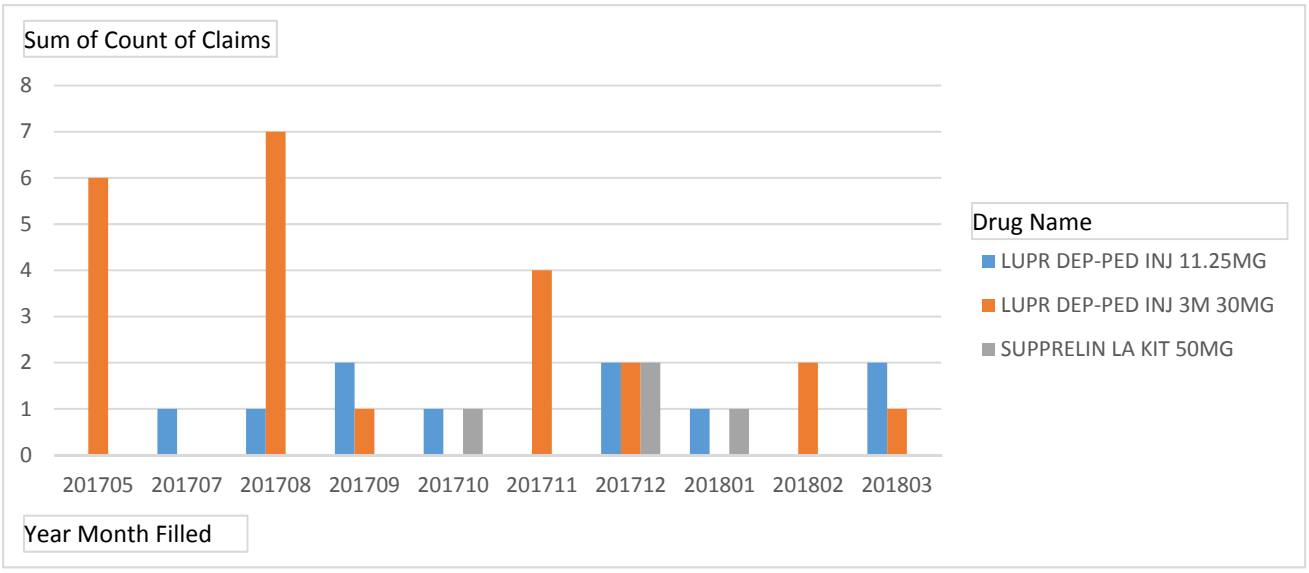
Date	Action/Description
	analog) drug products; added Triptodur (triptorelin) ○ Added language to indicate: ▪ Triptodur is medically necessary for the treatment of central precocious puberty when all of the listed criteria are met ▪ Triptodur treatment should be discontinued at the appropriate age of onset of puberty at the discretion of the physician ○ Updated coverage guidelines for treatment of endometriosis: ▪ Replaced references to diagnosis/treatment of "endometriosis" with "endometriosis *or suspected endometriosis*" ▪ Modified medical necessity criteria for initial therapy: – Updated list of drug products to which contraindication, intolerance, or therapeutic failure must be demonstrated; replaced "oral contraceptives" with "oral contraceptives *or depot medroxyprogesterone (e.g., Depot Provera)*" • Updated list of applicable HCPCS codes; added J3490 • Added state exceptions language to indicate this policy is not approved for use in the Kansas market • Updated supporting information to reflect the most current background information, clinical evidence, FDA information, and references • Archived previous policy version 2016D0038G

GnRH Agonists

April 1, 2017 - March 31, 2018

Fee for Service Medicaid

Year Month Filled	Drug Name	Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201705	LUPR DEP-PED INJ 3M 30MG	6	6	418	6	$ 48,523.26
201707	LUPR DEP-PED INJ 11.25MG	1	1	84	1	$ 7,343.62
201708	LUPR DEP-PED INJ 11.25MG	1	1	27	1	$ 2,454.65
201708	LUPR DEP-PED INJ 3M 30MG	7	7	510	7	$ 56,610.47
201709	LUPR DEP-PED INJ 11.25MG	2	2	174	2	$ 14,687.24
201709	LUPR DEP-PED INJ 3M 30MG	1	1	30	1	$ 8,087.21
201710	LUPR DEP-PED INJ 11.25MG	1	1	90	1	$ 7,343.62
201710	SUPPRELIN LA KIT 50MG	1	1	90	1	$ 29,491.54
201711	LUPR DEP-PED INJ 3M 30MG	4	4	238	4	$ 32,348.84
201712	LUPR DEP-PED INJ 11.25MG	2	2	174	2	$ 14,687.24
201712	LUPR DEP-PED INJ 3M 30MG	2	2	118	2	$ 16,174.42
201712	SUPPRELIN LA KIT 50MG	2	2	60	2	$ 19,181.84
201801	LUPR DEP-PED INJ 11.25MG	1	1	90	1	$ 8,032.96
201801	SUPPRELIN LA KIT 50MG	1	1	90	1	$ 1,269.76
201802	LUPR DEP-PED INJ 3M 30MG	2	2	120	2	$ 17,692.90
201803	LUPR DEP-PED INJ 11.25MG	2	2	174	2	$ 8,162.96
201803	LUPR DEP-PED INJ 3M 30MG	1	1	90	1	$ 8,846.45



GnRH Agonists

April 1, 2017 - March 31, 2018

Fee for Service Medicaid

Specialty of Prescriber

Sum of Count of Claims	Member Age											
Specialty of Prescriber	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**17**	**30**	**Grand Total**
Endocrinology	**2**		**1**	**4**		**1**	**3**	**4**	**1**	**2**		**18**
4	2					1		4	1	2		10
5			1	4			3					8
NP	**1**	**2**	**1**		**3**							**7**
3	1	2			3							6
7			1									1
Pediatrics			**1**	**2**	**5**	**2**						**10**
2			1	2	5	2						10
Unknown				**1**							**1**	**2**
1											1	1
6				1								1
Grand Total	**3**	**2**	**3**	**7**	**8**	**3**	**3**	**4**	**1**	**2**	**1**	**37**

Lupron Utilization

SilverSummit Health Plan

Place-holder for SSHP utilization

GnRH Utilization
March 1, 2017 - February 28, 2018
Anthem Nevada Medicaid

Count of HC_ID			LABEL_NAME								
YR	MO	AGE	LUPR DEP-PED INJ 11.25MG	LUPR DEP-PED INJ 15MG	LUPR DEP-PED INJ 3M 30MG	LUPRON DEPOT INJ 11.25MG	LUPRON DEPOT INJ 22.5MG	LUPRON DEPOT INJ 3.75MG	LUPRON DEPOT INJ 45MG	LUPRON DEPOT INJ 7.5MG	Grand Total
2017			**2**	**3**	**5**	**22**	**1**	**32**	**3**	**6**	**74**
	3				**1**	**6**		**5**		**1**	**13**
		13			1						1
		23				1					1
		29				1					1
		31				1					1
		33				1					1
		34						1			1
		35						1			1
		36						1			1
		36						1			1
		38				1					1
		42						1			1
		45								1	1
		48				1					1
	4				**1**			**5**		**1**	**7**
		10			1						1
		23						1			1
		36						1			1
		37						1			1
		42						1			1
		45						1			1
		45								1	1
	5					**5**		**4**		**2**	**11**
		23						1			1
		31						1			1
		31				1					1
		33				1					1
		36						1			1
		36						1			1
		37				1					1
		37				1					1
		42				1					1
		45								1	1

2017	5	46								1	1
	6			**1**	**1**	**1**		**3**		**1**	**7**
		13			1						1
		14		1							1
		31						1			1
		33				1					1
		36						1			1
		36						1			1
		46								1	1
	7				**1**			**3**			**4**
		11			1						1
		31						1			1
		36						1			1
		37						1			1
	8		**1**	**1**		**3**		**2**		**1**	**8**
		14		1							1
		16	1								1
		23				1					1
		23				1					1
		32						1			1
		34				1					1
		37						1			1
		46								1	1
	9					**3**		**2**			**5**
		23						1			1
		24				1					1
		32				1					1
		32						1			1
		44				1					1
	10			**1**		**2**		**3**			**6**
		15		1							1
		22				1					1
		23						1			1
		35				1					1
		36						1			1
		38						1			1
	11		**1**		**1**			**2**	**1**		**5**
		11			1						1
		16	1								1
		30						1			1
		32						1			1
		62							1		1
	12					**2**	**1**	**3**	**2**		**8**
		30						1			1
		34				1					1
		34				1					1
		36						1			1

2017	12	36						1			1
		53							1		1
		62					1				1
		64							1		1
2018				**1**		**2**		**9**			**12**
	1			**1**		**1**		**5**			**7**
		15		1							1
		23				1					1
		24						1			1
		30						1			1
		30						1			1
		36						1			1
		36						1			1
	2					**1**		**4**			**5**
		28						1			1
		30						1			1
		31						1			1
		34				1					1
		36						1			1
Grand Total			**2**	**4**	**5**	**24**	**1**	**41**	**3**	**6**	**86**

Health Plan of Nevada

Leuprolide & Lupron Depot Utilization

March 1, 2017 - February 28, 2018

Year/Month Filled/Paid	Drug Name	Count of Members	Count of Claims	Sum of Qty
2017/03	LEUPROLIDE & LUPRON DEPOT	16	16	16
2017/04	LEUPROLIDE & LUPRON DEPOT	9	9	9
2017/05	LEUPROLIDE & LUPRON DEPOT	8	8	8
2017/06	LEUPROLIDE & LUPRON DEPOT	12	12	12
2017/07	LEUPROLIDE & LUPRON DEPOT	11	11	11
2017/08	LEUPROLIDE & LUPRON DEPOT	16	16	16
2017/09	LEUPROLIDE & LUPRON DEPOT	13	13	13
2017/10	LEUPROLIDE & LUPRON DEPOT	11	11	11
2017/11	LEUPROLIDE & LUPRON DEPOT	6	6	6
2017/12	LEUPROLIDE & LUPRON DEPOT	5	5	5
2018/01	LEUPROLIDE & LUPRON DEPOT	10	10	10
2018/02	LEUPROLIDE & LUPRON DEPOT	14	14	14

PLEASE NOTE: Utilization comes from standard claims as well as capitated encounters where the amount paid is $0.

YY. GnRH Analogs

Therapeutic Class: GnRH Analogs
Last Reviewed by the DUR Board: July 28, 2016

GnRH Analogs 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. This prior authorization criteria only applies to recipients who are under 18 years of age. Approval of Lupron® (leuprolide) will be given if all the following criteria, per individual diagnosis, are met and documented:

      1. The recipient has a diagnosis of idiopathic or neurogenic central precocious puberty (CPP), and

         a. The requested dose and frequency is based on FDA-approved guidelines; and

         b. The medication is being prescribed by or in consultation with a pediatric endocrinologist; and

         c. There is an onset of secondary sex characteristics before age eight years (females) or nine years (males); and

         d. The recipient is currently less than 11 years of age (females) or 12 years of age (males).

      2. The recipient has a diagnosis of of endometriosis, and

         a. The requested dose and frequency is based on FDA-approved guidelines; and

         b. The recipient has had an inadequate response, adverse reaction or contraindication to an NSAID; and

         c. The recipient has had an inadequate response, adverse reaction or contraindication to a hormonal contraceptive.

      3. The recipient has a diagnosis of uterine leiomyomata (fibroids), and

         a. The requested dose and frequency is based on FDA-approved guidelines; and

         b. The recipient is symptomatic; and

c. Documentation has been submitted of the anticipated surgery date (or notation that surgery is planned once the fibroids shrink) or clinical rational why surgical intervention is not required.

4. The recipient has a diagnosis of prostate cancer, and

a. The requested dose and frequency is based on FDA-approved guidelines.

2. Prior Authorization Guidelines

a. Prior authorization approval will be given for an appropriate length of therapy based on the diagnosis, unless the prescriber indicates a shorter duration of approval.

1. CPP: One year, or until the member reaches the age of 11 years (female) or 12 years (male).

2. Endometriosis: One year.

3. Uterine Leiomyomata (fibroids): One month or until the time of the documented surgery (maximum of three months).

4. Prostate Cancer: One year.

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

Therapeutic Class Overview

Gonadotropin-releasing hormone (GnRH) agonists/ luteinizing hormone-releasing hormone (LHRH) agonists

INTRODUCTION

- Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function *(Britto et al 2016)*. Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors *(Macedo et al 2014).*
  - While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls and 9 to 9.5 years in boys for the lower limit of normal pubertal development *(Carel et al 2004)*.
- Central precocious puberty (CPP) is characterized by the early onset of pubertal manifestations in girls and boys *(Carel et al 2004)*.
  - CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion *(Carel and Léger 2008).*
  - These manifestations consist primarily of breast development in girls and testicular enlargement in boys *(Carel and Léger 2008)*.
- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity *(Brown and Farquhar 2015).*
  - Endometriosis commonly manifests as chronic pain and infertility *(Armstrong 2011).*
  - It affects 6% to 10% of women of reproductive age; it is present in approximately 38% of women with infertility and in up to 87% of women with chronic pelvic pain (*Armstrong 2011).*
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion and finally suppression of the release of gonadal sex hormones *(Fuqua 2013, Klein et al 2016).*
  - There are several GnRH agonists available in varying doses and formulations. Depot formulations are generally preferred due to improved compliance *(Guaraldi et al 2016).*
  - GnRH agonists are generally considered safe and are well-tolerated *(Guaraldi et al 2016).*
- GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:
    - Lupron Depot-Ped (leuprolide), available as monthly or every 3 month intramuscular (IM) injections.
    - Synarel (nafarelin) intranasal spray, a short-acting spray that requires multiple inhalations daily.
      - Nafarelin is also indicated for the management of endometriosis.
      - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks.
      - Trelstar (triptorelin pamoate) IM injection, which was the first FDA-approved triptorelin formulation, is indicated for the palliative treatment of advanced prostate cancer. Prior to the FDA-approval of Triptodur, Trelstar monthly and every 3 month injections were used off-label to treat CPP *(Klein et al 2016)*.
  - The optimal time to discontinue a GnRH agonist has not been established, but retrospective analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes *(Carel and Léger 2008).*
- Zoladex (goserelin) 3.6 mg implant is a GnRH agonist that is indicated for the management of endometriosis and as an endometrial thinning agent prior to endometrial ablation.
  - Goserelin 3.6 mg implant carries additional indications for the management and palliative treatment of prostate cancer and the palliative treatment of breast cancer.
  - The goserelin implant is also available in a 10.8 mg dose, which is only indicated for the management and palliative treatment of prostate cancer.
- Lupron Depot 3.75 mg monthly and 11.25 mg every 3 month IM injections are indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms.
- Lupron Depot 3.75 mg concomitantly with iron therapy is indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a 1-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate.

- Experience with Lupron Depot in females has been limited to women 18 years of age and older.
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Lupaneta Pack (leuprolide acetate 3.75 mg depot suspension; norethindrone acetate 5 mg tablets)	-
Lupron Depot-Ped (leuprolide acetate for depot suspension) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25 mg, 30 mg (3-month)	-
Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (monthly) & 11.25 mg (3-month)	-
Supprelin LA (histrelin) 50 mg implant	-
Synarel (nafarelin) nasal spray	-
Triptodur (triptorelin) 22.5 mg extended-release suspension	-
Zoladex (goserelin) 3.6 mg implant	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) 3.6 mg implant
Treatment of children with CPP			✔	✔	✔	✔	
Management of endometriosis, including pain relief and reduction of endometriotic lesions		✔			✔		✔
Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding							✔
Initial management of the painful symptoms of endometriosis	✔						
Management of recurrence of endometriosis symptoms	✔	✔					
Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata		✔					

(*Prescribing information: Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 3.75 mg 2013, Lupron Depot 11.25 mg 2013, Supprelin LA 2017, Synarel 2017, Triptodur 2017, Zoladex [3.6 mg] 2016*)

- 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

CPP

- The choice of GnRH agonist formulation depends on patient and clinician preference. These preparations have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis (*Harrington and Palmert 2017)*.
  - In a multicenter trial with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse events (AEs) were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial *(Harrington and Palmert 2017, Rahhal et al 2009, Silverman et al 2015*).
  - A randomized controlled trial (RCT) with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups *(Fuld et al 2011).*
  - In a phase 3, randomized, open-label study (n = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses *(Lee et al 2012).*
  - Clinical trials with nafarelin demonstrated a reduction in the peak response of LH to GnRH stimulation from a pubertal response to a pre-pubertal response within 1 month of treatment. Additionally, breast development was arrested or regressed in 82% of girls, while genital development was arrested or regressed in 100% of boys *(Synarel Product Information 2017)*.
  - The efficacy of triptorelin 6-month injection was evaluated in an open-label, single-arm clinical trial in females and males with CPP, ages 2 to 9 (n = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients *(Klein et al 2016)*.

Endometriosis

- A Cochrane Review meta-analysis of 41 trials (n = 4935) in patients with endometriosis compared the safety and effectiveness of GnRH agonists to no treatment, placebo, danazol, intrauterine progestins, or other GnRH agonists (*Brown et al 2010*).
  - GnRH agonists were more effective than no treatment or placebo.
  - There was no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis.
  - There was a benefit in overall resolution for GnRH agonists compared with danazol.
  - There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel.
  - More AEs were reported in the GnRH agonist group.
  - No route of administration for GnRH agonists appeared to be superior to another.
- An RCT (n = 315) compared the efficacy of goserelin (3.6 mg every 28 days) to danazol 400 mg orally twice daily in females with endometriosis. Goserelin was found to be similar in efficacy and safety as compared to danazol. Both treatments significantly reduced mean subjective signs and symptoms scores during and after treatment *(Rock et al 1993).*
- A meta-analysis of 13 RCTs (n = 945) evaluated the effectiveness of GnRH agonists for endometriosis, with and without add-back therapy. Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid AEs that are caused by GnRH agonist-induced hormone suppression. The evidence suggested that add-back therapy was more effective for symptomatic relief than GnRH agonists alone, both immediately after treatment and at 6 months. Add-back therapy increased estrogen levels, but did not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia *(Wu et al 2014).*

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics: Evaluation and referral of children with signs of early puberty *(Kaplowitz and Bloch 2016)*
  - Treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant.
  - If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered.
  - Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

Endometriosis

- American College of Obstetrics and Gynecology (ACOG) Updates: Guideline on Diagnosis and Treatment of Endometriosis (*Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and GnRH agonists can be used for the initial treatment of pain in women with suspected endometriosis.
    - However, recurrence rates are high after the medication is discontinued. Empiric therapy with another suppressive medication is an option. For example, empiric therapy with a 3-month course of a GnRH agonist is appropriate if the initial treatment with an oral contraceptive or NSAID is unsuccessful.
  - In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptives can be used to treat recurrent pain.
    - Oral or depot medroxyprogesterone acetate is also an effective treatment option.
    - If none of the above therapies are successful, then progestins, GnRH agonists, and androgens may be used.
    - The use of Mirena (levonorgestrel-releasing intrauterine system) reduces pelvic pain associated with endometriosis, but AEs are common.
  - If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain.
    - Add-back regimens have been used in women undergoing long-term therapy; they may include progestins alone, low dose progestins, progestins plus bisphosphonates, or estrogens.

Uterine fibroids

- Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program: Management of Uterine Fibroids *(AHRQ 2017)*
  - GnRH agonists, mifepristone, ulipristal, and uterine artery embolism reduce fibroid size, and improve symptoms and quality of life. Myomectomy and hysterectomy also improve quality of life.
    - Moderate-strength evidence suggests that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms.
    - Low strength evidence suggests that fibroid-related quality of life improves with GnRH agonists (with and without add-back therapy).
  - For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years for 6 to 7% after medical treatment or myomectomy and 44% after urinary artery embolization (UAE). For older women, the chance was 9 to 19% after medical treatment or UAE and 0% after myomectomy.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.
- Lupaneta Pack carries additional contraindications, including undiagnosed uterine bleeding, breast feeding, known/suspected/history of breast or other hormone-sensitive cancers, thrombotic/thromboembolic disorders, and liver tumors/liver disease.

Warnings and Precautions

- An initial rise in gonadotropin and sex steroid levels may be seen during the first 2 to 4 weeks of therapy, due to the initial stimulatory effect of the drug. (leuprolide, histrelin, triptorelin)
- Psychiatric events have been reported in patients taking GnRH agonists. Symptoms including crying, irritability, anger, and aggression. (leuprolide, histrelin, nafarelin, triptorelin)
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system (CNS) anomalies or tumors, or concomitant medications that may be associated with convulsions. (leuprolide, histrelin, nafarelin, triptorelin)
- Loss of bone mineral density can occur with Lupaneta Pack, so its use is not recommended for more than two 6-month treatment courses.
- Endometrial cysts have been reported during the first 2 months of therapy. Many, but not all, occurred in women with polycystic ovarian disease. These cystic enlargements may resolve after 4 to 6 weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Key Adverse Effects
- The common AEs within this medication class (excluding histrelin) include hot flushes/sweats, headache, depression/emotional lability, acne, decreased libido, insomnia, and weight gain.
- Injection site pain was one of the most commonly reported AEs for leuprolide. Implant site reaction was reported in 51% of patients in clinical trials with histrelin.
- Infections such as bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection were observed with triptorelin.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lupaneta Pack (leuprolide/ norethindrone)	11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide every 3 months for up to 6 months and norethindrone daily for up to 6 months. Retreatment should be considered for up to another 6 months if endometriosis symptoms recur	Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on bone mineral density Bone mineral density should be assessed prior to retreatment
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg monthly or 11.25 mg every 3 months, alone or in combination with norethindrone acetate Uterine leiomyomata: 3.75 mg monthly or one 11.25 mg injection with concomitant iron therapy; 11.25 mg is indicated only for women for whom 3 months of hormonal suppression is deemed necessary	Endometriosis: The choice of leuprolide depot alone or with norethindrone acetate therapy for initial management of the signs and symptoms of endometriosis should be made by the health care provider in consultation with the patient, and should take into consideration the risks and benefits of the addition of norethindrone acetate to leuprolide depot alone. The recommended duration of treatment is 6 months. Uterine leiomyomata: The recommended duration of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				therapy is up to 3 months
Lupron Depot-Ped (leuprolide acetate depot) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25, 30 mg (3-month)	Powder for injection	IM	CPP: Monthly	
Supprelin LA (histrelin)	Implant	SC	CPP: Every 12 months	Implant injected in the inner aspect of the upper arm
Synarel (nafarelin)	Nasal spray	Intranasal	CPP: Twice daily (up to 3 times daily when a dose increase is required) Endometriosis: Twice daily	Sneezing during or immediately after treatment should be avoided, as this may impair drug absorption For the endometriosis indication, treatment should be started between days 2 and 4 of the menstrual cycle
Triptodur (triptorelin)	Injection	IM	CPP: Every 24 weeks	
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Every 28 days for a total of 6 months Endometrial thinning: Every 28 days for a total of 1 to 2 months	No adjustment necessary in renal or hepatic impairment For the endometriosis indication, data are limited to patients ≥ 18 years of age treated for 6 months. Retreatment is not recommended.

See the current prescribing information for full details

CONCLUSION

- CPP is characterized by the early onset of pubertal manifestations in girls and boys.
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (LH and FSH) secretion and finally suppression of the release of gonadal sex hormones,
- There are several FDA-approved GnRH agonists available in the form of implants, depot injections, and nasal spray. Depot formulations are generally preferred due to improved compliance.
- These GnRH agonists have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis.
- According to the American Academy of Pediatrics 2016 guidelines on the evaluation and referral of children with signs of early puberty, treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.
- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity.
- A Cochrane Review meta-analysis of 41 trials (n = 4935) in patients with endometriosis found no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis. However, a benefit in

overall resolution for GnRH agonists compared with danazol was observed. Additionally, there was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel. No route of administration for GnRH appeared to be superior to another.

- ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, nonsteroidal anti-inflammatory drugs (NSAIDs), and GnRH agonists for the initial treatment of pain in women with suspected endometriosis. GnRH agonists can be used empirically in case of recurrence of endometriosis.
- AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms and quality of life (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low strength-evidence).

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Nevada Medicaid
Hepatitis C Direct-acting Antivirals
Pharmacy Coverage Guideline

CRITERIA FOR COVERAGE/NONCOVERAGE

Initial Authorization:

Approval Length: 24 weeks

All of the following criteria must be met:

1. Diagnosis of hepatitis C
2. Genotype has been confirmed
3. Liver disease has been assessed
4. Prescriber certifies the shortest duration of treatment will be used based on the indication of the requested drug
5. Prescribed by or in consultation with one of the following:
    a. Hepatologist
    b. Gastrointestinal specialist
    c. Infectious disease specialist
    d. HIV specialist

Nevada Medicaid
Hepatitis C Direct-acting Antivirals
Pharmacy Coverage Guideline

CRITERIA FOR COVERAGE/NONCOVERAGE

Initial Authorization:

Approval Length: 24 weeks

All of the following criteria must be met:

1. Diagnosis of hepatitis C ~~–~~ As evidenced by detectable HCV RNA levels in the last 6 months
2. Genotype has been confirmed
3. Liver disease has been assessed
4. Prescriber certifies the shortest duration of treatment will be used based on the indication of the requested drug
5. Prescribed by or in consultation with one of the following:
    a. Hepatologist
    b. Gastrointestinal specialist
    c. Infectious disease specialist
    d. HIV specialist

~~We~~SilverSummit ~~Healthplan~~ would want to allow preference for our preferred product Mavyret. If they meet the FDA guidelines for Mavyret that is the only drug we would approve based on these guidelines above.

Mavyret is indicated for the treatment of:

- Patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A).
- Adult patients with genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Hep C PA Criteria

Anthem/Amerigroup

Place-holder for PA criteria

HEALTH PLAN OF NEVADA
A UnitedHealthcare Company

Clinical Pharmacy Program Guidelines for Hepatitis C Agents – Health Plan of Nevada Medicaid

Program	Prior Authorization
Medication	Daklinza® (daclatasvir), Epclusa (sofosbuvir/velpatasvir), Harvoni™ (ledipasvir/sofosbuvir), Mavyret™ (glecaprevir/pibrentasvir), Olysio® (simeprevir), Sovaldi® (sofosbuvir), Technivie™ (ombitasvir, paritaprevir, and ritonavir tablets), Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), Viekira XR™ (dasabuvir, ombitasvir, paritaprevir, and ritonavir extended-release tablets), Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir), Zepatier™ (elbasvir/grazoprevir)

1. Background:

Mavyret is indicated for the treatment of patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). Mavyret is also 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, but not both.

Daklinza (daclatasvir) is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with Sovaldi (sofosbuvir), with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection.

Epclusa is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and also adult patients with decompensated cirrhosis in combination with ribavirin.

Harvoni (ledipasvir/sofosbuvir) is indicated for the treatment of chronic hepatitis C (CHC) genotype 1, 4, 5, or 6 infection in adults and pediatric patients 12 years of age and older or weighing at least 35kg.

Olysio (simeprevir) is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or 4 infection as a component of a combination antiviral treatment regimen.

Sovaldi is a indicated for the treatment of adult patients with genotype 1, 2, 3, or 4 chronic HCV infection without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen and pediatric patients 12 years of age and older or weighing at least 35kg with genotype 2 or 3 chronic HCV without cirrhosis or with compensated cirrhosis in combination with ribavirin.

Technivie is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic HCV infection without cirrhosis or with compensated cirrhosis.

Viekira Pak and Viekira XR are indicated for the treatment of chronic HCV genotype 1a or 1b in patients without cirrhosis or with compensated cirrhosis.

Vosevi is indicated for the treatment of adult patients with chronic 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 or genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Zepatier is indicated for treatment of chronic HCV genotype 1 or 4 infection in adults. Zepatier is indicated for use with ribavirin in certain patient populations.

2. Coverage Criteria:

A. Chronic Hepatitis C

1. Diagnosis of chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection

-AND-

2. **One** of the following:

a. **All** of the following:

(1) The request is for Mavyret

-AND-

(2) The patient is without cirrhosis or has compensated cirrhosis (Child-Pugh A)

-AND-

(3) **One** of the following:

(a) **Both** of the following:

i. Patient is genotype 1, 2, 3, 4, 5, or 6

ii. Patient is treatment naïve

-OR-

(b) **All** of the following:

i. Patient is treatment-experienced

ii. Patient is genotype 1

iii. **One** of the following:

- Patient previously treated with an NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor
- Patient previously treated with an NS3/4 protease inhibitor without prior treatment with an NS5A inhibitor

-OR-

(c) **All** of the following:

i. Patient is treatment-experienced

ii. Patient is genotype 1, 2, 3, 4, 5, or 6

iii. Patient not previously treated with an HCV NS3/4A protease inhibitor or NS5A inhibitor

-AND-

(4) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Mavyret for Treatment Naïve Patients

HCV Genotype	**Treatment Duration**	
	No cirrhosis	Compensated cirrhosis^ (Child-Pugh A)
1, 2, 3, 4, 5, or 6	8 weeks	12 weeks

Mavyret for Treatment Experienced Patients

		Treatment Duration	
HCV Genotype	**Patients previously treated with a regimen**	**No cirrhosis**	**Compensated cirrhosis^ (Child-Pugh A)**

	containing:		
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	16 weeks

1. In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.

2. In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin.

3. PRS = prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

-OR-

b. **All** of the following:

(1) The request is for Daklinza

-AND-

(2) **One** of the following:

(a) Patient is genotype 1 or 3 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Daklinza therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below,

based on patient genotype and characteristics

	Patient Population	Treatment and Duration
Genotype 1	Without cirrhosis	Daklinza + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis^	
	Decompensated (Child-Pugh B or C) cirrhosis^	Daklinza + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	Daklinza + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis^	Daklinza + sofosbuvir + ribavirin for 12 weeks

-OR-

c. **All** of the following:

(1) The request is for Epclusa

-AND-

(2) **One** of the following:

(a) Patient is genotype 1, 2, 3, 4, 5, or 6 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Epclusa therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis^ (Child-Pugh A)	EPCLUSA for 12 weeks

Patients with decompensated cirrhosis^(Child-Pugh B and C)	EPCLUSA + ribavirin for 12 weeks

-OR-

d. **All** of the following:

(1) The request is for Harvoni

-AND-

(2) **One** of the following:

(a) Patient is genotype 1, 4, 5, or 6 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Harvoni therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Recommended adult treatment regimen and duration:

Genotype	Patient Population	Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	HARVONI 12 weeks*
	Treatment-experienced without cirrhosis	HARVONI 12 weeks
	Treatment-experienced with compensated cirrhosis^ (Child-Pugh A)	HARVONI 24 weeks
	Treatment-naïve and treatment-experienced with decompensated cirrhosis^ (Child-Pugh B or C)	HARVONI + ribavirin 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis, or	HARVONI + ribavirin 12 weeks

	with compensated cirrhosis^ (Child-Pugh A)	
Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	HARVONI 12 weeks

*HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL

Recommended treatment duration for pediatric patients 12 years of age and older or weighing at least 35kg:

	Pediatric patient population 12 years of age and older or weighing at least 35kg	**Regimen and Duration**
Genotype 1	Treatment naïve without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	HARVONI 12 weeks
	Treatment-experienced without cirrhosis	HARVONI 12 weeks
	Treatment-experienced with compensated cirrhosis^ (Child-Pugh A)	HARVONI 24 weeks
Genotype 4, 5, or 6	Treatment naïve and treatment experienced, without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	HARVONI 12 weeks

-OR-

e. **All** of the following:

(1) The request is for Olysio

-AND-

(2) **One** of the following:

(a) Patient is genotype 1 or 4 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Olysio therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Patient Population	Treatment Regimen	Duration
Genotype 1 without cirrhosis	OLYSIO + sofosbuvir	12 weeks
Genotype 1 with compensated cirrhosis^ (Child-Pugh A)	OLYSIO + sofosbuvir	24 weeks
Genotype 1 or 4 without cirrhosis or with compensated cirrhosis^ (Child-Pugh A), with or without HIV-1 co-infection	OLYSIO + Peg-IFN-alfa + RBV	12 weeks*
*Followed by 12 or 36 additional weeks of Peg-IFN-alfa + RBV depending on prior response status and presence of HIV-1 co-infection		

-OR-

f. **All** of the following:

(1) The request is for Sovaldi

-AND-

(2) **One** of the following:

(a) Patient is genotype 1, 2, 3, or 4 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Sovaldi therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Recommended Adult Treatment Regimen and Duration

	Adult Patient Population	Regimen and Duration
Genotype 1 or 4	Treatment naïve without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	SOVALDI + peginterferon alfa + ribavirin 12 weeks
Genotype 2	Treatment naïve and treatment experienced without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	SOVALDI + ribavirin 12 weeks
Genotype 3	Treatment naïve and treatment experienced without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	SOVALDI + ribavirin 24 weeks

SOVALDI in combination with ribavirin for 24 weeks can be considered for adult patients with genotype 1 infection who are interferon ineligible.
SOVALDI should be used in combination with ribavirin for treatment of HCV in adult patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first.

Recommended Treatment Regimen and Duration for Pediatric Patients 12 Years of Age and Older or Weighing at Least 35kg

	Pediatric Patient Population 12 Years of Age and Older or Weighing at Least 35kg	Regimen and Duration
Genotype 2	Treatment naïve and treatment experienced without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	SOVALDI + ribavirin 12 weeks
Genotype 3	Treatment naïve and treatment experienced	SOVALDI + ribavirin 24 weeks

	without cirrhosis or with compensated cirrhosis^ (Child-Pugh A)	

-OR-

g. **All** of the following:

(1) The request is for Technivie

-AND-

(2) **One** of the following:

(a) Patient is genotype 4 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Technivie therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis or with compensated cirrhosis^	TECHNIVIE + ribavirin*	12 weeks
*TECHNIVIE administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin		

-OR-

h. **All** of the following:

(1) The request is for Viekira Pak or Viekira XR

-AND-

(2) **One** of the following:

(a) Patient is genotype 1 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Viekira Pak or Viekira XR therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK/VIEKIRA XR + ribavirin	12 weeks
Genotype 1a, with compensated cirrhosis^	VIEKIRA PAK/VIEKIRA XR + ribavirin	24 weeks**
Genotype 1b, with or without compensated cirrhosis^	VIEKIRA PAK/VIEKIRA XR	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection
**VIEKIRA PAK/VIEKIRA XR administered with ribavirin for 12 weeks may be considered in some patients based on prior treatment history

-OR-

i. **All** of the following:

(1) The request is for Vosevi

-AND-

(2) The patient is without cirrhosis or has compensated cirrhosis (Child-Pugh A)

-AND-

(3) **One** of the following:

(a) **Both** of the following:

- Patient is genotype 1, 2, 3, 4, 5, or 6 and had virologic failure after completing previous treatment of at least 4 weeks' duration with an HCV regimen containing an NS5A inhibitor
- If patient is genotype 1 and has not been previously treated with an NS3/4A inhibitor, history of intolerance or contraindication to Mavyret

-OR-

(b) **All** of the following:

- Patient is genotype 1a or 3 and had virologic failure after completing previous treatment of at least 4 weeks' duration with an HCV regimen containing sofobuvir without an NS5A inhibitor
- If patient is genotype 1a and has been treated with or without an NS3/4A inhibitor, history of intolerance or contraindication to Mavyret
- If patient is genotype 3 and has not been treated with an NS3/4A inhibitor, history of intolerance or contraindication to Mavyret

-OR-

(c) Patient is currently on Vosevi therapy

-AND-

(4) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Genotype	Patients previously treated with an HCV regimen containing:	VOSEVI Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[1]	12 weeks
1a or 3	Sofosbuvir without an NS5A inhibitor[2]	12 weeks

1. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
2. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

-OR-

j. **All** of the following:

(1) The request is for Zepatier

-AND-

(2) One of the following:

(a) Patient is genotype 1 or 4 and has a history of intolerance or contraindication to Mavyret

-OR-

(b) Patient is currently on Zepatier therapy

-AND-

(3) The requested regimen is an approvable regimen, as outlined below, based on patient genotype and characteristics

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: treatment naïve or PegIFN/RBV experienced* without baseline NS5A polymorphisms+	ZEPATIER	12 weeks
Genotype 1a: treatment naïve or PegIFN/RBV experienced* with baseline NS5A polymorphisms+	ZEPATIER + ribavirin	16 weeks
Genotype 1b: treatment naïve or PegIFN/RBV experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI experienced++	ZEPATIER + ribavirin	12 weeks
Genotype 4: treatment naïve	ZEPATIER	12 weeks

Genotype 4: PegIFN/RBV experienced*	ZEPATIER + ribavirin	16 weeks

*Peginterferon alfa + ribavirin
+Polymorphisms at amino acid positions 28, 30, 31, or 93
++Peginterferon alfa + ribavirin + HCV NS3/4 A protease inhibitor

^ For requests of duration of therapy extended due to cirrhosis, submission of medical records (e.g.: chart notes, laboratory values) documenting stage 4 hepatic fibrosis including ONE of the following is required:

(1) Liver biopsy confirming a METAVIR score of F4, or alternative scoring equivalent

-OR-

(2) Transient elastography (Fibroscan) score greater than or equal to 12.5 kPa

-OR-

(3) FibroTest (FibroSURE) score of greater than or equal to 0.75

-OR-

(4) APRI score greater than 2.0

-OR-

(5) Radiological imaging consistent with cirrhosis (e.g., evidence of portal hypertension)

-OR-

(6) Physical findings or clinical evidence consistent with cirrhosis as attested by the prescribing physician

Comparison of Scoring Systems for Histological Stage (Fibrosis)

METAVIR	Batts-Ludwig	Knodell	Ishak
0	0	0	0
1	1	1	1
1	1	1	2
2	2	--	3
3	3	3	4
4	4	4	5
4	4	4	6

UnitedHealthcare Pharmacy – Community and State Preferred Products						
	Genotype					
	1	**2**	**3**	**4**	**5**	**6**
Daklinza						
Epclusa						
Harvoni						
Mavyret	**X**	**X**	**X**	**X**	**X**	**X**
Olysio						
Solvadi						
Technivie						
Viekira						
Vosevi						
Zepatier						

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4. Mavyret [package insert]. North Chicago, IL: AbbVie, Inc.; August 2017.
5. Olysio [package insert]. Titusville, NJ: Janssen Therapeutics; May 2017.
6. Sovaldi [package insert]. Foster City, CA: Gilead Sciences, Inc.; April 2017.
7. Technivie [package insert]. North Chicago, IL: AbbVie, Inc.; March 2017.
8. Viekira Pak [package insert]. North Chicago, IL: AbbVie, Inc.; March 2017.
9. Viekira XR [package insert]. North Chicago, IL: AbbVie, Inc.; March 2017.

10. Vosevi [package insert]. Foster City, CA: Gilead Sciences, Inc.; July 2017.
11. Zepatier [package insert]. Whitehouse Station, NJ: Merck & Co.; February 2017.

Program	Prior Authorization – Hepatitis C Agents
Change Control	
Date	Change
1/2018	New policy hepatitis C policy created to incorporate all direct acting antiviral agents. Mavyret will be the preferred product for all genotypes starting 1/1/18.

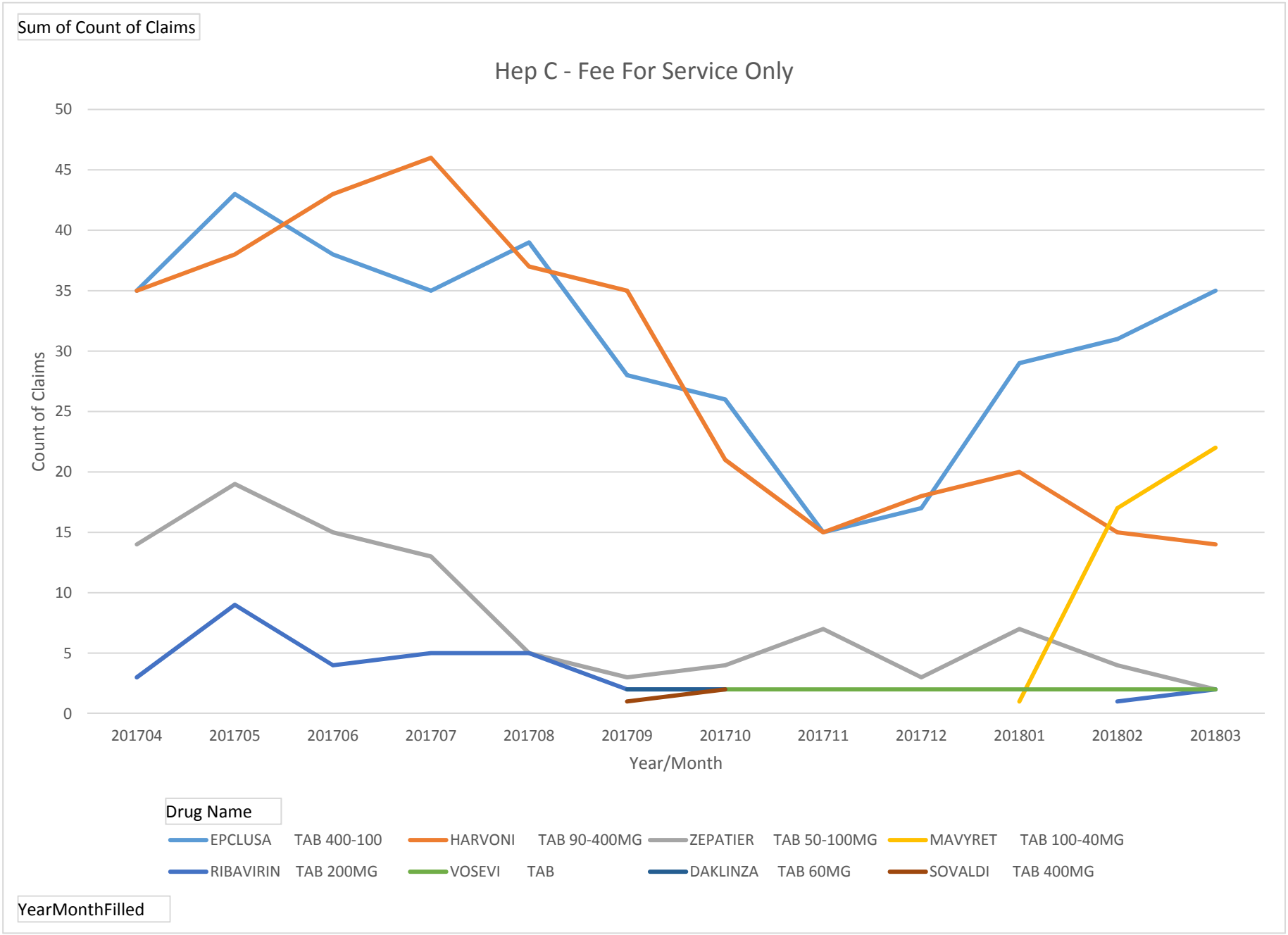
Hepatitis C Treatment

April 1, 2017 - March 31, 2018

Fee For Service Medicaid

Year Month Filled	Drug Name	Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201704	DAKLINZA TAB 60MG	3	3	42	42	$ 30,422.76
201704	EPCLUSA TAB 400-100	23	35	602	602	$ 490,674.54
201704	HARVONI TAB 90-400MG	22	35	520	520	$ 536,801.66
201704	RIBAVIRIN TAB 200MG	3	3	84	448	$ 322.66
201704	SOVALDI TAB 400MG	1	1	14	14	$ 13,664.37
201704	ZEPATIER TAB 50-100MG	9	14	252	252	$ 163,942.38
201705	EPCLUSA TAB 400-100	29	43	812	812	$ 647,868.84
201705	HARVONI TAB 90-400MG	24	38	700	700	$ 733,095.08
201705	RIBAVIRIN TAB 200MG	6	9	196	1008	$ 1,391.11
201705	ZEPATIER TAB 50-100MG	12	19	364	364	$ 218,586.76
201706	EPCLUSA TAB 400-100	26	38	753	756	$ 623,845.06
201706	HARVONI TAB 90-400MG	27	43	742	742	$ 778,940.65
201706	RIBAVIRIN TAB 200MG	4	4	112	504	$ 756.06
201706	ZEPATIER TAB 50-100MG	10	15	308	308	$ 162,615.57
201707	EPCLUSA TAB 400-100	24	35	624	630	$ 491,921.20
201707	HARVONI TAB 90-400MG	28	46	826	826	$ 840,020.57
201707	RIBAVIRIN TAB 200MG	4	5	121	586	$ 790.69
201707	ZEPATIER TAB 50-100MG	9	13	218	238	$ 97,785.42
201708	EPCLUSA TAB 400-100	23	39	694	686	$ 587,892.52
201708	HARVONI TAB 90-400MG	24	37	658	658	$ 626,968.46
201708	RIBAVIRIN TAB 200MG	4	5	123	604	$ 936.66
201708	ZEPATIER TAB 50-100MG	5	5	92	112	$ 35,555.22
201709	DAKLINZA TAB 60MG	2	2	42	42	$ 10,224.07
201709	EPCLUSA TAB 400-100	20	28	462	462	$ 396,687.98
201709	HARVONI TAB 90-400MG	21	35	658	658	$ 666,264.98
201709	RIBAVIRIN TAB 200MG	2	2	58	288	$ 442.71
201709	SOVALDI TAB 400MG	1	1	14	14	$ 14,010.17
201709	ZEPATIER TAB 50-100MG	3	3	84	84	$ 17,776.22
201710	DAKLINZA TAB 60MG	1	2	42	42	$ 30,650.94
201710	EPCLUSA TAB 400-100	18	26	518	518	$ 422,446.82
201710	HARVONI TAB 90-400MG	13	21	364	364	$ 398,958.63
201710	RIBAVIRIN TAB 200MG	2	2	58	288	$ 442.71
201710	SOVALDI TAB 400MG	1	2	42	42	$ 42,020.34
201710	VOSEVI TAB	1	2	42	42	$ 37,400.34
201710	ZEPATIER TAB 50-100MG	4	4	98	98	$ 8,896.90
201711	EPCLUSA TAB 400-100	11	15	294	294	$ 255,339.72
201711	HARVONI TAB 90-400MG	12	15	364	364	$ 305,694.23
201711	VOSEVI TAB	2	2	56	56	$ 49,860.34
201711	ZEPATIER TAB 50-100MG	5	7	140	140	$ 53,334.22
201712	EPCLUSA TAB 400-100	12	17	392	392	$ 316,359.76
201712	HARVONI TAB 90-400MG	12	18	350	350	$ 322,610.00
201712	VOSEVI TAB	2	2	42	42	$ 37,400.34

201712	ZEPATIER TAB 50-100MG	3	3	84	84	$ 53,306.46
201801	EPCLUSA TAB 400-100	24	29	700	700	$ 560,211.47
201801	HARVONI TAB 90-400MG	16	20	434	434	$ 322,610.93
201801	MAVYRET TAB 100-40MG	1	1	28	84	$ 866.55
201801	VOSEVI TAB	2	2	56	56	$ 49,860.34
201801	ZEPATIER TAB 50-100MG	5	7	154	154	$ 79,974.96
201802	EPCLUSA TAB 400-100	28	31	784	784	$ 681,968.55
201802	HARVONI TAB 90-400MG	11	15	322	322	$ 353,300.99
201802	MAVYRET TAB 100-40MG	17	17	476	1428	$ 212,229.27
201802	RIBAVIRIN TAB 200MG	1	1	28	112	$ 149.79
201802	VOSEVI TAB	2	2	56	56	$ 49,860.34
201802	ZEPATIER TAB 50-100MG	4	4	98	98	$ 62,195.96
201803	EPCLUSA TAB 400-100	29	35	924	924	$ 779,378.10
201803	HARVONI TAB 90-400MG	9	14	336	336	$ 368,861.02
201803	MAVYRET TAB 100-40MG	20	22	616	1848	$ 290,623.74
201803	RIBAVIRIN TAB 200MG	2	2	56	224	$ 228.56
201803	SOVALDI TAB 400MG	1	1	28	28	$ 28,010.17
201803	VOSEVI TAB	2	2	56	56	$ 49,860.34
201803	ZEPATIER TAB 50-100MG	2	2	56	56	$ 35,537.64


Sum of Count of Claims
Hep C - Fee For Service Only
Count of Claims
50
45
40
35
30
25
20
15
10
5
0
201704
201705
201706
201707
201708
201709
201710
201711
201712
201801
201802
201803
Year/Month
Drug Name
EPCLUSA TAB 400-100
HARVONI TAB 90-400MG
ZEPATIER TAB 50-100MG
MAVYRET TAB 100-40MG
RIBAVIRIN TAB 200MG
VOSEVI TAB
DAKLINZA TAB 60MG
SOVALDI TAB 400MG
YearMonthFilled

Hep C Utilization

8/1/17 - 3/31/18

SilverSummit

Row Labels	Count of Member ID	Sum of Days Supply	Sum of Metric Qty
Epclusa	**8**	**224**	**224**
9/22/2017	1	28	28
10/16/2017	1	28	28
11/7/2017	1	28	28
11/15/2017	1	28	28
12/11/2017	1	28	28
1/8/2018	1	28	28
2/22/2018	1	28	28
3/19/2018	1	28	28
Mavyret	**12**	**336**	**1008**
11/7/2017	1	28	84
12/5/2017	1	28	84
1/16/2018	1	28	84
1/18/2018	1	28	84
2/9/2018	2	56	168
2/13/2018	1	28	84
3/8/2018	2	56	168
3/12/2018	1	28	84
3/15/2018	1	28	84
3/27/2018	1	28	84
Zepatier	**8**	**224**	**224**
8/22/2017	1	28	28
10/2/2017	1	28	28
10/12/2017	1	28	28
10/24/2017	1	28	28
11/6/2017	1	28	28
11/22/2017	1	28	28
11/29/2017	1	28	28
1/4/2018	1	28	28
Grand Total	**28**	**784**	**1456**

Hep C Utilization

Amerigroup

March 1, 2017 - February 28, 2018

Drug	Daklinza			Epclusa			Harvoni		
Month	claim #	mbr #	amount paid	claim #	mbr #	amount paid	claim #	mbr #	amount paid
March	2	1	30,240.00	10	8	167,462.40	20	14	529,200.00
April	1	1	20,160.00	9	7	191,385.60	9	8	226,800.00
May				7	6	155,500.80	4	3	75,600.00
June				4	3	71,769.60	5	3	105,840.00
July				1	1	23,923.20	4	3	75,600.00
August	2	1	30,240.00	8	5	119,616.00	6	4	105,840.00
September				10	9	179,424.00	3	3	90,720.00
October				11	9	215,308.80	2	2	45,360.00
November				15	11	275,116.80	4	3	60,480.00
December				9	6	131,577.60	5	3	120,960.00
Jan-18				8	5	155,500.80	2	2	60,480.00
Feb-18				5	4	83,731.20	1	1	30,240.00
Grand tota	**5**	**3**	**$80,640.00**	**97**	**74**	**$1,770,316.80**	**65**	**49**	**$1,527,120.00**

Drug	Mavyret			Sovaldi			Vosevi		
Month	claim #	mbr #	amount paid	claim #	mbr #	amount paid	claim #	mbr #	amount paid
March				3	2	67,200.00			
April				2	2	53,760.00			
May				1	1	26,880.00			
June				1	1	26,880.00			
July									
August				2	1	40,320.00	1	1	25,120.47
September							1	1	23,923.20
October							1	1	23,923.20
November									
December	1	1	13,116.54						
Jan-18	1	1	13,034.17						
Feb-18	1	1	12,672.00				1	1	23,923.20
Grand total	**3**	**3**	**$38,822.71**	**9**	**7**	**$215,040.00**	**4**	**4**	**$96,890.07**

Drug	Zepatier		
Month	claim #	mbr #	amount paid
March	3	1	34,944.00
April	4	3	61,152.00
May	15	10	148,512.00
June	32	20	375,648.00
July	20	17	270,816.00
August	33	25	454,272.00
Septembe	31	24	376,327.08
October	32	24	419,941.56
November	29	21	358,789.56
December	27	19	331,968.00
Jan-18	29	18	393,120.00
Feb-18	20	16	305,760.00
Grand tota	**275**	**198**	**$3,531,250.20**

Hep C PA Approval

Amerigroup

March 1, 2017 - February 28, 2018

Month	Approved	Denied	Grand Tota	**Approved %**	**Denied %**
March	12	14	**26**	46.15%	53.85%
April	9	15	**24**	37.50%	62.50%
May	19	17	**36**	52.78%	47.22%
June	25	22	**47**	53.19%	46.81%
July	17	13	**30**	56.67%	43.33%
August	16	16	**32**	50.00%	50.00%
September	23	15	**38**	60.53%	39.47%
October	16	11	**27**	59.26%	40.74%
November	16	16	**32**	50.00%	50.00%
December	13	16	**29**	44.83%	55.17%
Jan-18	85	107	**192**	44.27%	55.73%
Feb-18	25	58	**83**	30.12%	69.88%
Grand total	276	320	**596**	**46.31%**	**53.69%**

Health Plan of Nevada

Hepatitis C Utilization

March 1, 2017 - February 28, 2018

Year/Month Filled/Paid	Drug Name	Count of Members	Count of Claims	Sum of Qty
2017/03	RIBASPHERE CAP 200MG	3	3	448
2017/03	HARVONI TAB 90-400MG	2	2	56
2017/03	ZEPATIER TAB 50-100MG	38	40	1,120
2017/03	SOVALDI TAB 400MG	1	1	28
2017/03	MODERIBA TAB 200MG	1	1	140
2017/03	RIBASPHERE TAB 200MG	1	1	140
2017/03	EPCLUSA TAB 400-100	20	21	588
2017/04	RIBASPHERE CAP 200MG	4	4	588
2017/04	ZEPATIER TAB 50-100MG	41	43	1,204
2017/04	MODERIBA TAB 200MG	1	1	140
2017/04	RIBASPHERE TAB 200MG	1	1	140
2017/04	SOVALDI TAB 400MG	1	1	28
2017/04	EPCLUSA TAB 400-100	21	23	644
2017/04	HARVONI TAB 90-400MG	2	2	56
2017/04	RIBAVIRIN TAB 200MG	1	1	168
2017/05	EPCLUSA TAB 400-100	26	34	952
2017/05	RIBASPHERE CAP 200MG	4	6	924
2017/05	SOVALDI TAB 400MG	1	1	28
2017/05	RIBASPHERE TAB 200MG	1	1	140
2017/05	RIBAVIRIN TAB 200MG	1	2	336
2017/05	ZEPATIER TAB 50-100MG	39	43	1,204
2017/05	HARVONI TAB 90-400MG	1	1	28
2017/06	RIBASPHERE TAB 200MG	1	1	140
2017/06	RIBASPHERE CAP 200MG	1	1	112
2017/06	RIBAVIRIN TAB 200MG	2	2	308
2017/06	ZEPATIER TAB 50-100MG	41	42	1,176
2017/06	EPCLUSA TAB 400-100	25	25	700
2017/07	EPCLUSA TAB 400-100	15	16	448
2017/07	ZEPATIER TAB 50-100MG	33	34	952
2017/07	RIBAVIRIN TAB 200MG	3	3	476
2017/07	RIBASPHERE TAB 200MG	1	1	140
2017/07	RIBASPHERE CAP 200MG	1	2	224
2017/08	ZEPATIER TAB 50-100MG	33	36	1,008
2017/08	RIBAVIRIN TAB 200MG	4	4	560
2017/08	HARVONI TAB 90-400MG	1	1	28
2017/08	EPCLUSA TAB 400-100	15	17	476
2017/09	HARVONI TAB 90-400MG	1	1	28
2017/09	EPCLUSA TAB 400-100	14	14	392

2017/09	ZEPATIER TAB 50-100MG	25	25	700
2017/09	RIBAVIRIN TAB 200MG	2	2	280
2017/10	RIBASPHERE CAP 200MG	1	1	28
2017/10	EPCLUSA TAB 400-100	10	12	336
2017/10	MAVYRET TAB 100-40MG	1	1	84
2017/10	RIBAVIRIN TAB 200MG	5	7	784
2017/10	ZEPATIER TAB 50-100MG	31	33	924
2017/11	RIBASPHERE CAP 200MG	2	2	168
2017/11	MAVYRET TAB 100-40MG	1	2	168
2017/11	ZEPATIER TAB 50-100MG	37	39	1,092
2017/11	RIBAVIRIN TAB 200MG	2	2	196
2017/11	RIBAPAK PAK 1200/DAY	1	1	56
2017/11	EPCLUSA TAB 400-100	17	19	532
2017/11	HARVONI TAB 90-400MG	1	1	28
2017/12	ZEPATIER TAB 50-100MG	40	44	1,232
2017/12	RIBASPHERE CAP 200MG	2	2	168
2017/12	EPCLUSA TAB 400-100	18	21	588
2017/12	RIBAVIRIN TAB 200MG	3	4	420
2017/12	HARVONI TAB 90-400MG	2	3	84
2017/12	VOSEVI TAB	1	1	28
2017/12	RIBAPAK PAK 1200/DAY	1	2	112
2018/01	ZEPATIER TAB 50-100MG	31	38	1,064
2018/01	RIBASPHERE CAP 200MG	1	1	140
2018/01	EPCLUSA TAB 400-100	16	19	532
2018/01	VOSEVI TAB	2	2	56
2018/01	MAVYRET TAB 100-40MG	11	11	924
2018/01	HARVONI TAB 90-400MG	3	3	84
2018/01	RIBAVIRIN TAB 200MG	3	3	364
2018/01	RIBAPAK PAK 1200/DAY	1	1	56
2018/02	EPCLUSA TAB 400-100	9	10	280
2018/02	HARVONI TAB 90-400MG	1	1	28
2018/02	MAVYRET TAB 100-40MG	35	36	3,024
2018/02	ZEPATIER TAB 50-100MG	14	14	392
2018/02	RIBAVIRIN TAB 200MG	3	3	364
2018/02	VOSEVI TAB	2	2	56

Health Plan of Nevada

Hepatitis C Prior Authorizations

October 1, 2017 - December 31, 2017

HPN Hep C PA Data			
Month/Year	Approved	Denied*	Grand Total
03/2017	32	2	34
04/2017	30	3	33
05/2017	23	2	25
06/2017	20	2	22
07/2017	16	1	17
08/2017	21	6	27
09/2017	14	4	18
10/2017	27	5	32
11/2017	25	3	28
12/2017	21	6	27
01/2018	24	10	34
02/2018	23	4	27
Grand Total	276	48	324

*Prior authorization requests can be denied for many reasons. Common reasons in Hepatitis C are: requests for additional information are not responded to, therapy duration exceeds the FDA and guideline recommended durations, non-formulary medications are being requested, requests are for unsupported retreatment regimens or off-label use.

**Data has been scrubbed to remove duplicate denials and denials that were subsequently approved to create a report that details Hep C therapy approvals.

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

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 *(Gane et al 2017, 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*: • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily *Duration of therapy:* • 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). *Duration of therapy:* • 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). *Duration of therapy:* • 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. • 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. • Not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher simeprevir exposures. *Duration of therapy:* • 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. *Duration of therapy:* • 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). *Duration of therapy:* • 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). *Duration of therapy:* • 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). *Duration of therapy:* • 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. • Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). *Duration of therapy:* • 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. • 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. *Duration of therapy:* • 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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- The following chart includes the suggested criteria from OptumRx then each of the MCO's criteria where **differences** are seen.

	OptumRx	Anthem	HPN	SSH
High Dollar Claims	Single Point of Sale Claims that exceed **$10,000** will require PA	**$5000** limit	$10,000 limit in claims system	No current criteria
Initial Auth Criteria	1. One of the following: a. Medication is being prescribed for an FDA-approved indication, OR b. One of the following: i. Diagnosis is supported as a use of AHFS DI ii. Diagnosis is supported in the FDA Uses/Non-FDA Uses section in DRUGDEX Evaluation with a Strength of Recommendation rating of IIb or better (see DRUGDEX Strength of Recommendation table in Background section) iii. Both of the following: 1. Diagnosis is listed in the FDA Uses/Non-FDA Uses section in DRUGDEX Evaluation and carries a Strength of Recommendation of III or Class Indeterminant (see DRUGDEX Strength of Recommendation table in Background section) 2. Efficacy is rated as "Effective" or "Evidence Favors Efficacy" (see DRUGDEX Efficacy Rating and Prior Authorization Approval Status table in Background section) iv. Diagnosis is supported in any other section in DRUGDEX v. The use is supported by clinical research in two articles from major peer reviewed medical journals that present data supporting the proposed off-label use or uses as generally safe and effective unless there is clear and convincing contradictory evidence presented in a major peer-reviewed journal 2. One of the following: a. The dosage quantity/duration of the medication is reasonably safe and effective based on information contained in the FDA approved labeling, peer-reviewed medical literature, or accepted standards of	1. $5000 limit under Rx benefit (excluding any specialty drug or medial injectable); any drug over that amount requires medical necessity review	FDA-approved indication	Agrees with OptumRx suggested criteria

	medical practice, OR b. The dosage/quantity/duration of the medication is reasonably safe and effective based on one of the following compendia: • American Hospital Formulary Service (AHFS) • Thomson Reuters (Healthcare) Micromedex/DrugDex (not Drug Points) • Elsevier Gold Standard's Clinical Pharmacology • National Comprehensive Cancer Network Drugs and Biologics			
Approval Duration	Approval length: 12 months for initial			

Nevada Medicaid
High Dollar Claim
Pharmacy Coverage Guideline

CRITERIA FOR COVERAGE/NONCOVERAGE

Single Point of Sale claims that exceed $10,000 will require prior authorization. Other PA criteria, if exist, will replace this criteria.

Approval Length: 12 months

The requested medication must meet the following criteria:

1. One of the following:
    a. Medication is being prescribed for an FDA-approved indication

    OR

    b. One of the following:
        i. Diagnosis is supported as a use of AHFS DI
        ii. Diagnosis is supported in the FDA Uses/Non-FDA Uses section in DRUGDEX Evaluation with a Strength of Recommendation rating of IIb or better (see DRUGDEX Strength of Recommendation table in Background section)
        iii. Both of the following:
            1. Diagnosis is listed in the FDA Uses/Non-FDA Uses section in DRUGDEX Evaluation and carries a Strength of Recommendation of III or Class Indeterminant (see DRUGDEX Strength of Recommendation table in Background section)
            2. Efficacy is rated as "Effective" or "Evidence Favors Efficacy" (see DRUGDEX Efficacy Rating and Prior Authorization Approval Status table in Background section)
        iv. Diagnosis is supported in any other section in DRUGDEX
        v. The use is supported by clinical research in two articles from major peer reviewed medical journals that present data supporting the proposed off-label use or uses as generally safe and effective unless there is clear and convincing contradictory evidence presented in a major peer-reviewed medical journal

AND

2. One of the following:
    a. The dosage quantity/duration of the medication is reasonably safe and effective based on information contained in the FDA approved labeling, peer-reviewed medical literature, or accepted standards of medical practice

    OR

    b. The dosage/quantity/duration of the medication is reasonably safe and effective based on one of the following compendia:
        - American Hospital Formulary Service (AHFS) Compendium
        - Thomson Reuters (Healthcare) Micromedex/DrugDex (not Drug Points) Compendium
        - Elsevier Gold Standard's Clinical Pharmacology Compendium
        - National Comprehensive Cancer Network Drugs and Biologics Compendium

The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.[i]

The National Organization for Rare Disorders (NORD) estimates 30 million Americans suffer from 7,000 rare diseases.

Orphan drugs sales are expected to double between 2016 and 2022 to hit $209 billion. Orphan drugs will be 21.4% of worldwide prescription sales by 2022. The average cost per patient per year for an orphan drug was $140,443 in 2016 compared to $27,756 for non-orphan.[ii]

Recent Orphan Drug Approvals

Drug	Disease	Annual Cost
Spinraza	Spinal Muscular Atrophy	$750,000[1]
Brineura	CNL2 Disease	$700,000
Exondys 51	Duchene Muscular Dystrophy	$300,000 plus
Radicava	ALS	$150,000

Proposal:

Orphan Drugs for discussion with state policy makers

- Orphan drug for currently treated orphan disease (e.g. hemophilia) – no change in current rates unless disproportionate number of members in population
- Orphan drug for previously untreated disease and cost exceeds $100,000 per year
    - Kick payment or carve-out for first 2 years to establish utilization patterns
- Orphan drug for currently treated disease but new treatment is 50% higher than current treatments, exceeds $100,000 per year and given a breakthrough designation by the FDA
    - Kick payment or carve-out for first 2 years to establish utilization patterns

High Cost non-orphan drugs

- New treatment for condition impacting more than 1% of the population with a cost of more than $50,000 per year (double the average cost for non-orphan drugs)
    - Kick payment or carve-out for first 2 years to establish utilization patterns

Process

Envolve Pharmacy Solutions will monitor the drug pipeline and provide a monthly report on status of pipeline for orphan drugs or anticipated high cost non-orphan drugs based on projections from analysts, breakthrough status, or other information.

[1] $750,00 first year of treatment and $350,000 subsequent years

Upon approval of the medication Envolve and Centene will estimate potential patient population based on medical diagnosis or other drug history. Envolve will provide an update to Centene finance and plan leadership on potential financial impact for the new medication.

[i] FDA.org
[ii] EvaluatePharma Orphan Drug Report 2017

High Dollar Claims
March 1, 2017 - February 28, 2018
Fee for Service Medicaid
Breakdown of Products

Drug Class and Drug Name	Amt Paid	Number of Claims
ADRENALS	**$ 247,505.62**	**20**
EMFLAZA	$ 247,505.62	20
AMINOGLYCOSIDE ANTIBIOTIC	**$ 40,586.80**	**4**
TOBI PODHALER	$ 40,586.80	4
AMMONIA DETOXICANTS	**$ 773,209.04**	**32**
BUPHENYL	$ 145,759.64	12
RAVICTI	$ 627,449.40	20
ANTHELMINTICS	**$ 29,840.56**	**2**
ALBENZA	$ 29,840.56	2
ANTICONVULSANTS, MISCELLA	**$ 735,447.72**	**58**
SABRIL	$ 723,823.66	57
VIGABATRIN	$ 11,624.06	1
ANTINEOPLASTIC AGENTS	**$ 5,659,536.78**	**428**
AFINITOR	$ 1,618,159.91	112
AFINITOR DISPERZ	$ 192,706.92	5
ALECENSA	$ 39,971.34	3
BOSULIF	$ 148,533.47	11
CALQUENCE	$ 28,148.34	2
ERIVEDGE	$ 69,279.60	6
IBRANCE	$ 948,959.16	86
ICLUSIG	$ 82,855.85	5
IMATINIB MESYLATE	$ 50,782.71	4
IMBRUVICA	$ 66,678.54	6
JAKAFI	$ 11,557.17	1
MEKINIST	$ 10,488.40	1
NEXAVAR	$ 65,958.40	4
OPDIVO	$ 86,616.46	8
POMALYST	$ 161,116.10	12
REVLIMID	$ 730,467.09	48
SPRYCEL	$ 571,324.97	48
STIVARGA	$ 14,891.66	1
TAGRISSO	$ 114,458.80	8
TASIGNA	$ 222,216.85	19
VENCLEXTA	$ 10,334.74	1
VOTRIENT	$ 177,445.90	16
XALKORI	$ 59,869.54	4
XTANDI	$ 156,439.68	15
ZELBORAF	$ 20,275.18	2
ANTISENSE OLIGONUCLEOTIDE	**$ 6,187,800.03**	**59**
EXONDYS 51	$ 2,187,505.10	30
SPINRAZA	$ 4,000,294.93	29

ANTITOXINS AND IMMUNE GLO	**$**	**977,316.88**	**49**
GAMMAGARD LIQUID	$	118,138.50	10
GAMMAPLEX	$	104,262.43	4
PRIVIGEN	$	754,915.95	35
ANXIOLYTICS,SEDATIVES,AND	**$**	**66,740.25**	**5**
HETLIOZ	$	66,740.25	5
BENZODIAZEPINES (ANXIOLYT	**$**	**10,628.47**	**1**
DIAZEPAM RECTAL GEL	$	10,628.47	1
BIGUANIDES	**$**	**293,333.69**	**17**
GLUMETZA	$	239,374.21	13
METFORMIN HCL ER	$	53,959.48	4
CENTRAL NERVOUS SYSTEM AG	**$**	**155,523.24**	**13**
XYREM	$	155,523.24	13
CYSTIC FIBROSIS (CFTR) CO	**$**	**1,550,778.15**	**75**
ORKAMBI	$	1,550,778.15	75
CYSTIC FIBROSIS (CFTR) PO	**$**	**167,344.10**	**7**
KALYDECO	$	167,344.10	7
DISEASE-MODIFYING ANTIRHE	**$**	**709,419.23**	**53**
CIMZIA STARTER KIT	$	44,732.91	4
ENBREL	$	51,676.28	4
ENBREL SURECLICK	$	93,017.95	7
HUMIRA	$	79,871.94	6
HUMIRA PEN	$	265,735.76	18
HUMIRA PEN-CROHNS DISEASE	$	143,828.01	11
REMICADE	$	30,556.38	3
ENZYMES	**$**	**1,507,266.41**	**25**
ELAPRASE	$	1,104,035.90	22
STRENSIQ	$	403,230.51	3
GI DRUGS, MISCELLANEOUS	**$**	**239,559.67**	**5**
ENTYVIO	$	10,851.61	1
GATTEX	$	211,597.89	3
OCALIVA	$	17,110.17	1
GONADOTROPINS	**$**	**47,644.09**	**2**
SUPPRELIN LA	$	47,644.09	2
HCV POLYMERASE INHIBITOR	**$**	**6,441,587.89**	**387**
EPCLUSA	$	6,024,572.66	368
SOVALDI	$	192,633.53	9
VOSEVI	$	224,381.70	10
HCV PROTEASE INHIBITOR AN	**$**	**211,362.72**	**16**
MAVYRET	$	211,362.72	16
HCV REPLICATION COMPLEX I	**$**	**6,862,223.03**	**367**
DAKLINZA	$	162,542.01	13
HARVONI	$	6,123,575.83	322
ZEPATIER	$	576,105.19	32
HEAVY METAL ANTAGONISTS	**$**	**1,085,593.82**	**64**
EXJADE	$	52,951.51	3
FERRIPROX	$	178,498.94	9

JADENU	$	820,048.63	50
JADENU SPRINKLE	$	12,817.77	1
SYPRINE	$	21,276.97	1
HEMATOPOIETIC AGENTS	**$**	**156,380.01**	**11**
NEULASTA	$	88,747.62	8
PROMACTA	$	67,632.39	3
HEMOSTATICS	**$**	**38,838,340.27**	**279**
ADVATE	$	16,338,872.46	62
ADYNOVATE	$	744,741.83	19
ALPHANATE/VON WILLEBRAND	$	977,169.86	18
ALPROLIX	$	663,914.52	16
AMICAR	$	22,874.25	2
BENEFIX	$	234,008.81	15
CORIFACT	$	167,600.34	12
ELOCTATE	$	396,069.91	23
HELIXATE FS	$	303,705.93	4
HUMATE-P	$	122,116.70	8
IDELVION	$	36,248.57	1
KOGENATE FS	$	5,437,859.52	36
NOVOEIGHT	$	2,685,055.86	12
NOVOSEVEN RT	$	9,744,223.74	22
NUWIQ	$	371,151.34	10
WILATE	$	315,425.19	7
XYNTHA SOLOFUSE	$	277,301.44	12
IMMUNOMODULATORY AGENTS	**$**	**1,401,511.82**	**49**
ACTIMMUNE	$	771,326.16	16
AUBAGIO	$	378,403.56	21
COPAXONE	$	47,902.73	3
GILENYA	$	62,338.60	3
GLATIRAMER ACETATE	$	15,109.92	1
OCREVUS	$	65,020.34	2
TECFIDERA	$	61,410.51	3
INSULINS	**$**	**185,766.66**	**12**
HUMALOG MIX 50/50 KWIKPEN	$	12,714.05	1
HUMULIN R U-500 (CONCENTR	$	96,036.71	6
HUMULIN R U-500 KWIKPEN	$	10,520.84	1
NOVOLOG	$	35,724.76	1
TRESIBA FLEXTOUCH	$	30,770.30	3
MUCOLYTIC AGENTS	**$**	**30,139.06**	**2**
PULMOZYME	$	30,139.06	2
NON-SEL.ALPHA-ADRENERGIC	**$**	**19,448.55**	**1**
PHENOXYBENZAMINE HYDROCHL	$	19,448.55	1
OPIATE AGONISTS	**$**	**717,989.46**	**45**
SUBSYS	$	717,989.46	45
OTHER MISCELLANEOUS THERA	**$**	**1,318,933.25**	**32**
CERDELGA	$	311,436.21	13
KUVAN	$	189,930.51	3

ORFADIN	$	817,566.53	16
OXAZOLIDINONE ANTIBIOTICS	**$**	**20,073.57**	**1**
SIVEXTRO	$	20,073.57	1
PHOSPHODIESTERASE TYPE 5	**$**	**10,553.62**	**1**
ADCIRCA	$	10,553.62	1
PITUITARY	**$**	**2,727,845.31**	**43**
H.P. ACTHAR	$	2,727,845.31	43
RESPIRATORY TRACT AGENTS,	**$**	**510,857.30**	**38**
GLASSIA	$	130,750.04	12
PROLASTIN-C	$	135,747.40	12
ZEMAIRA	$	244,359.86	14
SKIN AND MUCOUS MEMBRANE	**$**	**602,810.61**	**34**
COSENTYX	$	35,418.50	2
COSENTYX SENSOREADY PEN	$	131,516.22	7
SANTYL	$	21,593.30	2
STELARA	$	354,772.89	19
TALTZ	$	49,341.01	3
TREMFYA	$	10,168.69	1
SOMATOSTATIN AGONISTS	**$**	**42,512.34**	**2**
SOMATULINE DEPOT	$	42,512.34	2
SOMATOTROPIN AGONISTS	**$**	**351,773.06**	**28**
GENOTROPIN	$	339,887.39	27
NORDITROPIN FLEXPRO	$	11,885.67	1
VASODILATING AGENTS (RESP	**$**	**1,618,538.48**	**95**
LETAIRIS	$	27,774.00	1
REMODULIN	$	459,982.89	17
TRACLEER	$	214,458.57	21
TYVASO REFILL	$	181,077.04	12
TYVASO STARTER	$	16,760.17	1
UPTRAVI	$	718,485.81	43
VESICULAR MONOAMINE TRANS	**$**	**312,181.55**	**17**
INGREZZA	$	84,481.36	8
XENAZINE	$	227,700.19	9
Grand Total	**$**	**82,865,903.11**	**2379**

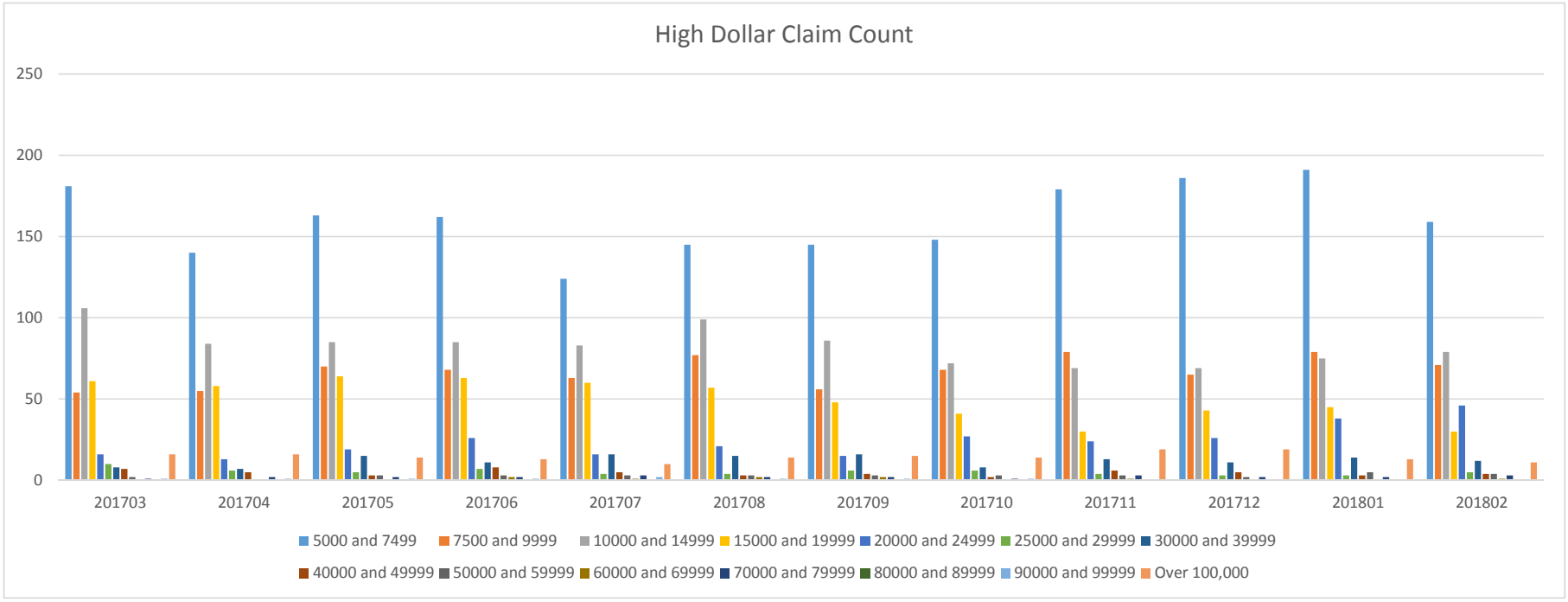
High Dollar Claims

March 1, 2017 - February 28, 2018

Fee for Service Medicaid

Pharmacy Paid Amount

Year Month	1000 and 2499	2500 and 4999	5000 and 7499	7500 and 9999	10000 and 14999	15000 and 19999	20000 and 24999	25000 and 29999	30000 and 39999	40000 and 49999	50000 and 59999	60000 and 69999	70000 and 79999	80000 and 89999	90000 and 99999	Over 100,000	Over 10,000
201703	2807	648	181	54	106	61	16	10	8	7	2	0	1	0	1	16	**228**
201704	2056	471	140	55	84	58	13	6	7	5	0	0	2	0	1	16	**192**
201705	2337	530	163	70	85	64	19	5	15	3	3	0	2	0	1	14	**211**
201706	2539	504	162	68	85	63	26	7	11	8	3	2	2	0	1	13	**221**
201707	2262	491	124	63	83	60	16	4	16	5	3	1	3	0	2	10	**203**
201708	2553	564	145	77	99	57	21	4	15	3	3	2	2	0	1	14	**221**
201709	2485	492	145	56	86	48	15	6	16	4	3	2	2	0	1	15	**198**
201710	2432	553	148	68	72	41	27	6	8	2	3	0	1	0	1	14	**175**
201711	2569	572	179	79	69	30	24	4	13	6	3	1	3	0	0	19	**172**
201712	2587	579	186	65	69	43	26	3	11	5	2	0	2	0	0	19	**180**
201801	2710	649	191	79	75	45	38	3	14	3	5	0	2	0	0	13	**198**
201802	2363	593	159	71	79	30	46	5	12	4	4	1	3	0	0	11	**195**



High Cost Claim Utilization

SilveSummit

Place-holder for utilization.

High Cost Claim Utilization

Anthem/Amerigroup

Place-holder for utilization.

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
ABACA/LAMIVU TAB 600-300	118	124	3720
ABACAVIR TAB 300MG	23	23	1368
ACTEMRA INJ 162/0.9	47	51	124.2
ADCIRCA TAB 20MG	43	45	2130
ADEMPAS TAB 1.5MG	1	1	90
ADEMPAS TAB 1MG	1	1	90
ADEMPAS TAB 2.5MG	28	30	2535
ADEMPAS TAB 2MG	1	1	90
AFINITOR TAB 10MG	9	12	196
AFINITOR TAB 5MG	4	4	112
AFINITOR TAB 7.5MG	4	4	112
ALECENSA CAP 150MG	4	4	960
ALKERAN TAB 2MG	1	1	50
AMPYRA TAB 10MG	46	48	2880
ARANESP INJ 100MCG	15	16	20
ARANESP INJ 25MCG	4	5	5
ARANESP INJ 40MCG	1	2	0.8
ARANESP INJ 500MCG	1	1	1
ATAZANAVIR CAP 200MG	1	1	60
ATAZANAVIR CAP 300MG	27	28	840
ATRIPLA TAB	407	418	12540
AUBAGIO TAB 14MG	103	111	3108
AUBAGIO TAB 7MG	7	7	196
AVONEX PEN KIT 30MCG	33	38	38
AVONEX PREFL KIT 30MCG	19	20	20
BENLYSTA INJ 200MG/ML	6	6	24
BETASERON INJ 0.3MG	1	1	14
BETHKIS NEB 300/4ML	6	6	1344
BICALUTAMIDE TAB 50MG	78	81	2440
BOSULIF TAB 100MG	2	2	120
BOSULIF TAB 500MG	4	5	150
CAPECITABINE TAB 150MG	17	24	1504
CAPECITABINE TAB 500MG	105	130	11024
CAYSTON INH 75MG	11	11	924
CHOR GONADOT INJ 10000UNT	2	2	5
CIMZIA KIT STARTER	19	19	57
CIMZIA PREFL KIT 200MG/ML	172	183	185
COMPLERA TAB	390	407	12240
COPAXONE INJ 20MG/ML	9	10	300
COPAXONE INJ 40MG/ML	103	109	1308
COSENTYX INJ 150MG/ML	7	7	13
COSENTYX INJ 300DOSE	14	14	34
COSENTYX PEN INJ 150MG/ML	19	22	31

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
COSENTYX PEN INJ 300DOSE	37	39	110
CYCLOPHOSPH CAP 50MG	21	21	1382
CYCLOSPORINE CAP 100MG	9	10	1050
CYCLOSPORINE CAP 100MG MD	11	11	900
CYCLOSPORINE CAP 25MG	27	29	4650
CYCLOSPORINE CAP 25MG MOD	11	11	1800
CYCLOSPORINE CAP 50MG MOD	2	2	120
CYCLOSPORINE SOL MODIFIED	3	4	200
DESCOVY TAB 200/25	480	499	14956
DIDANOSINE CAP 400MG	1	1	30
DUPIXENT INJ 300/2ML	48	52	208
EDURANT TAB 25MG	30	31	930
EFAVIRENZ TAB 600MG	3	3	90
EMFLAZA TAB 18MG	8	8	240
EMFLAZA TAB 30MG	6	6	330
EMFLAZA TAB 36MG	1	2	60
EMFLAZA TAB 6MG	8	8	240
EMTRIVA CAP 200MG	27	28	840
ENBREL INJ 25/0.5ML	26	28	67.32
ENBREL INJ 25MG	24	24	148
ENBREL INJ 50MG/ML	60	61	274.4
ENBREL SRCLK INJ 50MG/ML	248	271	1168.16
ENTECAVIR TAB 0.5MG	85	89	2384
ENTECAVIR TAB 1MG	17	17	510
EPCLUSA TAB 400-100	206	231	6468
EPOGEN INJ 10000/ML	4	4	8
ERIVEDGE CAP 150MG	8	8	240
ESBRIET CAP 267MG	6	6	1494
ESBRIET TAB 801MG	7	7	630
EVOTAZ TAB 300-150	36	36	1080
EXJADE TAB 500MG	1	1	60
FIRAZYR INJ 30MG/3ML	8	9	171
FORTEO SOL 600/2.4	27	31	74.4
FOSAMPRENAVI TAB 700MG	1	1	120
GAMMAKED INJ 5GM/50ML	1	1	250
GAMMAPLEX INJ 5%	1	1	400
GENGRAF CAP 100MG	7	7	420
GENOTROPIN INJ 0.2MG	1	1	28
GENOTROPIN INJ 0.6MG	5	5	70
GENOTROPIN INJ 0.8MG	5	5	70
GENVOYA TAB	1234	1294	38790
GILENYA CAP 0.5MG	37	38	1140
GILOTRIF TAB 30MG	12	13	390

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
GILOTRIF TAB 40MG	4	4	120
GLATIRAMER INJ 40MG/ML	18	18	216
GRANIX INJ 480/0.8	1	1	4
H.P. ACTHAR INJ 80UNIT	3	3	35
HARVONI TAB 90-400MG	14	15	420
HUMIRA KIT 40MG/0.8	139	154	320
HUMIRA PEN INJ 40MG/0.8	1286	1401	2934
HUMIRA PEN INJ CROHNS	27	27	162
HUMIRA PEN INJ PSORIASI	31	31	124
HYDROXYUREA CAP 500MG	172	178	10009
HYDROXYUREA POW	7	7	955
IBRANCE CAP 100MG	7	8	168
IBRANCE CAP 125MG	30	34	714
IBRANCE CAP 75MG	2	2	42
ICLUSIG TAB 45MG	2	2	60
IDELVION SOL 1000UNIT	1	2	4144
IDELVION SOL 2000UNIT	1	2	8046
IMATINIB MES TAB 100MG	1	1	30
IMATINIB MES TAB 400MG	49	51	1545
IMBRUVICA CAP 140MG	17	18	1740
INTELENCE TAB 200MG	32	33	1964
INTRON A INJ 10MU	5	6	17
ISENTRESS TAB 400MG	320	344	20047
ISENTRESS HD TAB 600MG	3	3	180
JADENU TAB 180MG	11	12	1080
JADENU TAB 360MG	12	12	1260
JADENU TAB 90MG	6	6	1380
JAKAFI TAB 10MG	3	3	180
JAKAFI TAB 5MG	3	3	180
KALETRA TAB 200-50MG	20	22	2640
KALYDECO PAK 50MG	8	8	448
KALYDECO TAB 150MG	8	9	504
KEVZARA INJ 200/1.14	11	11	25.08
KINERET INJ	18	22	534.66
KUVAN POW 500MG	8	8	480
KUVAN TAB 100MG	12	13	7800
LAMIVUD/ZIDO TAB 150-300	4	4	234
LAMIVUDINE SOL 10MG/ML	13	13	2118
LAMIVUDINE TAB 150MG	6	6	180
LAMIVUDINE TAB 300MG	7	7	210
LENVIMA CAP 14 MG	1	1	60
LETAIRIS TAB 10MG	62	67	2010
LETAIRIS TAB 5MG	6	6	196

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
LEXIVA TAB 700MG	7	7	840
LONSURF TAB 20-8.19	2	2	120
LOPIN/RITON SOL 80-20/ML	11	11	1760
LUPR DEP-PED INJ 11.25MG	1	1	1
LUPR DEP-PED INJ 3M 30MG	1	1	1
LUPRON DEPOT INJ 11.25MG	1	1	1
LUPRON DEPOT INJ 3.75MG	2	2	2
MAKENA INJ 250MG/ML	119	127	511
MAVYRET TAB 100-40MG	48	50	4200
MEKINIST TAB 2MG	14	14	420
MERCAPTOPUR TAB 50MG	145	159	8270
MODERIBA TAB 200MG	2	2	280
MYCOPHENOLAT CAP 250MG	159	173	28390
MYCOPHENOLAT SUS 200MG/ML	24	25	4000
MYCOPHENOLAT TAB 500MG	469	495	53624
MYCOPHENOLIC TAB 180MG DR	24	25	1500
MYCOPHENOLIC TAB 360MG DR	82	90	8752
MYLERAN TAB 2MG	7	8	480
MYTESI TAB 125MG	2	2	120
NATPARA INJ 50MCG	16	17	34
NATPARA INJ 75MCG	10	11	22
NEULASTA INJ 6MG/0.6M	8	9	9.6
NEUPOGEN INJ 300/0.5	5	5	25
NEUPOGEN INJ 300MCG	7	8	88
NEUPOGEN INJ 480/0.8	2	2	8
NEUPOGEN INJ 480MCG	1	1	1.6
NEVIRAPINE SUS 50MG/5ML	1	1	240
NEVIRAPINE TAB 400MG ER	35	36	1080
NEXAVAR TAB 200MG	26	28	1995
NORDITROPIN INJ 10/1.5ML	8	8	78
NORDITROPIN INJ 15/1.5ML	38	44	225
NORDITROPIN INJ 30/3ML	5	6	54
NORTHERA CAP 100MG	1	1	90
NORVIR CAP 100MG	5	5	150
NORVIR SOL 80MG/ML	2	2	80
NORVIR TAB 100MG	445	460	14550
NUCALA INJ 100MG	8	8	8
NUTROPIN AQ INJ 10MG/2ML	119	133	974
NUTROPIN AQ INJ 20MG/2ML	106	122	690
NUTROPIN AQ INJ NUSPIN 5	13	18	70
OCALIVA TAB 5MG	7	8	240
OCTREOTIDE INJ 1000MCG	1	1	10
OCTREOTIDE INJ 100MCG	7	7	720

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
OCTREOTIDE INJ 200MCG	1	1	210
OCTREOTIDE INJ 50MCG/ML	3	4	360
ODEFSEY TAB	328	345	10350
OFEV CAP 100MG	5	5	300
OPSUMIT TAB 10MG	47	49	1470
ORENCIA INJ 125MG/ML	15	16	64
ORENCIA CLCK INJ 125MG/ML	24	24	96
ORENITRAM TAB 0.125MG	2	2	87
ORENITRAM TAB 0.25MG	7	7	693
ORENITRAM TAB 1MG	1	1	27
ORFADIN CAP 20MG	2	2	240
ORKAMBI TAB 200-125	11	11	1232
OTEZLA TAB 10/20/30	6	6	330
OTEZLA TAB 30MG	106	110	6570
PLEGRIDY INJ PEN	4	4	4
PLEGRIDY PEN INJ STARTER	1	1	1
POMALYST CAP 4MG	3	4	84
PRALUENT INJ 75MG/ML	25	27	54
PREZCOBIX TAB 800-150	490	514	15412
PREZISTA SUS 100MG/ML	7	7	1400
PREZISTA TAB 600MG	14	15	900
PREZISTA TAB 800MG	328	339	10304
PROGRAF CAP 0.5MG	1	1	30
PROGRAF CAP 1MG	7	7	1050
PROMACTA TAB 12.5MG	1	1	30
PROMACTA TAB 25MG	1	1	30
PROMACTA TAB 50MG	30	32	942
PROMACTA TAB 75MG	1	1	30
PULMOZYME SOL 1MG/ML	62	64	5505
REBIF INJ 44/0.5	22	22	132
REBIF REBIDO INJ 22/0.5	9	9	54
REBIF REBIDO INJ 44/0.5	43	46	276
REPATHA SURE INJ 140MG/ML	3	4	8
REVLIMID CAP 10MG	24	25	602
REVLIMID CAP 15MG	5	7	196
REVLIMID CAP 25MG	32	39	644
REVLIMID CAP 5MG	3	3	84
REYATAZ CAP 150MG	1	1	60
REYATAZ CAP 200MG	10	10	600
REYATAZ CAP 300MG	171	177	5290
RIBAPAK PAK 1200/DAY	3	4	224
RIBASPHERE CAP 200MG	19	22	2800
RIBASPHERE TAB 200MG	5	5	700

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
RIBAVIRIN TAB 200MG	29	33	4256
SABRIL POW 500MG	4	4	240
SAMSCA TAB 15MG	5	5	20
SELZENTRY TAB 150MG	10	10	600
SELZENTRY TAB 300MG	8	8	480
SEROSTIM INJ 4MG	2	2	28
SILDENAFIL TAB 20MG	78	81	8922
SIMPONI INJ 100MG/ML	28	32	33
SIMPONI INJ 50/0.5ML	25	30	15
SIROLIMUS TAB 0.5MG	10	10	960
SIROLIMUS TAB 1MG	3	3	210
SOVALDI TAB 400MG	3	3	84
SPRYCEL TAB 100MG	15	17	510
SPRYCEL TAB 140MG	16	19	540
SPRYCEL TAB 20MG	12	14	1260
SPRYCEL TAB 50MG	1	1	30
SPRYCEL TAB 70MG	12	12	360
STELARA INJ 45MG/0.5	42	45	22.5
STELARA INJ 90MG/ML	38	39	39
STIVARGA TAB 40MG	5	5	420
STRENSIQ INJ 40MG/ML	4	4	48
STRIBILD TAB	653	679	20370
SUCRAID SOL 8500/ML	2	2	708
SUSTIVA TAB 600MG	25	27	810
SUTENT CAP 50MG	7	7	196
SYNAGIS INJ 100MG/ML	2	2	2
TABLOID TAB 40MG	2	2	46
TACROLIMUS CAP 0.5MG	173	188	18690
TACROLIMUS CAP 1MG	300	320	53617
TACROLIMUS CAP 5MG	11	14	616
TAFINLAR CAP 75MG	14	14	1620
TAGRISSO TAB 40MG	4	4	120
TAGRISSO TAB 80MG	6	6	180
TALTZ INJ 80MG/ML	8	9	13
TARCEVA TAB 100MG	11	12	360
TARCEVA TAB 150MG	16	17	510
TASIGNA CAP 150MG	58	61	6188
TASIGNA CAP 200MG	6	7	560
TECFIDERA CAP 120MG	6	6	336
TECFIDERA CAP 240MG	313	325	19500
TECFIDERA MIS STARTER	13	13	780
TEMOZOLOMIDE CAP 100MG	7	7	35
TEMOZOLOMIDE CAP 140MG	10	12	135

Health Plan of Nevada

Specialty Drug List Utilization

March 1, 2017 - February 28, 2018

Drug Name	Sum Members	Sum of Claims	Qty
TEMOZOLOMIDE CAP 180MG	3	3	30
TEMOZOLOMIDE CAP 250MG	1	1	5
TENOFOVIR TAB 300MG	64	68	2014
TETRABENAZIN TAB 12.5MG	5	7	390
THYROGEN INJ 1.1MG	1	1	2
TIVICAY TAB 50MG	974	1017	31422
TOBRAMYCIN NEB 300/5ML	1	1	280
TREMFYA INJ 100MG/ML	2	2	2
TRETINOIN CAP 10MG	7	7	1142
TRIPTODUR SUS 22.5MG	1	1	1
TRIUMEQ TAB	1261	1316	39383
TRUVADA TAB 100-150	3	4	120
TRUVADA TAB 200-300	1907	2003	59763
TYBOST TAB 150MG	1	1	30
UPTRAVI TAB 1000MCG	11	11	660
UPTRAVI TAB 1400MCG	11	11	660
UPTRAVI TAB 200/800	1	1	200
UPTRAVI TAB 200MCG	1	1	140
VENCLEXTA TAB 100MG	2	2	240
VENCLEXTA TAB START PK	1	1	42
VIGABATRIN PAK 500MG	4	4	240
VIREAD TAB 300MG	268	280	8143
VIVITROL INJ 380MG	16	17	17
VOSEVI TAB	5	5	140
VOTRIENT TAB 200MG	6	7	480
XALKORI CAP 250MG	4	4	240
XELJANZ TAB 5MG	30	31	1860
XELJANZ XR TAB 11MG	27	27	810
XERMELO TAB 250MG	8	9	756
XTANDI CAP 40MG	9	9	1080
XYREM SOL 500MG/ML	18	19	9360
ZARXIO INJ 300/0.5	7	8	48
ZARXIO INJ 480/0.8	11	12	83.2
ZEJULA CAP 100MG	2	2	180
ZEPATIER TAB 50-100MG	403	431	12068
ZIAGEN SOL 20MG/ML	1	1	720
ZIDOVUDINE SYP 50MG/5ML	24	25	5855
ZORTRESS TAB 0.25MG	3	3	540
ZYTIGA TAB 250MG	4	4	480
Grand Total	**18088**	**19146**	**751394.92**

Total Acetaminophen Dose per Month
April 1, 2017 - March 31, 2018
Fee for Service Medicaid Only

Enc Member ID	Year	Month	Monthly GM of APAP
19			104,220
	2017		104,220
		4	3,750
		5	11,250
		6	15,000
		7	18,750
		8	18,750
		9	11,250
		10	15,000
		11	10,470
181			75,600
	2017		57,600
		5	7,200
		6	7,200
		7	7,200
		8	7,200
		9	3,600
		10	7,200
		11	7,200
		12	10,800
	2018		18,000
		1	7,200
		2	3,600
		3	7,200
163			39,000
	2017		27,300
		6	3,900
		7	3,900
		8	3,900
		9	3,900
		10	3,900
		11	3,900
		12	3,900
	2018		11,700
		1	3,900
		2	3,900
		3	3,900
113			38,350
	2017		38,350
		5	3,900
		6	7,800
		7	3,900

113	2017	8	7,800
		10	11,050
		11	3,900
146			33,540
	2017		29,640
		5	3,900
		7	3,900
		8	3,900
		9	7,800
		10	3,900
		11	3,120
		12	3,120
	2018		3,900
		1	3,900
128			31,200
	2017		31,200
		5	3,900
		6	3,900
		7	3,900
		8	3,900
		9	3,900
		10	3,900
		11	3,900
		12	3,900
159			30,600
	2017		30,600
		8	3,750
		9	7,500
		10	11,550
		11	3,900
		12	3,900
107			30,550
	2017		30,550
		5	3,250
		6	7,800
		7	3,900
		9	7,800
		10	3,900
		11	3,900
172			28,205
	2017		24,549
		5	4,179
		8	3,656
		9	4,179
		10	4,179
		11	4,179
		12	4,179

172	2018		3,656
		1	3,656
7			27,300
	2017		27,300
		5	3,900
		6	3,900
		7	3,900
		8	3,900
		9	3,900
		10	3,900
		11	3,900
123			27,300
	2017		27,300
		6	3,900
		7	3,900
		8	3,900
		9	3,900
		10	3,900
		11	3,900
		12	3,900
Grand Total			**465,865**

Total Acetaminophen Dose per Month

April 1, 2017 - March 31, 2018

Fee for Service Medicaid Only

Member 19

APAP claim detail 2018 04

Month Year	DrugLabelName	Days Supply	Sum of Qty
Apr-17	BUT/APAP/CAF CAP CODEINE	5	30
Apr-17	APAP/CODEINE TAB 300-60MG	5	30
Apr-17	BUT/APAP/CAF CAP CODEINE	5	30
Apr-17	APAP/CODEINE TAB 300-60MG	5	30
Apr-17	BUT/APAP/CAF CAP CODEINE	5	30
Apr-17	APAP/CODEINE TAB 300-60MG	5	30
Apr-17	BUT/APAP/CAF CAP CODEINE	5	30
Apr-17	BUT/APAP/CAF CAP CODEINE	5	30
Apr-17	APAP/CODEINE TAB 300-60MG	5	30
May-17	BUT/APAP/CAF CAP CODEINE	5	30
May-17	APAP/CODEINE TAB 300-60MG	5	30
May-17	APAP/CODEINE TAB 300-60MG	5	30
May-17	BUT/APAP/CAF CAP CODEINE	5	30
May-17	BUT/APAP/CAF CAP CODEINE	5	30
May-17	APAP/CODEINE TAB 300-60MG	5	30
Jun-17	APAP/CODEINE TAB 300-60MG	5	30
Jun-17	BUT/APAP/CAF CAP CODEINE	5	30
Jun-17	APAP/CODEINE TAB 300-60MG	5	30
Jun-17	BUT/APAP/CAF CAP CODEINE	5	30
Jun-17	APAP/CODEINE TAB 300-60MG	5	30
Jun-17	BUT/APAP/CAF CAP CODEINE	5	30
Jun-17	BUT/APAP/CAF CAP CODEINE	5	30
Jun-17	APAP/CODEINE TAB 300-60MG	5	30
Jul-17	APAP/CODEINE TAB 300-60MG	5	30
Jul-17	BUT/APAP/CAF CAP CODEINE	5	30
Jul-17	APAP/CODEINE TAB 300-60MG	5	30
Jul-17	BUT/APAP/CAF CAP CODEINE	5	30
Jul-17	APAP/CODEINE TAB 300-60MG	5	30
Jul-17	BUT/APAP/CAF CAP CODEINE	5	30
Jul-17	BUT/APAP/CAF CAP CODEINE	5	30
Jul-17	APAP/CODEINE TAB 300-60MG	5	30
Jul-17	BUT/APAP/CAF CAP CODEINE	5	30
Jul-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	BUT/APAP/CAF CAP CODEINE	5	30
Aug-17	BUT/APAP/CAF CAP CODEINE	5	30
Aug-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	BUT/APAP/CAF CAP CODEINE	5	30
Aug-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	BUT/APAP/CAF CAP CODEINE	5	30

Aug-17	APAP/CODEINE TAB 300-60MG	5	30
Aug-17	BUT/APAP/CAF CAP CODEINE	5	30
Sep-17	BUT/APAP/CAF CAP CODEINE	5	30
Sep-17	APAP/CODEINE TAB 300-60MG	5	30
Sep-17	BUT/APAP/CAF CAP CODEINE	5	30
Sep-17	APAP/CODEINE TAB 300-60MG	5	30
Sep-17	APAP/CODEINE TAB 300-60MG	5	30
Sep-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	APAP/CODEINE TAB 300-60MG	5	30
Oct-17	APAP/CODEINE TAB 300-60MG	5	30
Oct-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	APAP/CODEINE TAB 300-60MG	5	30
Oct-17	APAP/CODEINE TAB 300-60MG	5	30
Oct-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	BUT/APAP/CAF CAP CODEINE	5	30
Oct-17	APAP/CODEINE TAB 300-60MG	5	30
Nov-17	BUT/APAP/CAF CAP CODEINE	5	26
Nov-17	APAP/CODEINE TAB 300-60MG	5	30
Nov-17	APAP/CODEINE TAB 300-60MG	5	30
Nov-17	BUT/APAP/CAF CAP CODEINE	5	26
Nov-17	APAP/CODEINE TAB 300-60MG	5	30
Nov-17	BUT/APAP/CAF CAP CODEINE	5	26
Nov-17	BUT/APAP/CAF CAP CODEINE	2	12
Nov-17	APAP/CODEINE TAB 300-60MG	5	30
Nov-17	BUT/APAP/CAF CAP CODEINE	5	30
Dec-17	APAP/CODEINE TAB 300-60MG	5	30
Dec-17	BUT/APAP/CAF CAP CODEINE	5	30
Dec-17	APAP/CODEINE TAB 300-60MG	5	30
Dec-17	BUT/APAP/CAF CAP CODEINE	5	30
Dec-17	APAP/CODEINE TAB 300-60MG	5	30
Dec-17	BUT/APAP/CAF CAP CODEINE	5	30
Dec-17	APAP/CODEINE TAB 300-60MG	5	30
Dec-17	BUT/APAP/CAF CAP CODEINE	5	30
Dec-17	APAP/CODEINE TAB 300-60MG	5	30
Dec-17	BUT/APAP/CAF CAP CODEINE	5	30
Jan-18	BUT/APAP/CAF CAP CODEINE	5	30
Jan-18	BUT/APAP/CAF CAP CODEINE	15	30
Jan-18	APAP/CODEINE TAB 300-30MG	7	12
Jan-18	APAP/CODEINE TAB 300-30MG	7	12
Jan-18	BUT/APAP/CAF CAP CODEINE	15	30
Feb-18	APAP/CODEINE TAB 300-30MG	7	12
Feb-18	BUT/APAP/CAF CAP CODEINE	15	30
Feb-18	APAP/CODEINE TAB 300-30MG	7	12
Feb-18	APAP/CODEINE TAB 300-30MG	7	12
Feb-18	APAP/CODEINE TAB 300-30MG	7	30

Feb-18	BUT/APAP/CAF CAP CODEINE	15	30
Mar-18	APAP/CODEINE TAB 300-30MG	7	30
Mar-18	APAP/CODEINE TAB 300-30MG	15	30
Mar-18	BUT/APAP/CAF CAP CODEINE	15	30

Total Acetaminophen Dose per Month

April 1, 2017 - March 31, 2018

Fee for Service Medicaid Only

Member 181

APAP claim detail 2018 04

Fill Date	DrugLabelName	Days Supply	Sum of Qty
Apr-17	APAP/CODEINE TAB 300-60MG	18	180
Apr-17	APAP/CODEINE TAB 300-60MG	18	180
May-17	APAP/CODEINE TAB 300-60MG	15	180
May-17	APAP/CODEINE TAB 300-60MG	15	180
Jun-17	APAP/CODEINE TAB 300-60MG	15	180
Jun-17	APAP/CODEINE TAB 300-60MG	15	180
Jul-17	APAP/CODEINE TAB 300-60MG	15	180
Jul-17	APAP/CODEINE TAB 300-60MG	15	180
Aug-17	APAP/CODEINE TAB 300-60MG	15	180
Aug-17	APAP/CODEINE TAB 300-60MG	15	180
Sep-17	APAP/CODEINE TAB 300-60MG	15	180
Oct-17	APAP/CODEINE TAB 300-60MG	15	180
Oct-17	APAP/CODEINE TAB 300-60MG	15	180
Nov-17	APAP/CODEINE TAB 300-60MG	15	180
Nov-17	APAP/CODEINE TAB 300-60MG	15	180
Dec-17	APAP/CODEINE TAB 300-60MG	15	180
Dec-17	APAP/CODEINE TAB 300-60MG	15	180
Dec-17	APAP/CODEINE TAB 300-60MG	15	180
Jan-18	APAP/CODEINE TAB 300-60MG	15	180
Jan-18	APAP/CODEINE TAB 300-60MG	15	180
Feb-18	APAP/CODEINE TAB 300-60MG	15	180
Mar-18	APAP/CODEINE TAB 300-60MG	15	180
Mar-18	APAP/CODEINE TAB 300-60MG	15	180

Acetaminophen Utilization

July 1, 2017 - March 31, 2018

SilverSummit Health Plan

Unique Identifier	FILLED MONTH	DRUG_DESCRIPTION	DAYS SUPPLY	METRIC QTY	APAP PER DAY	TOTAL APAP DAY
012401	2017-07	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
022001	2017-09	OXYCOD/APAP TAB 5-325MG	4	45	3656.25	3250
	2017-11	HYDROCO/APAP TAB 5-325MG	3	25	2708.333333	3250
	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
033301	2017-09	OXYCOD/APAP TAB 5-325MG	1	10	3250	3250
065701	2017-09	HYDROCO/APAP TAB 5-325MG	1	10	3250	3250
084401	2017-12	HYDROCO/APAP TAB 5-325MG	4	47	3818.75	3818.75
259201	2017-09	HYDROCO/APAP TAB 5-325MG	6	60	3250	3250
622901	2017-10	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
974901	2018-02	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
975301	2017-08	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
977401	2017-10	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
368401	2017-11	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
544301	2017-08	HYDROCO/APAP TAB 5-325MG	2	14	2275	3006.25
	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3006.25
	2018-01	HYDROCO/APAP TAB 5-325MG	3	30	3250	3006.25
550701	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
553401	2017-09	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
554301	2017-10	OXYCOD/APAP TAB 5-325MG	1	10	3250	3250
562701	2017-08	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
		OXYCOD/APAP TAB 5-325MG	4	40	3250	3250
603401	2017-08	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
648101	2017-10	HYDROCO/APAP TAB 7.5-325	3	30	3250	3250
651001	2017-08	HYDROCO/APAP TAB 5-325MG	4	40	3250	3250
030701	2017-10	PAIN & FEVER TAB 500MG	15	120	4000	4000
		PAIN & FEVER TAB 500MG	15	120	4000	4000
	2017-11	PAIN & FEVER TAB 500MG	15	120	4000	4000
		PAIN & FEVER TAB 500MG	15	120	4000	4000
450001	2017-12	ACETAMIN TAB 325MG	3	30	3250	3250
452301	2017-12	ACETAMIN TAB 325MG	3	30	3250	3250
484401	2017-10	HYDROCO/APAP TAB 5-325MG	5	60	3900	3900
488101	2018-01	HYDROCO/APAP TAB 5-325MG	5	60	3900	3900
437001	2017-08	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
529201	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
532101	2017-08	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
	2017-09	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
533902	2018-03	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
006701	2017-11	APAP/CODEINE TAB 300-30MG	3	40	4000	4000
008901	2017-09	HYDROCO/APAP TAB 5-325MG	3	35	3791.666667	3791.666667
012101	2017-09	HYDROCO/APAP TAB 7.5-325	7	84	3900	3900
690101	2017-10	PAIN & FEVER TAB 500MG	7	50	3571.428571	3040
	2017-11	APAP/CODEINE TAB 300-30MG	3	18	1800	3040
734501	2017-11	MAPAP TAB 325MG	3	30	3250	3250

489501	2018-02	CHLD SILAPAP LIQ 160/5ML	1	118	3776	3776
496301	2018-01	MAPAP CAP 500MG	3	30	5000	5000
861401	2017-08	MAPAP TAB 500MG	6	40	3333.333333	3333.333333
883001	2017-12	HYDROCO/APAP TAB 5-325MG	5	60	3900	3900
639001	2017-09	CHLD SILAPAP LIQ 160/5ML	1	120	3840	3840
655101	2017-11	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
681101	2017-12	MAPAP TAB 500MG	8	50	3125	3125
747901	2017-10	HYDROCO/APAP TAB 7.5-325	3	30	3250	3250
790601	2018-03	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
814701	2017-11	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
840501	2017-09	OXYCOD/APAP TAB 5-325MG	5	60	3900	3900
891301	2017-11	MAPAP TAB 325MG	3	30	3250	3250
027401	2017-09	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
048901	2017-11	BUT/APAP/CAF TAB	3	30	3250	3250
182401	2018-03	MAPAP TAB 325MG	10	120	3900	3900
181501	2017-09	HYDROCO/APAP TAB 5-325MG	4	40	3250	3250
841301	2017-11	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
850201	2017-11	OXYCOD/APAP TAB 5-325MG	5	60	3900	3900
972401	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
503701	2017-10	ARTHRTS PAIN TAB 650MG	5	30	3900	3900
508201	2017-11	OXYCOD/APAP TAB 5-325MG	1	10	3250	3250
510001	2018-02	MAPAP TAB 325MG	5	50	3250	3250
533901	2018-02	CHLD SILAPAP LIQ 160/5ML	4	473	3784	3784
601401	2017-12	PAIN & FEVER SOL 160/5ML	5	480	3072	3072
172301	2017-10	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
098201	2017-12	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
990601	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
478701	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
617901	2018-01	MAPAP TAB 325MG	3	30	3250	3250
967201	2017-10	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
465401	2017-10	MAPAP TAB 325MG	2	24	3900	3900
490601	2017-10	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
594201	2018-01	HYDROCO/APAP TAB 5-325MG	4	40	3250	3250
602701	2018-03	MAPAP TAB 325MG	10	120	3900	3900
241701	2017-12	HYDROCO/APAP TAB 5-325MG	5	60	3900	3900
254001	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
592201	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
598801	2017-12	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
628601	2017-11	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
629701	2017-11	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
233301	2017-11	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
309701	2018-03	MAPAP TAB 325MG	3	30	3250	3250
384601	2017-11	HYDROCO/APAP TAB 5-325MG	1	10	3250	3250
209101	2017-12	MAPAP TAB 325MG	5	50	3250	3250
220501	2017-12	HYDROCO/APAP TAB 5-325MG	4	40	3250	3250
093101	2017-12	HYDROCO/APAP TAB 5-325MG	1	12	3900	3900
103601	2018-03	MAPAP TAB 500MG	16	100	3125	3125
106501	2017-12	HYDROCO/APAP TAB 5-325MG	5	60	3900	3900
112401	2017-11	OXYCOD/APAP TAB 5-325MG	2	20	3250	3250
096301	2017-12	MAPAP TAB 325MG	3	30	3250	3250
478101	2017-11	BUT/APAP/CAF CAP CODEINE	1	10	3250	3250

909801	2017-12	CHLD SILAPAP LIQ 160/5ML	5	473	3027.2	3027.2
910101	2018-01	MAPAP TAB 500MG	5	40	4000	4000
335701	2017-12	MAPAP TAB 325MG	3	30	3250	3250
503001	2018-03	HYDROCO/APAP TAB 5-325MG	1	10	3250	3250
533301	2018-01	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
639101	2017-12	OXYCOD/APAP TAB 5-325MG	4	40	3250	3250
392501	2018-03	HYDROCO/APAP TAB 5-325MG	1	12	3900	3900
751001	2018-02	BUT/APAP/CAF TAB	3	30	3250	3250
910401	2018-02	HYDROCO/APAP TAB 5-325MG	3	28	3033.333333	3033.333333
930601	2017-12	OXYCOD/APAP TAB 5-325MG	3	30	3250	3250
499201	2017-12	HYDROCO/APAP TAB 5-325MG	3	30	3250	3250
952901	2018-03	CHLD SILAPAP LIQ 160/5ML	2	240	3840	3840
640601	2018-02	MAPAP TAB 325MG	3	30	3250	3250
963801	2018-03	HYDROCO/APAP TAB 7.5-325	3	30	3250	3250
089301	2018-02	MAPAP TAB 325MG	4	50	4062.5	4062.5
693001	2018-03	HYDROCO/APAP TAB 7.5-325	1	10	3250	3250
582401	2018-03	ACETAMIN TAB 325MG	5	50	3250	3250
455601	2018-03	HYDROCO/APAP TAB 5-325MG	2	20	3250	3250
876701	2018-03	OXYCOD/APAP TAB 5-325MG	5	50	3250	3250
885201	2018-03	MAPAP TAB 500MG	16	100	3125	3125
178101	2018-03	MAPAP TAB 500MG	4	30	3750	3750
302001	2018-03	PAIN & FEVER SOL 160/5ML	8	900	3600	3600
313201	2018-03	HYDROCO/APAP TAB 5-325MG	5	47	3055	3055
839601	2018-03	MAPAP TAB 500MG	4	30	3750	3750
960701	2018-03	HYDROCO/APAP TAB 5-325MG	5	50	3250	3250
070601	2018-03	MAPAP TAB 325MG	3	30	3250	3250

Acetaminophen Utilization

Amerigroup/Anthem

Place holder for utilization.

Acetaminophen Utilization

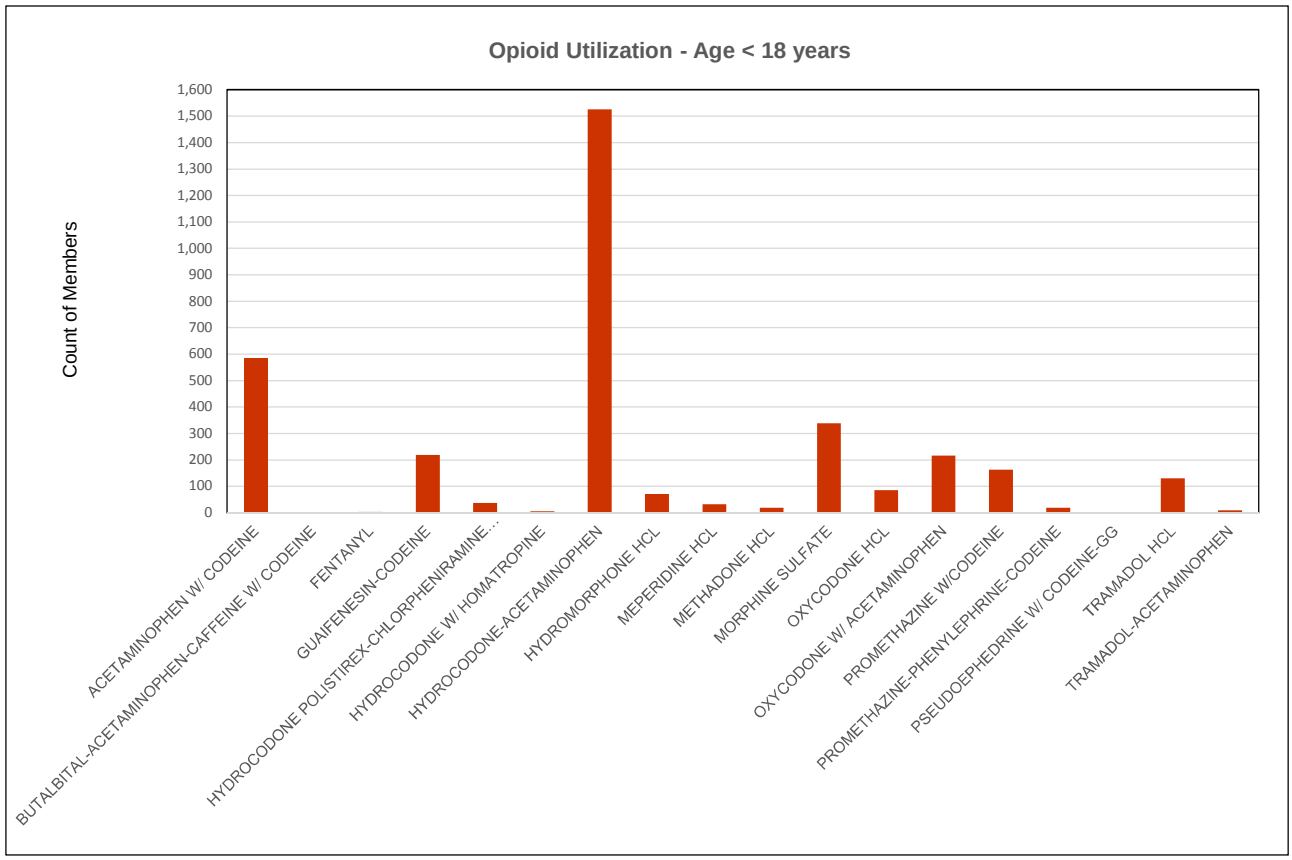
Health Plan of Nevada

Place holder for u6tilization.

Opioid Utilization in Children under 18 - Fee For Service Medicaid Only

March 1, 2017 - February 28, 2018

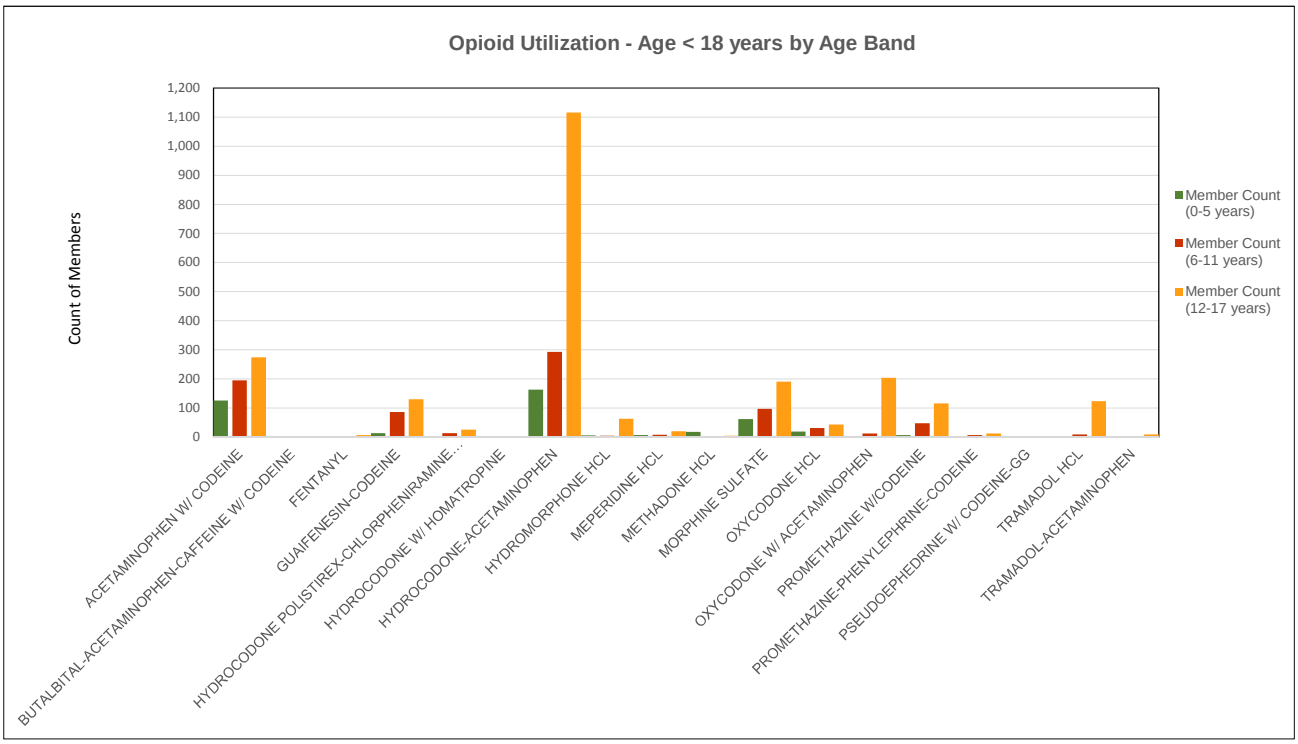
Drug Name	Count of Utilizing Members
ACETAMINOPHEN W/ CODEINE	585
BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE	2
FENTANYL	4
GUAIFENESIN-CODEINE	219
HYDROCODONE POLISTIREX-CHLORPHENIRAMINE POLISTIREX	37
HYDROCODONE W/ HOMATROPINE	6
HYDROCODONE-ACETAMINOPHEN	1,526
HYDROMORPHONE HCL	71
MEPERIDINE HCL	33
METHADONE HCL	19
MORPHINE SULFATE	338
OXYCODONE HCL	86
OXYCODONE W/ ACETAMINOPHEN	216
PROMETHAZINE W/CODEINE	163
PROMETHAZINE-PHENYLEPHRINE-CODEINE	19
PSEUDOEPHEDRINE W/ CODEINE-GG	2
TRAMADOL HCL	131
TRAMADOL-ACETAMINOPHEN	9



Opioid Utilization in Children under 18 - Fee For Service Medicaid Only

March 1, 2017 - February 28, 2018

Drug Name	Member Count (0-5 years)	Member Count (6-11 years)	Member Count (12-17 years)
ACETAMINOPHEN W/ CODEINE	125	194	274
BUTALBITAL-ACETAMINOPHEN-CAFFEINE W/ CODEINE	0	0	3
FENTANYL	0	0	6
GUAIFENESIN-CODEINE	13	85	130
HYDROCODONE POLISTIREX-CHLORPHENIRAMINE POLISTIREX	0	13	25
HYDROCODONE W/ HOMATROPINE	1	2	3
HYDROCODONE-ACETAMINOPHEN	162	292	1,115
HYDROMORPHONE HCL	5	4	62
MEPERIDINE HCL	6	7	20
METHADONE HCL	17	0	4
MORPHINE SULFATE	61	97	190
OXYCODONE HCL	18	31	43
OXYCODONE W/ ACETAMINOPHEN	2	12	203
PROMETHAZINE W/CODEINE	6	47	115
PROMETHAZINE-PHENYLEPHRINE-CODEINE	1	6	12
PSEUDOEPHEDRINE W/ CODEINE-GG	1	1	0
TRAMADOL HCL	0	9	123
TRAMADOL-ACETAMINOPHEN	0	0	9



Health Plan of Nevada

Opioids Utilization for Members Under 18 Years Old

March 1, 2017 - February 28, 2018

Drug Name	Member Count (0-5 years)	Member Count (6-11 years)	Member Count (12-17 years)	Total
HYDROCO/APAP TAB 5-325MG	3	17	212	232
HYDROCO/APAP SOL 7.5-325	53	51	17	121
APAP/CODEINE SOL 120-12/5	37	40	16	93
APAP/CODEINE TAB 300-30MG	0	9	72	81
HYDROCO/APAP TAB 7.5-325	0	2	72	74
OXYCOD/APAP TAB 5-325MG	0	2	43	45
PROMETH/COD SYP 6.25-10	2	8	23	33
TRAMADOL HCL TAB 50MG	0	1	31	32
VIRTUSSIN AC SOL 100-10/5	2	7	19	28
OXYCODONE TAB 5MG	0	0	20	20
GG/CODEINE SOL 100-10/5	1	4	9	14
HYDROCO/APAP TAB 10-325MG	2	0	7	9
CHERATUSSIN SYP 100-10/5	1	0	5	6
OXYCODONE SOL 5MG/5ML	4	1	1	6
PROMETH/PE/ SYP CODEINE	0	2	2	4
BUT/APAP/CAF CAP CODEINE	0	0	3	3
GUAIATUSSIN SYP 100-10/5	0	0	3	3
MORPHINE SUL SOL 10MG/5ML	1	1	1	3
OXYCOD/APAP TAB 7.5-325	1	0	1	2
TRAMADL/APAP TAB 37.5-325	0	0	2	2
ASCOMP/COD CAP 30MG	0	0	1	1
LORCET TAB 5-325MG	0	1	0	1
LORTAB ELX 10-300MG	0	1	0	1
METHADONE SOL 5MG/5ML	1	0	0	1
METHADONE TAB 10MG	0	0	1	1
OXYCOD/APAP TAB 10-325MG	0	0	1	1
OXYCODONE TAB 15MG	0	1	0	1

Recipients Receiving Four or More Opioids

April 1, 2017 - March 31, 2018

Fee for Service Medicaid

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
1	MORPHINE SUL TAB 100MG ER	4	240	120
1	MORPHINE SUL TAB 15MG ER	6	330	150
1	MORPHINE SUL TAB 200MG ER	1	60	30
1	MORPHINE SUL TAB 30MG ER	4	240	120
1	MORPHINE SUL TAB 60MG ER	4	240	120
1	OXYCOD/APAP TAB 10-325MG	13	2340	390
2	MORPHINE SUL CAP 30MG ER	1	30	30
2	MORPHINE SUL TAB 15MG ER	4	176	88
2	MORPHINE SUL TAB 30MG ER	5	300	150
2	OXYCODONE TAB 30MG	14	1552	388
3	HYDROMORPHON TAB 4MG	2	240	45
3	MORPHINE SUL TAB 30MG	3	540	90
3	MORPHINE SUL TAB 30MG ER	3	150	75
3	MORPHINE SUL TAB 60MG ER	8	720	240
3	OXYCODONE TAB 15MG	4	900	104
3	OXYCODONE TAB 20MG	8	1056	191
4	MORPHINE SUL TAB 15MG ER	2	180	60
4	MORPHINE SUL TAB 30MG ER	3	240	90
4	MORPHINE SUL TAB 60MG ER	7	420	210
4	OXYCODONE TAB 30MG	13	1785	351
5	BUT/APAP/CAF CAP CODEINE	3	120	60
5	FENTANYL DIS 25MCG/HR	1	10	30
5	FENTANYL DIS 50MCG/HR	6	60	180
5	HYDROCO/APAP TAB 10-325MG	9	570	175
5	HYDROMORPHON LIQ 1MG/ML	5	2393	49
5	HYDROMORPHON TAB 8MG	11	1000	167
5	METHADONE TAB 10MG	1	90	30
5	METHADONE TAB 5MG	1	90	30
5	MORPHINE SUL TAB 30MG ER	1	90	30
5	OXYCOD/APAP TAB 5-325MG	1	15	4
6	HYDROCO/APAP TAB 10-325MG	12	2880	360
6	HYDROMORPHON TAB 4MG	14	747	393
6	OXYCOD/APAP TAB 10-325MG	1	240	30
6	OXYCODONE TAB 10MG	2	58	7
6	OXYCODONE TAB 20MG	1	6	3
7	HYDROCO/APAP TAB 10-325MG	2	180	60
7	HYDROMORPHON TAB 2MG	14	1072	264
7	MORPHINE SUL TAB 15MG ER	10	476	238
7	MORPHINE SUL TAB 30MG ER	4	200	100
8	HYDROCO/APAP TAB 10-325MG	3	360	90
8	HYDROCO/APAP TAB 7.5-325	11	924	268

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
8	OXYMORPHONE TAB 5MG ER	11	582	291
8	TRAMADOL HCL TAB 50MG	1	42	7
9	MORPHINE SUL TAB 15MG ER	9	540	270
9	MORPHINE SUL TAB 30MG ER	5	268	134
9	OXYCOD/APAP TAB 10-325MG	8	960	240
9	OXYCODONE TAB 15MG	6	735	159
10	FENTANYL DIS 12MCG/HR	1	10	30
10	FENTANYL DIS 25MCG/HR	2	20	60
10	MORPHINE SUL TAB 60MG ER	15	964	347
10	OXYCODONE TAB 15MG	13	1590	390
11	HYDROCO/APAP TAB 10-325MG	6	720	180
11	MORPHINE SUL TAB 15MG ER	6	360	180
11	MORPHINE SUL TAB 30MG ER	4	240	120
11	OXYCOD/APAP TAB 10-325MG	5	600	150
11	TRAMADOL HCL TAB 50MG	1	9	3
12	APAP/CODEINE TAB 300-30MG	1	20	5
12	MORPHABOND TAB 15MG ER	1	60	30
12	MORPHABOND TAB 30MG ER	1	60	30
12	MORPHINE SUL TAB 15MG ER	12	720	360
12	MORPHINE SUL TAB 30MG ER	12	720	360
12	OXYCOD/APAP TAB 10-325MG	12	1080	360
12	PRIMLEV TAB 10-300MG	1	90	30
12	TRAMADOL HCL TAB 50MG	1	20	5
13	BUTRANS DIS 15MCG/HR	2	8	56
13	HYDROCO/APAP TAB 10-325MG	11	1770	330
13	HYDROCO/APAP TAB 5-325MG	1	49	7
13	HYSINGLA ER TAB 100 MG	1	30	30
13	OXYCOD/APAP TAB 10-325MG	2	110	40
13	TRAMADOL HCL TAB 50MG	7	1016	187
14	OXYCOD/APAP TAB 10-325MG	2	32	8
14	OXYCOD/APAP TAB 5-325MG	1	18	3
14	OXYCODONE TAB 20MG	6	360	180
14	OXYCONTIN TAB 20MG CR	5	300	150
14	TRAMADOL HCL TAB 50MG	6	322	153
15	BUT/APAP/CAF CAP CODEINE	10	612	102
15	HYDROCO/APAP TAB 10-325MG	12	1604	305
15	MORPHINE SUL TAB 15MG ER	3	180	75
15	OXYCOD/APAP TAB 10-325MG	7	630	129
15	OXYCODONE TAB 10MG	5	460	53
16	MORPHINE SUL TAB 100MG ER	3	67	67
16	MORPHINE SUL TAB 60MG ER	12	607	337
16	OXYCODONE TAB 10MG	9	810	270
16	OXYCODONE TAB 30MG	3	402	67
17	BUPRENORPHIN DIS 10MCG/HR	6	24	168
17	MORPHINE SUL TAB 15MG ER	5	420	150

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
17	OXYCODONE TAB 5MG	13	1230	390
17	XTAMPZA ER CAP 13.5MG	1	60	30
18	HYDROCO/APAP TAB 10-325MG	13	1890	390
18	MORPHINE SUL TAB 15MG ER	1	30	30
18	MORPHINE SUL TAB 30MG ER	1	60	30
18	OXYCOD/APAP TAB 5-325MG	1	30	4
19	MORPHINE SUL TAB 15MG ER	4	120	120
19	MORPHINE SUL TAB 30MG ER	4	240	120
19	OXYCOD/APAP TAB 10-325MG	6	552	123
19	OXYCOD/APAP TAB 5-325MG	1	20	5
20	BUT/APAP/CAF CAP CODEINE	1	30	5
20	HYDROCO/APAP TAB 5-325MG	3	90	21
20	HYDROCOD/IBU TAB 7.5-200	13	1200	375
20	HYSINGLA ER TAB 20 MG	13	390	390
20	OXYCOD/APAP TAB 7.5-325	1	30	6
21	FENTANYL DIS 25MCG/HR	1	10	30
21	MORPHINE SUL TAB 30MG ER	7	420	210
21	MORPHINE SUL TAB 60MG ER	4	240	120
21	OXYCOD/APAP TAB 10-325MG	12	1620	340
22	HYDROMORPHON TAB 2MG	1	30	5
22	MORPHINE SUL TAB 15MG ER	1	60	30
22	MORPHINE SUL TAB 30MG ER	10	825	285
22	OXYCOD/APAP TAB 10-325MG	6	690	173
22	OXYCODONE TAB 10MG	1	120	30
22	OXYCODONE TAB 15MG	9	642	174
23	MORPHINE SUL TAB 30MG ER	9	510	270
23	OXYCODONE TAB 15MG	5	600	150
23	OXYCODONE TAB 30MG	4	465	120
23	TRAMADOL HCL TAB 50MG	10	300	300
24	EMBEDA CAP 60-2.4MG	1	60	30
24	HYDROCO/APAP TAB 10-325MG	13	2340	390
24	MORPHINE SUL TAB 15MG	3	180	90
24	MORPHINE SUL TAB 60MG ER	12	720	360
25	HYDROCO/APAP TAB 10-325MG	12	1170	360
25	METHADONE TAB 10MG	7	360	210
25	MORPHINE SUL TAB 60MG ER	13	1170	390
25	OXYCOD/APAP TAB 10-325MG	1	120	30
26	HYDROCO/APAP TAB 10-325MG	11	1500	360
26	HYSINGLA ER TAB 30 MG	9	270	270
26	HYSINGLA ER TAB 40 MG	1	30	30
26	OXYCOD/APAP TAB 10-325MG	5	404	83
26	TRAMADOL HCL TAB 50MG	2	60	14
27	FENTANYL DIS 12MCG/HR	1	10	30
27	FENTANYL DIS 25MCG/HR	8	80	240
27	OXYCOD/APAP TAB 10-325MG	12	720	360

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
27	OXYCODONE TAB 10MG	1	16	4
28	EMBEDA CAP 20-0.8MG	2	60	60
28	HYSINGLA ER TAB 20 MG	1	30	30
28	MORPHINE SUL TAB 15MG ER	6	261	134
28	MORPHINE SUL TAB 30MG ER	2	120	60
28	OXYCOD/APAP TAB 10-325MG	12	1188	325
29	MORPHINE SUL TAB 15MG ER	9	540	270
29	MORPHINE SUL TAB 30MG ER	1	60	30
29	MORPHINE SUL TAB 60MG ER	2	120	60
29	OXYCODONE TAB 15MG	13	1470	390
29	OXYCODONE TAB 30MG	13	1560	390
30	OPANA ER TAB 15MG	4	240	120
30	OPANA ER TAB 20MG	1	60	30
30	OXYCOD/APAP TAB 10-325MG	10	600	300
30	OXYCOD/APAP TAB 7.5-325	1	60	30
30	OXYMORPHONE TAB 15MG ER	6	360	180
31	HYDROCO/APAP TAB 5-325MG	4	240	28
31	HYDROMORPHON TAB 4MG	1	21	7
31	HYSINGLA ER TAB 40 MG	4	90	90
31	HYSINGLA ER TAB 80 MG	1	30	30
31	MORPHINE SUL TAB 15MG	1	120	8
31	MORPHINE SUL TAB 15MG ER	1	90	10
31	OXYCOD/APAP TAB 10-325MG	3	250	44
31	OXYCOD/APAP TAB 5-325MG	13	670	114
31	OXYCOD/APAP TAB 7.5-325	4	720	120
31	OXYCODONE TAB 10MG	2	228	38
31	OXYCODONE TAB 15MG	1	180	30
31	OXYCODONE TAB 30MG	1	180	30
32	EMBEDA CAP 30-1.2MG	1	30	30
32	MORPHINE SUL TAB 15MG ER	1	60	30
32	MORPHINE SUL TAB 60MG ER	2	120	60
32	OPANA ER TAB 20MG	1	60	30
32	OXYCODONE TAB 10MG	9	1620	270
33	FENTANYL DIS 75MCG/HR	1	10	30
33	HYDROMORPHON TAB 8MG	2	300	50
33	MORPHINE SUL TAB 15MG ER	1	90	30
33	MORPHINE SUL TAB 30MG ER	2	120	60
33	MORPHINE SUL TAB 60MG ER	1	60	30
33	SUBSYS SPR 1200MCG	2	240	45
34	HYDROCO/APAP TAB 10-325MG	2	56	14
34	METHADONE TAB 10MG	14	2340	390
34	OXYCODONE TAB 15MG	1	150	31
34	OXYCODONE TAB 30MG	13	1440	360
34	TRAMADOL HCL TAB 50MG	1	20	4
35	HYDROCO/APAP TAB 5-325MG	6	540	180

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
35	MORPHABOND TAB 15MG ER	1	90	30
35	MORPHINE SUL TAB 15MG ER	4	360	120
35	MORPHINE SUL TAB 30MG ER	6	360	180
35	OXYCOD/APAP TAB 5-325MG	5	450	150
36	EMBEDA CAP 20-0.8MG	1	30	30
36	OPANA ER TAB 20MG	4	240	120
36	OXYCODONE TAB 20MG	3	360	90
36	OXYCODONE TAB 30MG	2	240	60
37	FENTANYL DIS 12MCG/HR	10	100	300
37	FENTANYL DIS 50MCG/HR	11	110	330
37	OXYCODONE TAB 15MG	13	1560	390
37	SUBSYS SPR 200MCG	17	1320	330
38	MORPHINE SUL TAB 15MG ER	7	585	208
38	MORPHINE SUL TAB 30MG ER	2	120	60
38	OXYCODONE TAB 10MG	5	600	150
38	OXYCODONE TAB 15MG	3	360	90
38	OXYCODONE TAB 30MG	3	270	90
39	FENTANYL DIS 100MCG/H	1	20	30
39	FENTANYL DIS 75MCG/HR	1	10	30
39	HYDROMORPHON TAB 4MG	1	21	7
39	HYDROMORPHON TAB 8MG	1	90	30
39	MORPHINE SUL TAB 15MG ER	2	111	37
39	MORPHINE SUL TAB 30MG ER	3	210	90
39	OXYCODONE SOL 5MG/5ML	1	180	5
39	OXYCODONE TAB 10MG	1	150	30
39	OXYCODONE TAB 15MG	2	360	60
40	MORPHINE SUL TAB 15MG	12	840	360
40	MORPHINE SUL TAB 15MG ER	6	360	180
40	MORPHINE SUL TAB 30MG ER	4	120	120
40	TRAMADOL HCL TAB 50MG	1	60	30
41	HYDROMORPHON TAB 2MG	2	180	60
41	HYDROMORPHON TAB 4MG	6	604	165
41	MORPHINE SUL TAB 15MG ER	8	600	240
41	MORPHINE SUL TAB 30MG ER	13	960	390
42	FENTANYL DIS 12MCG/HR	1	5	15
42	FENTANYL DIS 25MCG/HR	3	30	90
42	FENTANYL DIS 50MCG/HR	3	30	90
42	HYDROCO/APAP TAB 5-300MG	1	15	3
42	OXYCODONE TAB 10MG	5	570	150
42	TRAMADOL HCL TAB 50MG	4	360	120
43	FENTANYL DIS 100MCG/H	6	60	180
43	FENTANYL DIS 12MCG/HR	2	20	60
43	FENTANYL DIS 75MCG/HR	7	70	210
43	OXYCODONE TAB 10MG	13	1290	390
44	MORPHINE SUL TAB 15MG ER	4	240	120

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
44	OXYCODONE TAB 10MG	1	120	30
44	OXYCODONE TAB 15MG	1	150	30
44	OXYCODONE TAB 20MG	2	240	60
45	HYDROMORPHON TAB 8MG	5	750	150
45	HYSINGLA ER TAB 100 MG	1	30	30
45	OXYCODONE TAB 30MG	6	457	157
45	OXYCONTIN TAB 80MG CR	5	300	150
46	FENTANYL DIS 12MCG/HR	1	10	30
46	MORPHINE SUL TAB 15MG ER	2	120	60
46	MORPHINE SUL TAB 30MG ER	3	180	90
46	OXYCOD/APAP TAB 5-325MG	1	8	1
46	OXYCODONE TAB 15MG	13	1800	385
47	EMBEDA CAP 60-2.4MG	1	30	30
47	EMBEDA CAP 80-3.2MG	1	90	30
47	OXYCODONE TAB 15MG	12	2160	360
47	OXYCODONE TAB 80MG ER	8	720	240
47	OXYCONTIN TAB 80MG CR	2	180	60
48	HYDROMORPHON TAB 2MG	11	820	246
48	HYDROMORPHON TAB 4MG	2	72	19
48	MORPHINE SUL TAB 15MG ER	1	90	30
48	MORPHINE SUL TAB 30MG ER	9	620	250
48	MORPHINE SUL TAB 60MG ER	2	120	60
49	MORPHINE SUL TAB 30MG ER	10	435	292
49	OXYCODONE TAB 15MG	12	1470	351
49	OXYCODONE TAB 5MG	1	15	5
49	TRAMADOL HCL TAB 50MG	12	1190	335
50	MORPHINE SUL TAB 100MG ER	1	90	30
50	MORPHINE SUL TAB 200MG ER	9	810	270
50	MORPHINE SUL TAB 30MG	12	2160	298
50	OXYCOD/APAP TAB 10-325MG	11	1680	245
50	TRAMADOL HCL TAB 50MG	8	1680	240
51	OXYCOD/APAP TAB 10-325MG	10	840	300
51	OXYCODONE TAB 10MG	7	840	210
51	OXYCODONE TAB 10MG ER	1	60	30
51	OXYCODONE TAB 15MG	2	240	60
51	OXYCODONE TAB 5MG	2	60	10
52	OXYCODONE TAB 30MG	13	1560	390
52	OXYCODONE TAB 40MG ER	2	120	60
52	OXYCONTIN TAB 20MG CR	2	120	60
52	OXYCONTIN TAB 40MG CR	5	300	150
52	OXYCONTIN TAB 60MG CR	3	180	90
53	HYDROCO/APAP TAB 10-325MG	9	964	238
53	HYDROCO/APAP TAB 7.5-325	4	480	120
53	HYSINGLA ER TAB 40 MG	4	97	97
53	TRAMADOL HCL TAB 100MG ER	4	240	120

Encypted ID	Drug Label Name	Count of Claims	Sum of Qty	Sum of Days Supply
53	TRAMADOL HCL TAB 50MG	5	470	109
54	BUPRENORPHIN DIS 20MCG/HR	7	28	196
54	BUTRANS DIS 20MCG/HR	5	20	140
54	NUCYNTA TAB 100MG	10	780	310
54	OXYCODONE TAB 20MG	3	510	90
54	OXYCODONE TAB 30MG	9	1620	270
55	HYDROMORPHON TAB 8MG	13	1200	390
55	OPANA ER TAB 40MG	2	120	60
55	OXYMORPHONE TAB 30MG ER	1	60	30
55	OXYMORPHONE TAB 40MG ER	9	500	250
55	OXYMORPHONE TAB HCL 10MG	10	300	300
56	HYDROCO/APAP TAB 7.5-325	12	628	344
56	MORPHABOND TAB 30MG ER	5	218	109
56	OXYCODONE TAB 20MG ER	2	120	60
56	OXYCONTIN TAB 30MG CR	6	360	180
57	HYDROCO/APAP TAB 5-325MG	1	12	2
57	OXYCOD/APAP TAB 10-325MG	1	80	20
57	OXYCODONE TAB 5MG	17	2196	373
57	OXYCONTIN TAB 10MG CR	16	732	366
57	OXYCONTIN TAB 20MG CR	1	14	7
58	MORPHABOND TAB 15MG ER	2	120	60
58	MORPHABOND TAB 30MG ER	2	120	60
58	MORPHINE SUL TAB 15MG ER	5	300	150
58	MORPHINE SUL TAB 30MG ER	9	510	255
58	MORPHINE SUL TAB 60MG ER	2	90	45
58	OXYCODONE TAB 15MG	1	60	10
58	OXYCODONE TAB 20MG	11	1590	305
58	OXYCODONE TAB 30MG	2	210	45
59	HYDROMORPHON TAB 2MG	1	120	30
59	HYDROMORPHON TAB 4MG	11	1320	330
59	MORPHINE SUL TAB 15MG ER	1	60	30
59	MORPHINE SUL TAB 30MG ER	11	660	330
60	FENTANYL DIS 12MCG/HR	1	15	30
60	FENTANYL DIS 25MCG/HR	4	55	110
60	FENTANYL DIS 50MCG/HR	7	105	210
60	OXYCODONE TAB 15MG	14	1528	412
61	OXYCOD/APAP TAB 5-325MG	1	20	5
61	OXYCODONE TAB 10MG	6	570	180
61	OXYCODONE TAB 15MG	3	270	90
61	OXYCODONE TAB 20MG	8	1350	240
62	FENTANYL DIS 25MCG/HR	5	50	150
62	FENTANYL DIS 50MCG/HR	7	70	210
62	HYDROMORPHON TAB 2MG	1	56	14
62	OXYCODONE TAB 10MG	12	1440	360

Top 10 Prescribers by Count of Claims

Comparison 10/1/16 - 9/30/17 to 4/1/17 - 3/31/18

Fee For Service Medicaid Only

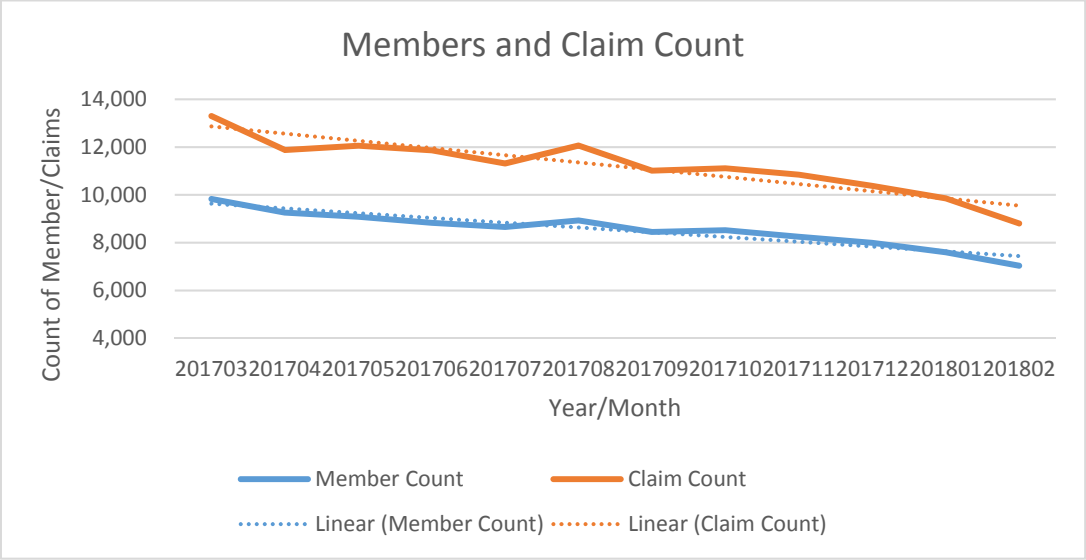
	Encrypted ID	Previous Rank	Specialty	Degree	City	Member Count	Claim Count	Sum of Days Supply	Sum of Qty	Sum of Pd Amt
April 1, 2017 - March 31, 2018	A	1	PAIN MANAGEMENT	NP	Las Vegas	188	1,954	57,840	182,956	$ 144,870
	B	10		NP	Fallon	242	1,757	29,589	158,382	$ 52,436
	C		Anesthesiology	DO	Henderson	192	1,533	44,362	179,610	$ 140,314
	D	2		PA	Las Vegas	114	1,439	42,549	163,079	$ 69,480
	E	3		PA	Las Vegas	172	1,312	38,637	117,085	$ 111,394
	F	6	PAIN MANAGEMENT	MD	Carson City	135	1,306	34,277	98,128	$ 430,613
	G	7		PA	Las Vegas	261	1,183	34,829	103,241	$ 80,919
	H			PA	Las Vegas	155	1,177	32,794	111,536	$ 83,787
	I	5	Oncology	PA	Las Vegas	165	1,084	30,342	103,253	$ 58,355
	J			NP	Las Vegas	135	964	27,222	94,231	$ 52,491
Oct 1, 2016 - Sept 30, 2017	A		PAIN MANAGEMENT	NP	Las Vegas	218	2,193	64,905	205,568	$ 195,920
	D			PA	Las Vegas	138	1,608	47,212	182,787	$ 112,334
	E			PA	Las Vegas	172	1,300	38,341	115,709	$ 124,162
	M			PA	Las Vegas	180	1,279	36,064	125,230	$ 93,265
	I		Oncology	PA	Las Vegas	196	1,277	35,538	124,461	$ 76,039
	F		PAIN MANAGEMENT	MD	Carson City	123	1,204	32,714	105,283	$ 352,220
	G			PA	Las Vegas	238	1,133	33,419	97,989	$ 83,486
	K		Oral Surgery	DDS	Reno	997	1,117	4,780	19,138	$ 12,621
	L		PAIN MANAGEMENT	MD	Las Vegas	141	1,069	29,508	99,031	$ 39,848
	B			NP	Fallon	202	1,011	17,596	94,364	$ 30,799

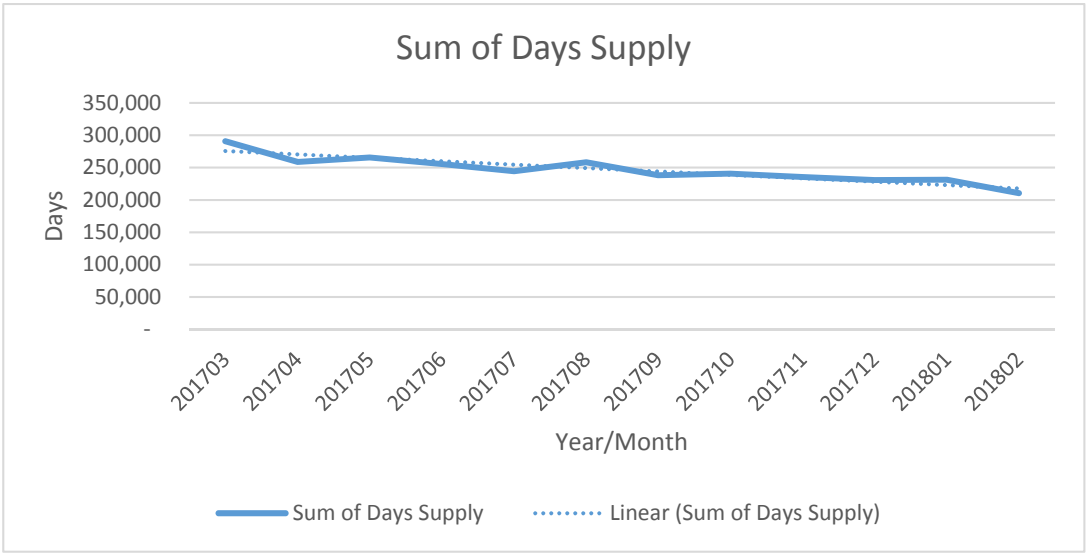
Opioid Utilization

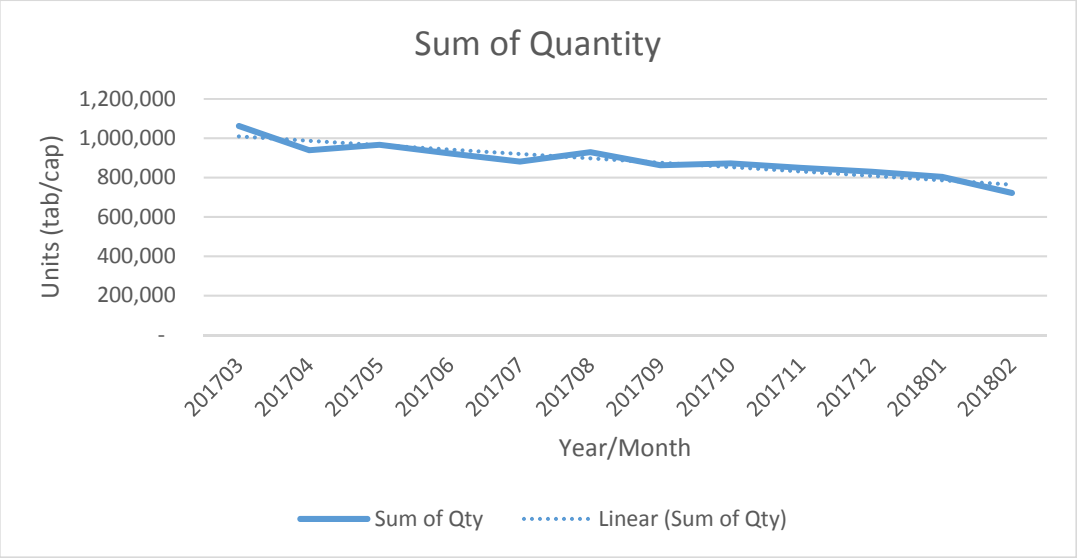
March 1, 2017 - February 28, 2018

Fee for Service Medicaid

Year Month Filled	Member Count	Claim Count	Sum of Days Supply	Sum of Qty	Sum of Pd Amt
201703	9,831	13,302	290,813	1,062,292	$ 676,039.89
201704	9,258	11,876	258,869	939,598	$ 593,564.85
201705	9,084	12,061	265,723	966,721	$ 602,405.47
201706	8,832	11,867	255,450	922,730	$ 596,342.97
201707	8,655	11,317	244,339	881,364	$ 564,725.24
201708	8,931	12,064	258,247	929,117	$ 597,967.30
201709	8,447	11,016	238,254	862,634	$ 531,196.94
201710	8,522	11,118	240,713	872,643	$ 554,505.93
201711	8,248	10,849	235,519	849,795	$ 533,627.50
201712	7,995	10,377	230,882	830,210	$ 517,578.71
201801	7,602	9,854	231,187	804,368	$ 493,749.23
201802	7,036	8,804	210,432	722,010	$ 478,160.96



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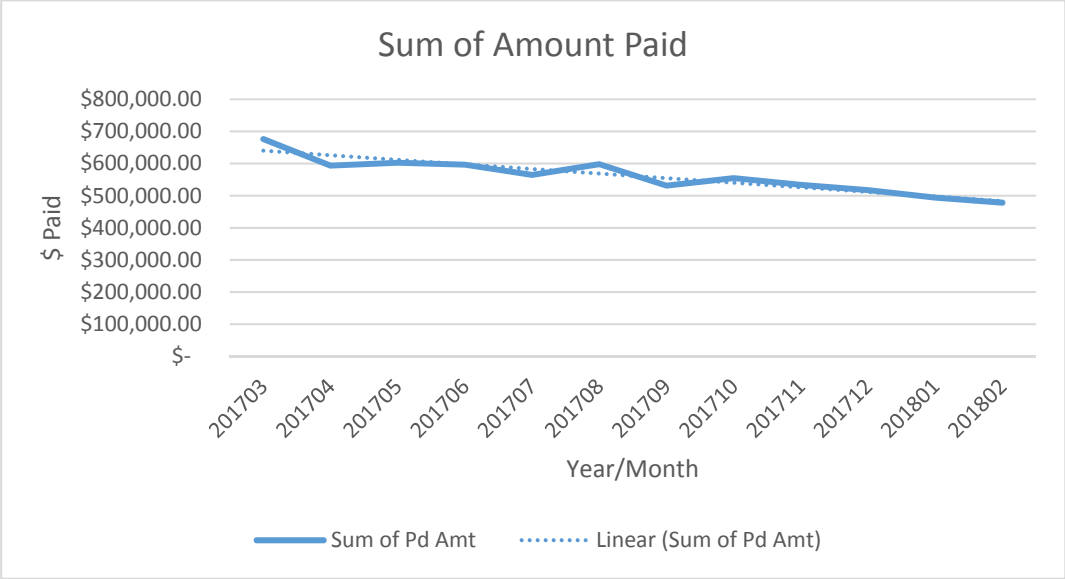
800,000
600,000
400,000
200,000
-
Units (tab/cap)
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
201801
201802
Year/Month
Sum of Qty
Linear (Sum of Qty)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$500,000.00
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$300,000.00
$200,000.00
$100,000.00
$-
$ Paid
201703
201704
201705
201706
201707
201708
201709
201710
201711
201712
201801
201802
Year/Month
Sum of Pd Amt
Linear (Sum of Pd Amt)

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Top 10 Opioid Prescriber Reports for Nevada SSHP

Top 10 Opioid Prescribers by Unique Util

1/1/2017 - 12/31/2017

Rank	Physician NPI	Unique Utilizers	Claim Count	Sum Metric Qty	Sum Days Supply	Billed Amt
1		105	243	21,489	7,033	$15,189.29
2		98	235	20,943	6,766	$16,491.49
3		80	223	21,324	6,445	$14,562.21
4		66	187	18,876	5,467	$19,477.21
5		66	66	5,738	1,922	$4,177.52
6		58	164	14,480	4,482	$17,797.24
7		56	200	10,337	4,662	$75,673.71
8		42	147	13,248	4,366	$14,481.22
9		35	195	4,675	2,790	$33,292.14
10		32	157	13,874	4,446	$15,463.12

Top 10 Opioid Prescribers by Claim Count

1/1/2017 - 12/31/2017

Rank	Physician NPI	Unique Utilizers	Claim Count	Sum Metric Qty	Sum Days Supply	Billed Amt
1		105	243	21,489	7,033	$15,189.29
2		98	235	20,943	6,766	$16,491.49
3		80	223	21,324	6,445	$14,562.21
4		56	200	10,337	4,662	$75,673.71
5		35	195	4,675	2,790	$33,292.14
6		66	187	18,876	5,467	$19,477.21
7		58	164	14,480	4,482	$17,797.24
8		32	157	13,874	4,446	$15,463.12
9		42	147	13,248	4,366	$14,481.22
10		29	77	7,212	2,195	$5,856.70

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Top 10 Opioid Prescribers by Sum Days Supply

1/1/2017 - 12/31/2017

Rank	Physician NPI	Unique Utilizers	Claim Count	Sum Metric Qty	Sum Days Supply	Billed Amt
1		105	243	21,489	7,033	$15,189.29
2		98	235	20,943	6,766	$16,491.49
3		80	223	21,324	6,445	$14,562.21
4		66	187	18,876	5,467	$19,477.21
5		56	200	10,337	4,662	$75,673.71
6		58	164	14,480	4,482	$17,797.24
7		32	157	13,874	4,446	$15,463.12
8		42	147	13,248	4,366	$14,481.22
9		35	195	4,675	2,790	$33,292.14
10		29	77	7,212	2,195	$5,856.70

Top 10 Opioid Prescribers by Sum Metric Quantity

1/1/2017 - 12/31/2017

Rank	Physician NPI	Unique Utilizers	Claim Count	Sum Metric Qty	Sum Days Supply	Billed Amt
1		105	243	21,489	7,033	$15,189.29
2		80	223	21,324	6,445	$14,562.21
3		98	235	20,943	6,766	$16,491.49
4		66	187	18,876	5,467	$19,477.21
5		58	164	14,480	4,482	$17,797.24
6		32	157	13,874	4,446	$15,463.12
7		42	147	13,248	4,366	$14,481.22
8		56	200	10,337	4,662	$75,673.71
9		29	77	7,212	2,195	$5,856.70
10		35	195	4,675	2,790	$33,292.14

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Top 10 Opioid Prescribers by Billed Amount

1/1/2017 - 12/31/2017

Rank	Physician NPI	Unique Utilizers	Claim Count	Sum Metric Qty	Sum Days Supply	Billed Amt
1		56	200	10,337	4,662	$75,673.71
2		35	195	4,675	2,790	$33,292.14
3		66	187	18,876	5,467	$19,477.21
4		58	164	14,480	4,482	$17,797.24
5		98	235	20,943	6,766	$16,491.49
6		32	157	13,874	4,446	$15,463.12
7		105	243	21,489	7,033	$15,189.29
8		80	223	21,324	6,445	$14,562.21
9		42	147	13,248	4,366	$14,481.22
10		29	77	7,212	2,195	$5,856.70

Top Opioid Prescribers
Anthem

By Claim Count								
PRESCRIBER ID	PROV_TYPE_CD	PRESCRIBER_CLSFCTN_CD	PHYSICIAN_CITY	PHYSICIAN STATE	MBR CNT	CLM CNT	DAYS SUPPLY	METRIC DEC QTY
R	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	186	1,555	45,989	139,126
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	312	1,509	42,607	130,950
J	Allopathic & Osteopathic Physicians	Anesthesiology	Greenfield	WI	165	1,482	41,193	139,646
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	226	1,423	40,203	136,193
D	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	373	1,395	38,817	127,013
C	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	137	1,219	35,360	100,343
C	Allopathic & Osteopathic Physicians	Physical Medicine & Reh	Las Vegas	NV	292	1,121	31,061	101,536
J	Dental Providers	Dentist	Las Vegas	NV	989	1,087	4,190	24,396
E	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	184	895	25,703	85,991
J	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	156	709	20,329	66,606

By Day Supply								
PRESCRIBER ID	PROV_TYPE_CD	PRESCRIBER_CLSFCTN_CD	PHYSICIAN_CITY	PHYSICIAN STATE	MBR CNT	CLM CNT	DAYS SUPPLY	METRIC DEC QTY
R	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	186	1,555	45,989	139,126
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	312	1,509	42,607	130,950
J	Allopathic & Osteopathic Physicians	Anesthesiology	Greenfield	WI	165	1,482	41,193	139,646
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	226	1,423	40,203	136,193
D	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	373	1,395	38,817	127,013
C	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	137	1,219	35,360	100,343
C	Allopathic & Osteopathic Physicians	Physical Medicine & Reh	Las Vegas	NV	292	1,121	31,061	101,536
E	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	184	895	25,703	85,991
J	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	156	709	20,329	66,606
J	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	111	708	20,282	67,103

By Member Count								
PRESCRIBER ID	PROV_TYPE_CD	PRESCRIBER_CLSFCTN_CD	PHYSICIAN_CITY	PHYSICIAN STATE	MBR CNT	CLM CNT	DAYS SUPPLY	METRIC DEC QTY
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	312	1,509	42,607	130,950
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	226	1,423	40,203	136,193
D	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	373	1,395	38,817	127,013
C	Allopathic & Osteopathic Physicians	Physical Medicine & Reh	Las Vegas	NV	292	1,121	31,061	101,536
J	Dental Providers	Dentist	Las Vegas	NV	989	1,087	4,190	24,396
Z	Allopathic & Osteopathic Physicians	Anesthesiology	Las Vegas	NV	210	637	17,071	52,263
J	Allopathic & Osteopathic Physicians	Orthopaedic Surgery	Las Vegas	NV	209	347	1,793	11,062
A	Dental Providers	Dentist	Reno	NV	266	276	1,482	8,403
M	Allopathic & Osteopathic Physicians	Internal Medicine	Las Vegas	NV	208	260	1,369	7,326
F	Allopathic & Osteopathic Physicians	Internal Medicine	Las Vegas	NV	219	241	1,209	2,562

By Amount Paid								
PRESCRIBER ID	PROV_TYPE_CD	PRESCRIBER_CLSFCTN_CD	PHYSICIAN_CITY	PHYSICIAN STATE	MBR CNT	CLM CNT	DAYS SUPPLY	METRIC DEC QTY
R	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	186	1,555	45,989	139,126
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	312	1,509	42,607	130,950
J	Allopathic & Osteopathic Physicians	Anesthesiology	Greenfield	WI	165	1,482	41,193	139,646
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	226	1,423	40,203	136,193
D	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	373	1,395	38,817	127,013
C	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	137	1,219	35,360	100,343
E	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	184	895	25,703	85,991
A	Allopathic & Osteopathic Physicians	Physical Medicine & Reh	Henderson	NV	131	470	13,022	29,492
W	Allopathic & Osteopathic Physicians	Anesthesiology	Las Vegas	NV	91	433	9,703	22,888
Q	Allopathic & Osteopathic Physicians	Family Medicine	Gardnerville	NV	22	159	4,130	5,756

By Total Quantity								
PRESCRIBER ID	PROV_TYPE_CD	PRESCRIBER_CLSFCTN_CD	PHYSICIAN_CITY	PHYSICIAN STATE	MBR CNT	CLM CNT	DAYS SUPPLY	METRIC DEC QTY
R	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	186	1,555	45,989	139,126
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	312	1,509	42,607	130,950
J	Allopathic & Osteopathic Physicians	Anesthesiology	Greenfield	WI	165	1,482	41,193	139,646
A	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	226	1,423	40,203	136,193
D	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	373	1,395	38,817	127,013
C	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Henderson	NV	137	1,219	35,360	100,343
C	Allopathic & Osteopathic Physicians	Physical Medicine & Reh	Las Vegas	NV	292	1,121	31,061	101,536
E	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	184	895	25,703	85,991
J	Physician Assistants & Advanced Practice Nursing Providers	Nurse Practitioner	Las Vegas	NV	111	708	20,282	67,103
J	Physician Assistants & Advanced Practice Nursing Providers	Physician Assistant	Las Vegas	NV	73	635	18,457	72,138

Health Plan of Nevada

Members on 4+ Unique Opioids Concurrently

October 1, 2017 - December 31, 2017

Member Count
8
No trends identified based on low member count

Health Plan of Nevada

Top Opioid Combinations

October 1, 2017 - December 31, 2017

Top Opioid Combinations		
Members	**GPI Name (1)**	**GPI Name (2)**
290	TRAMADOL HCL TAB 50MG	HYDROCO/APAP TAB 5-325MG
233	HYDROCO/APAP TAB 5-325MG	HYDROCO/APAP TAB 7.5-325
209	OXYCOD/APAP TAB 5-325MG	HYDROCO/APAP TAB 5-325MG
158	HYDROCO/APAP TAB 10-325MG	HYDROCO/APAP TAB 5-325MG
152	APAP/CODEINE TAB 300-30MG	HYDROCO/APAP TAB 5-325MG
115	TRAMADOL HCL TAB 50MG	HYDROCO/APAP TAB 10-325MG
112	HYDROCO/APAP TAB 10-325MG	HYDROCO/APAP TAB 7.5-325
98	TRAMADOL HCL TAB 50MG	HYDROCO/APAP TAB 7.5-325
96	MORPHINE SUL TAB 15MG ER	OXYCOD/APAP TAB 10-325MG
85	TRAMADOL HCL TAB 50MG	OXYCOD/APAP TAB 5-325MG
76	OXYCOD/APAP TAB 5-325MG	HYDROCO/APAP TAB 10-325MG
68	METHADONE TAB 10MG	OXYCODONE TAB 30MG
65	MORPHINE SUL TAB 15MG ER	HYDROCO/APAP TAB 10-325MG
65	OXYCOD/APAP TAB 5-325MG	OXYCOD/APAP TAB 10-325MG
59	OXYCOD/APAP TAB 10-325MG	HYDROCO/APAP TAB 10-325MG
52	TRAMADOL HCL TAB 50MG	APAP/CODEINE TAB 300-30MG
46	APAP/CODEINE TAB 300-30MG	HYDROCO/APAP TAB 7.5-325
46	OXYCOD/APAP TAB 5-325MG	HYDROCO/APAP TAB 7.5-325
44	MORPHINE SUL TAB 15MG ER	OXYCODONE TAB 30MG
42	MORPHINE SUL TAB 15MG ER	OXYCODONE TAB 10MG

Health Plan of Nevada

Top 10 Prescriber of OpioIds

October 1, 2017 - December 31, 2017

By Member Count

Encrypted ID	Member Count	Claim Count	Sum of Days	Sum of Qty
A	527	1,143	178	115,469
R	462	483	54	10,387
Q	454	932	161	86,652
T	357	614	71	61,361
O	327	490	65	48,480
M	327	469	44	44,477
S	294	304	37	6,767
H	288	622	176	62,252
G	262	539	122	51,491
X	252	519	146	50,625

By Count of Claims

Encrypted ID	Member Count	Claim Count	Sum of Days	Sum of Qty
A	527	1,143	178	115,469
Q	454	932	161	86,652
H	288	622	176	62,252
T	357	614	71	61,361
B	181	558	204	69,606
G	262	539	122	51,491
X	252	519	146	50,625
U	147	504	129	48,534
O	327	490	65	48,480
R	462	483	54	10,387

By Days Supply

Encrypted ID	Member Count	Claim Count	Sum of Days	Sum of Qty
P	78	126	305	13,366
N	164	304	295	24,012
K	216	417	284	39,546
F	135	288	271	28,730
D	76	184	266	15,249
W	82	135	262	9,589
E	97	194	258	18,126
V	74	187	248	24,168
I	150	342	246	31,985
J	73	124	245	9,629

By Sum of QTY

Encrypted ID	Member Count	Claim Count	Sum of Days	Sum of Qty
A	527	1,143	178	115,469
Q	454	932	161	86,652
B	181	558	204	69,606
H	288	622	176	62,252
T	357	614	71	61,361
G	262	539	122	51,491
X	252	519	146	50,625
U	147	504	129	48,534
O	327	490	65	48,480
M	327	469	44	44,477

By Pharmacy Paid Amt

Encrypted ID	Member Count	Claim Count	Sum of Days	Sum of Qty
L	46	87	177	7,925
N	164	304	295	24,012
H	288	622	176	62,252
A	527	1,143	178	115,469
B	181	558	204	69,606
M	327	469	44	44,477
Q	454	932	161	86,652
T	357	614	71	61,361
X	252	519	146	50,625
C	216	350	143	33,039

Opioid Overdose Services

July 1, 2016 - September 30, 2017

Fee For Service

Location of Service	Count of Members
Ambulance (air or water)	1
Ambulance (land)	45
Emergency Room - Hospital	207
Independent Laboratory	1
Inpatient Hospital	144
Office	4
Outpatient Hospital-On Campus	107
Total	**509**

MCO's

Location of Service	Count of Members
AMBULANCE - LAND	248
EMERGENCY ROOM - HOSPITAL	194
END-STAGE RENAL DISEASE TREATMENT FA	1
INDEPENDENT LABORATORY	1
INPATIENT HOSPITAL	163
INPATIENT PSYCHIATRIC FACILITY	1
OFFICE	43
OUTPATIENT HOSPITAL	100
Total	**751**

Top Opioid Prescriber by Claim Count - Comparison

March 1, 2017 - February 28, 2018

FFS

Enc Prescriber ID	Member Count	Claim Count	Sum of Days Supply	Sum of Qty	Sum of Pd Amt
X	188	1,954	57,840	182,956	$ 144,870.24
O	242	1,757	29,589	158,382	$ 52,436.24
A	192	1,533	44,362	179,610	$ 140,313.70
BB	114	1,439	42,549	163,079	$ 69,479.80
K	172	1,312	38,637	117,085	$ 111,393.76
M	135	1,306	34,277	98,128	$ 430,613.14
I	261	1,183	34,829	103,241	$ 80,918.60
F	155	1,177	32,794	111,536	$ 83,786.71
Z	165	1,084	30,342	103,253	$ 58,354.66
W	135	964	27,222	94,231	$ 52,491.49

SSHP

Enc Prescriber ID	Unique Utilizers	Claim Count	Sum Days Supply	Sum Metric	Billed Amt
I	105	243	7,033	21,489	$15,189.29
AA	98	235	6,766	20,943	$16,491.49
K	80	223	6,445	21,324	$14,562.21
N	56	200	4,662	10,337	$75,673.71
S	35	195	2,790	4,675	$33,292.14
B	66	187	5,467	18,876	$19,477.21
E	58	164	4,482	14,480	$17,797.24
D	32	157	4,446	13,874	$15,463.12
J	42	147	4,366	13,248	$14,481.22
P	29	77	2,195	7,212	$5,856.70

HPN

Enc Prescriber ID	Member Count	Claim Count	Sum of Days	Sum of Qty
L	527	1,143	178	115,469
R	454	932	161	86,652
H	288	622	176	62,252
U	357	614	71	61,361
A	181	558	204	69,606
G	262	539	122	51,491
Y	252	519	146	50,625
V	147	504	129	48,534
Q	327	490	65	48,480
T	462	483	54	10,387

Emergency Room Admissions with Diabetes Diagnosis

Fee for Service Medicaid Only

Summary

Diabeties-related primary diagnosis

FY 2017				FY 2018			
Patients	Service Count	Claims Paid	Allowed Amount	Patients	Service Count	Claims Paid	Allowed Amount
2,789	2,824	3,223	$ 312,248.47	2,340	2,377	2,728	$ 270,080.84

Diabeties-related secondary diagnosis

FY 2017				FY 2018			
Patients	Service Count	Claims Paid	Allowed Amount	Patients	Service Count	Claims Paid	Allowed Amount
12,905	13,057	15,510	$ 1,103,076.16	10,612	10,748	12,931	$ 976,380.33

Top 10 Drug Group by Paid Amt

Fee for Service

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

Q4 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
85	HEMATOLOGICAL AGENTS - MISC.*	2,904	$ 10,758,751.62
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	30,056	$ 5,871,009.27
12	ANTIVIRALS*	4,436	$ 5,553,514.06
27	ANTIDIABETICS*	17,269	$ 5,284,226.72
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	39,715	$ 4,715,098.00
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	3,604	$ 4,179,899.65
72	ANTICONVULSANTS*	42,649	$ 3,908,909.37
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	3,278	$ 3,094,916.09
74	NEUROMUSCULAR AGENTS*	356	$ 3,017,053.42
62	PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	4,721	$ 2,199,798.18

Top 10 Drug Group by Claim Count

Fee for Service

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

Q4 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	50,563	$1,733,043.38
72	ANTICONVULSANTS*	42,649	$3,908,909.37
58	ANTIDEPRESSANTS*	40,379	$845,943.59
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	39,715	$4,715,098.00
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	30,056	$5,871,009.27
57	ANTIANXIETY AGENTS*	23,658	$277,872.17
66	ANALGESICS - ANTI-INFLAMMATORY*	23,370	$2,037,887.69
36	ANTIHYPERTENSIVES*	22,242	$371,772.47
49	ULCER DRUGS*	21,223	$1,071,391.16
39	ANTIHYPERLIPIDEMICS*	20,483	$681,151.03

Top 10 Drug Classes by Paid Amt

Fee for Service

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

Q4 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	106	$ 10,231,948.35
2710	INSULIN**	5,671	$ 3,257,227.12
4420	SYMPATHOMIMETICS**	27,699	$ 3,154,566.99
1210	ANTIRETROVIRALS**	2,083	$ 3,013,382.63
7260	ANTICONVULSANTS - MISC.**	31,581	$ 2,689,322.15
7470	SPINAL MUSCULAR ATROPHY AGENTS (SMA)**	16	$ 2,375,162.72
1235	HEPATITIS AGENTS**	166	$ 2,357,004.30
5907	BENZISOXAZOLES**	7,044	$ 2,200,274.40
5940	ANTIPSYCHOTICS - MISC.**	2,746	$ 1,573,118.02
6240	MULTIPLE SCLEROSIS AGENTS**	325	$ 1,539,570.79

Top 10 Drug Classes by Claim Count

Fee for Service

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

Q4 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
7260	ANTICONVULSANTS - MISC.**	31,581	$ 2,689,322.15
4420	SYMPATHOMIMETICS**	27,699	$ 3,154,566.99
6599	OPIOID COMBINATIONS**	27,697	$ 586,127.34
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	22,851	$ 298,000.41
6510	OPIOID AGONISTS**	21,948	$ 912,093.39
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	19,141	$ 254,226.75
3940	HMG COA REDUCTASE INHIBITORS**	17,062	$ 374,381.72
5710	BENZODIAZEPINES**	16,330	$ 173,109.24
7510	CENTRAL MUSCLE RELAXANTS**	14,971	$ 259,985.27
2210	GLUCOCORTICOSTEROIDS**	13,819	$ 449,969.11

Top 50 Drugs by Amount - Q2 2017

Fee for Service

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

Fee for Service

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 Amount - Q4 2017

Fee for Service

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	15	$ 3,861,081.75	72,574	9
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	6	$ 2,721,661.02	210,000	30
7470005000	NUSINERSEN	16	$ 2,375,162.72	3	16
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	13	$ 2,213,038.81	95,073	20
5907005010	PALIPERIDONE PALMITATE	747	$ 1,701,137.98	1	24
5940002310	LURASIDONE HCL	1082	$ 1,270,883.76	18	15
1950206000	PALIVIZUMAB	415	$ 1,266,412.21	1	26
4420101010	ALBUTEROL SULFATE	18418	$ 1,122,535.78	36	15
6627001500	ADALIMUMAB	191	$ 1,068,310.03	1	10
2710400300	INSULIN GLARGINE	2047	$ 1,049,529.08	14	33
1235990240	LEDIPASVIR-SOFOSBUVIR	54	$ 1,027,262.86	8	8
1235990265	SOFOSBUVIR-VELPATASVIR	58	$ 994,146.30	11	11
9410003000	GLUCOSE BLOOD	6557	$ 960,063.54	75	24
7260005700	PREGABALIN	2398	$ 925,052.06	44	19
4420990270	FLUTICASONE-SALMETEROL	2461	$ 880,044.40	41	22
3030001000	CORTICOTROPIN	10	$ 764,123.70	2	4
3010002000	SOMATROPIN	204	$ 757,204.88	2	9
4927002510	ESOMEPRAZOLE MAGNESIUM	2684	$ 750,765.50	23	23
5925001500	ARIPIPRAZOLE	4592	$ 745,330.20	17	16
1210990429	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE	346	$ 664,130.13	16	16
4530402000	DORNASE ALFA	186	$ 660,085.40	49	16
2710400500	INSULIN LISPRO	933	$ 659,405.85	13	26
4530990230	LUMACAFTOR-IVACAFTOR	31	$ 586,078.20	39	10
8240157000	PEGFILGRASTIM	100	$ 548,897.82	1	2
7260003600	LACOSAMIDE	956	$ 548,146.29	56	14
7210000700	CLOBAZAM	395	$ 542,066.20	62	14
5915307010	QUETIAPINE FUMARATE	7964	$ 542,007.05	30	21
2710400200	INSULIN ASPART	912	$ 534,069.09	14	27
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2223	$ 527,676.73	8	23
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	1705	$ 520,907.74	22	24
6240552500	DIMETHYL FUMARATE	68	$ 491,731.56	17	9
6135303010	GUANFACINE HCL (ADHD)	1877	$ 486,639.20	18	18
1910002010	IMMUNE GLOBULIN (HUMAN) IV	105	$ 484,572.17	362	5
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	21	$ 465,235.74	11,932	12
3090685000	IDURSULFASE	35	$ 444,859.08	6	3
8580005000	ECULIZUMAB	20	$ 443,564.00	68	1
6110002510	LISDEXAMFETAMINE DIMESYLATE	1720	$ 441,076.56	21	21
2153253000	EVEROLIMUS	28	$ 438,115.47	9	8
6140002010	METHYLPHENIDATE HCL	2300	$ 423,075.05	32	18
9085006000	LIDOCAINE	2304	$ 415,329.84	75	15
6629003000	ETANERCEPT	95	$ 412,422.12	2	11
2710400600	INSULIN DETEMIR	812	$ 377,934.28	13	28
7460003500	ETEPLIRSEN	6	$ 377,661.02	26	9
4016000700	AMBRISENTAN	40	$ 370,591.20	18	18
9037403530	DICLOFENAC SODIUM (ACTINIC KERATOSES)	690	$ 369,511.59	168	19
2160005500	RADIUM RA 223 DICHLORIDE	12	$ 368,220.00	108	1
2755007010	SITAGLIPTIN PHOSPHATE	749	$ 358,272.62	35	35
9310002500	DEFERASIROX	53	$ 356,233.90	19	9
1210301510	DOLUTEGRAVIR SODIUM	243	$ 348,735.50	21	20
6510007510	OXYCODONE HCL	7735	$ 318,857.91	68	17

Top 50 Drugs by Claim Count - Q2 2017

Fee for Service

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

Fee for Service

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

Top 50 Drugs by Claim Count - Q4 2017

Fee for Service

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
4420101010	ALBUTEROL SULFATE	18418	$ 1,122,535.78	36	15
6599170210	HYDROCODONE-ACETAMINOPHEN	17475	$ 274,972.07	52	14
7260003000	GABAPENTIN	12790	$ 182,980.11	74	23
6610002000	IBUPROFEN	10590	$ 96,790.93	46	11
3940001010	ATORVASTATIN CALCIUM	9909	$ 112,903.78	30	30
5710001000	ALPRAZOLAM	9092	$ 100,721.08	48	21
6599000220	OXYCODONE W/ ACETAMINOPHEN	8582	$ 269,514.23	50	13
2810001010	LEVOTHYROXINE SODIUM	8140	$ 141,063.27	31	31
3610003000	LISINOPRIL	8069	$ 66,038.04	45	41
5915307010	QUETIAPINE FUMARATE	7964	$ 542,007.05	30	21
6510007510	OXYCODONE HCL	7735	$ 318,857.91	68	17
5812008010	TRAZODONE HCL	7414	$ 85,626.74	30	23
5025006505	ONDANSETRON HCL	7216	$ 33,929.28	4	1
9410003000	GLUCOSE BLOOD	6557	$ 960,063.54	75	24
3400000310	AMLODIPINE BESYLATE	6520	$ 46,402.68	39	38
0120001010	AMOXICILLIN	6464	$ 69,245.86	59	6
5816007010	SERTRALINE HCL	6399	$ 72,993.00	29	24
4220003230	FLUTICASONE PROPIONATE (NASAL)	6313	$ 74,805.08	13	26
7720203200	CHOLECALCIFEROL	6249	$ 48,678.67	26	24
6510005510	MORPHINE SULFATE	6220	$ 138,638.26	21	9
4450505010	MONTELUKAST SODIUM	6208	$ 91,868.91	25	25
6410001000	ASPIRIN	6058	$ 33,821.83	22	22
2725005000	METFORMIN HCL	6039	$ 251,679.37	80	40
5907007000	RISPERIDONE	5690	$ 93,012.22	35	21
7975001000	SODIUM CHLORIDE	5451	$ 13,359.89	460	1
0340001000	AZITHROMYCIN	5317	$ 69,434.58	6	3
2210004500	PREDNISONE	5046	$ 43,208.41	14	8
5025006500	ONDANSETRON	4968	$ 50,715.43	6	3
4155003000	LORATADINE	4895	$ 54,439.01	34	22
4927007010	PANTOPRAZOLE SODIUM	4892	$ 51,323.27	23	22
7510005010	CYCLOBENZAPRINE HCL	4796	$ 51,985.97	43	19
5816004000	FLUOXETINE HCL	4702	$ 87,473.59	32	25
4920002010	RANITIDINE HCL	4626	$ 61,795.57	49	25
7250001010	DIVALPROEX SODIUM	4597	$ 158,284.40	52	19
5925001500	ARIPIPRAZOLE	4592	$ 745,330.20	17	16
6510009510	TRAMADOL HCL	4418	$ 41,233.45	55	16
7210001000	CLONAZEPAM	4370	$ 46,204.59	39	19
7260004000	LAMOTRIGINE	4166	$ 206,097.02	44	22
4155002010	CETIRIZINE HCL	4116	$ 45,824.57	42	22
3320003010	METOPROLOL TARTRATE	4081	$ 33,708.72	64	35
7510009010	TIZANIDINE HCL	4048	$ 90,323.17	48	20
6610005200	MELOXICAM	4042	$ 36,483.87	27	24
5710006000	LORAZEPAM	3889	$ 40,713.00	19	9
4920003000	FAMOTIDINE	3888	$ 30,930.95	23	14
7260004300	LEVETIRACETAM	3838	$ 178,959.13	131	21
7720203000	ERGOCALCIFEROL	3731	$ 39,885.89	5	28
3940007500	SIMVASTATIN	3630	$ 29,028.61	31	31
5830004010	BUPROPION HCL	3541	$ 79,397.11	32	23
5816002010	CITALOPRAM HYDROBROMIDE	3528	$ 34,659.83	27	25
4650001030	DOCUSATE SODIUM	3486	$ 25,513.68	37	19

DUR Activity - Summary

January 1, 2018 - March 31, 2018

Fee For Service

DUR Conflict Code	Severity Level	SumOfTotal Alert Count	SumOfFinal Paid Count	SumOfFinal Reversed Count	SumOfFinal Rejected Count	SumOfOriginal Paid Claim Count	SumOfOriginal Paid to Reversed Claim Count	SumOfOriginal Rejected to Paid Claim Count	SumOfOriginal Rejected to Rejected Claim Count
COMPLIAN	0	54,620	42,990	6,561	5,069	43,436	5,759	5,339	5,043
DDI-DTMS	1	93,920	60,850	15,995	17,075	31,083	12,418	42,244	17,016
DDI-DTMS	2	386,710	273,789	53,928	58,993	267,731	47,886	54,324	58,613
DDI-DTMS	3	116,280	78,819	20,597	16,864	84,907	18,978	13,063	16,691
DOSECHEK	0	108,731	70,839	24,629	13,263	86,580	23,458	7,855	13,125
DRUG_AGE	1	78	54	11	13	55	8	7	13
DRUG_SEX	1	2	-	-	2	-	-	-	2
DUPRX	2	65,857	18,678	5,672	41,507	5,549	2,008	15,157	41,487
DUPTHER	0	159,658	75,596	24,124	59,938	39,469	15,459	51,665	59,859
TOO SOON	0	6,066	74	8	5,984	-	-	74	5,984
TOO SOON	1	1,354	17	5	1,332	-	-	17	1,332
TOO SOON	2	6,030	90	10	5,930	-	-	90	5,930
TOO SOON	3	1,167	21	-	1,146	-	-	21	1,146
		1000473	**621817**	**151540**	**227116**	**558810**	**125974**	**189856**	**226241**

DUR Activity - Detail

January 1, 2018 - March 31, 2018

Fee For Service

DUR Conflict Code	Severity Level	Submitted Generic Name-10	History Generic Name-10	Sum Of Total Alert Count	Sum Of Original Paid Claim Count	Sum Of Original Rejected Claim Count	Sum Of Original Rejected to Paid Claim Count
DDI-DTMS	2	ASPIRIN	LISINOPRIL	4596	2861	1735	393
DDI-DTMS	2	HYDROCODONE-ACETAMINOPHEN	ALPRAZOLAM	3503	2689	814	198
DDI-DTMS	2	QUETIAPINE FUMARATE	DIVALPROEX SODIUM	3455	1898	1557	1001
DDI-DTMS	2	DIVALPROEX SODIUM	QUETIAPINE FUMARATE	2910	2239	671	350
DDI-DTMS	2	MORPHINE SULFATE	GABAPENTIN	2869	2055	814	221
DDI-DTMS	3	ASPIRIN	METOPROLOL TARTRATE	2859	1736	1123	220
DDI-DTMS	2	LISINOPRIL	SIMVASTATIN	2847	2142	705	196
DDI-DTMS	2	LISINOPRIL	ASPIRIN	2815	2093	722	323
DDI-DTMS	2	ALPRAZOLAM	HYDROCODONE-ACETAMINOPHEN	2806	2348	458	141
DDI-DTMS	2	SIMVASTATIN	LISINOPRIL	2688	2092	596	252
DDI-DTMS	2	OXYCODONE HCL	ALPRAZOLAM	2688	2048	640	169
COMPLIAN	0	ALBUTEROL SULFATE		5555	5085	470	185
COMPLIAN	0	GABAPENTIN		1850	1679	171	73
COMPLIAN	0	ATORVASTATIN CALCIUM		1374	1146	228	99
COMPLIAN	0	MONTELUKAST SODIUM		1325	1265	60	20
COMPLIAN	0	LEVOTHYROXINE SODIUM		1217	1077	140	68
COMPLIAN	0	IBUPROFEN		1080	922	158	99
COMPLIAN	0	LISINOPRIL		972	648	324	165
COMPLIAN	0	TRAZODONE HCL		953	690	263	185
COMPLIAN	0	RANITIDINE HCL		853	775	78	16
COMPLIAN	0	AMLODIPINE BESYLATE		852	631	221	91

DUR Conflict Code	Severity Level	Submitted Generic Name-10	History Generic Name-10	Sum Of Total Alert Count	Sum Of Original Paid Claim Count	Sum Of Original Rejected Claim Count	Sum Of Original Rejected to Paid Claim Count
DOSECHEK	0	IPRATROPIUM-ALBUTEROL		5110	4548	562	248
DOSECHEK	0	CYCLOBENZAPRINE HCL		4442	2508	1934	1229
DOSECHEK	0	ONDANSETRON		2862	2529	333	225
DOSECHEK	0	METOPROLOL TARTRATE		2650	2310	340	106
DOSECHEK	0	ALBUTEROL SULFATE		2341	2005	336	116
DOSECHEK	0	LISINOPRIL		2068	2030	38	9
DOSECHEK	0	HEPARIN SODIUM (PORCINE)		2051	1869	182	24
DOSECHEK	0	CHOLECALCIFEROL		1894	1446	448	76
DOSECHEK	0	LEVETIRACETAM		1844	1590	254	64
DOSECHEK	0	QUETIAPINE FUMARATE		1608	1228	380	219
DRUG_AGE	1	ACETAMINOPHEN W/ CODEINE		31	11	20	6
DRUG_AGE	1	NITROFURANTOIN		14	12	2	0
DRUG_AGE	1	PROMETHAZINE HCL		13	13	0	0
DRUG_AGE	1	PROMETHAZINE-DM		12	12	0	0
DRUG_AGE	1	PROMETHAZINE W/CODEINE		6	5	1	1
DRUG_AGE	1	TRAMADOL-ACETAMINOPHEN		1	1	0	0
DRUG_AGE	1	DIPHTHERIA, ACELLULAR PERTUSSIS & TETANU		1	1	0	0
DRUG_SEX	1	EFLORNITHINE HCL		1	0	1	0
DRUG_SEX	1	BICALUTAMIDE		1	0	1	0

DUR Conflict Code	Severity Level	Submitted Generic Name-10	History Generic Name-10	Sum Of Total Alert Count	Sum Of Original Paid Claim Count	Sum Of Original Rejected Claim Count	Sum Of Original Rejected to Paid Claim Count
DUPRX	2	GABAPENTIN		1821	111	1710	520
DUPRX	2	ALBUTEROL SULFATE		1614	141	1473	436
DUPRX	2	LISINOPRIL		1436	138	1298	345
DUPRX	2	SODIUM CHLORIDE		1269	25	1244	2
DUPRX	2	QUETIAPINE FUMARATE		1195	71	1124	420
DUPRX	2	ATORVASTATIN CALCIUM		1140	93	1047	337
DUPRX	2	HYDROCODONE-ACETAMINOPHEN		1061	139	922	21
DUPRX	2	AMLODIPINE BESYLATE		1047	87	960	287
DUPRX	2	CLONIDINE HCL		966	80	886	263
DUPRX	2	METFORMIN HCL		960	41	919	246
DUPTHER	0	QUETIAPINE FUMARATE		5357	857	4500	2871
DUPTHER	0	HYDROCODONE-ACETAMINOPHEN		3262	1530	1732	609
DUPTHER	0	LISINOPRIL		3154	812	2342	936
DUPTHER	0	GABAPENTIN		3146	633	2513	1057
DUPTHER	0	RISPERIDONE		3145	563	2582	1662
DUPTHER	0	MORPHINE SULFATE		3115	2349	766	219
DUPTHER	0	ALBUTEROL SULFATE		2901	619	2282	880
DUPTHER	0	OXYCODONE W/ ACETAMINOPHEN		2784	1664	1120	358
DUPTHER	0	TRAZODONE HCL		2607	432	2175	1134
DUPTHER	0	AMLODIPINE BESYLATE		2349	610	1739	724

DUR Conflict Code	Severity Level	Submitted Generic Name-10	History Generic Name-10	Sum Of Total Alert Count	Sum Of Original Paid Claim Count	Sum Of Original Rejected Claim Count	Sum Of Original Rejected to Paid Claim Count
TOO SOON	2	ALBUTEROL SULFATE		244	0	244	2
TOO SOON	0	ALBUTEROL SULFATE		237	0	237	1
TOO SOON	2	GABAPENTIN		187	0	187	2
TOO SOON	0	GABAPENTIN		172	0	172	2
TOO SOON	0	QUETIAPINE FUMARATE		135	0	135	1
TOO SOON	0	ATORVASTATIN CALCIUM		134	0	134	2
TOO SOON	2	QUETIAPINE FUMARATE		118	0	118	2
TOO SOON	2	ATORVASTATIN CALCIUM		116	0	116	0
TOO SOON	0	TRAZODONE HCL		116	0	116	2
TOO SOON	2	GLUCOSE BLOOD		114	0	114	2