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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Posting:	**March 27, 2017**
Date of Meeting:	**Thursday, April 27, 2017 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:	**Best Western Plus Airport Plaza Hotel** **1981 Terminal Way** **Reno, NV 89502** **Phone: (775) 348-6370** **Webinar Registration** **https://optum.webex.com/optum/onstage/g.php?MTID=e94b5871d7666c230b4168ca1040b1027** **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:	**640 688 550** **Click "Join Now"** **Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. No phone number is required.**

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 26, 2017.

b. Status Update by the DHCFP; Chapter 1200 updates.

4. Board Actions

a. **For Possible Action:** Discussion and approval of Annual Drug Use Review Report.

i. Public comment on proposed report.
ii. Presentation on proposed report.
iii. Discussion by Board and review of proposed data for submission.
iv. Proposed approval of Annual DUR Report for submission to The Centers for Medicare and Medicaid Services (CMS).

5. Clinical Presentations

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

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 eteplirsen (Exondys 51®).

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 nusinersen (Spinraza®).

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

iv. Proposed adoption of updated prior authorization criteria.

6. Public Comment on any DUR Board Requested Report

7. DUR Board Requested Reports

a. Psychotropic medications used for children and adolescents.

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

b. Opioid Utilization – Top prescriber and member.

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

c. Gastroenterology studies in recipients with extended use of proton pump inhibitors.

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

d. Impact of 90-day maintenance medication requirement.

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

8. Public Comment on any Standard DUR Report

9. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q3 2016, Q4 2016 and Q1 2017(by Payment and by Claims).
ii. Top 50 Drugs of Q3 2016, Q4 2016 and Q1 2017 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q3 2016, Q4 2016 and Q1 2017.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

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

9. Closing Discussion

a. Public comments on any subject.

b. Date and location of the next meeting.

i. Discussion of the time of the next meeting.

c. Adjournment.

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

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If requested in writing, a copy of the meeting materials will be mailed to you. Requests and/or written comments may be sent to Ellen Felsing 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 10 days in advance of the meeting, by e-mail at ellen.felsing@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Ellen Felsing at (775) 684-3684.

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MEDICAID
DRUG USE REVIEW BOARD
DRAFT MEETING MINUTES

Date of Meeting: **Thursday, January 26, 2017 at 5:15 PM**

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

Place of Meeting: **Best Western Plus Airport Plaza Hotel**
1981 Terminal Way
Reno, NV 89502
Phone: (775) 348-6370

Committee Members Present: James Marx, MD; Paul Oesterman, Pharm.D.; Chris Shea, Pharm.D.;David England, Pharm.D

Committee Members Absent: Michael Owens, MD;Jeffrey Zollinger, DO

Others Present:
DHCFP: Shannon Sprout, Chief, Program Services; Mary Griffith, RN, Pharmacy Services Specialist; Darrell Faircloth, Deputy Attorney General

HPES: Beth Slamowitz, Pharm.D.

OptumRx: Carl Jeffery, Pharm.D.

Others: Krystal Joy, Otsuka; Betty Chan, Gilead; James Kotusky, Gilead; Sandy Sierawski, Pfizer; John DiMuro, MD
Others On-line: Mark Reynolds; Julayna Meyer, Envolve Health; Georgette Dzwilewski, Indivior; Chris Standfield; Michael Faithe, Amgen; Dr. Shirley Linzy; Jeanette Belz; Ann Nelson; Jeannine Murray, Anthem; Altamit Lewis, Amerigroup

1. Call to Order and Roll Call

Call to order: 5:22 PM

Paul Oesterman, Chair: We will go ahead and call the meeting of the Drug Use Review Board to order. Our first meeting of 2017. I will start with roll call on my far left.

Carl Jeffery, OptumRx

James Marx, Physician, Las Vegas

Dave England, Pharmacist, Las Vegas

Chris Shea, Pharmacist, Reno

Paul Oesterman, Chair, Pharmacist, Reno

Darrell Faircloth, Senior Deputy Attorney General's Office

Shannon Sprout, Chief, Policy Development and Program Management

Mary Griffith, Social Services Program Specialist

2. Public Comment on Any Matter on the Agenda

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from October 27, 2016.

Paul Oesterman, Chair: we have a quorum. I will start by asking for public comment on any item on the agenda. We have some people that have called in, so we will ask for their comment now. Seeing no comment. We will go to the administrative part of the agenda. The first is review and approval of the October meeting minutes. I will ask the Board to review the minutes.

James Marx: I move for approval.

Chris Shea: Second.

Paul Oesterman, Chair: Any further discussion?

Voting: Ayes across the board, the motion carries.

b. Status Update by DHCFP

Paul Oesterman, Chair: Our second administrative item is the status update from the Department and any Chapter 1200 changes.

Mary Griffith: This is Mary Griffith. The legislative session is starting February 6th. It is looking like it will be a very active one. Regarding the policy that was approved by the DUR board last October for the initial 7 day limit on opioid prescriptions, we anticipate that to be implemented after the April 26, 2017 public hearing, so we think it will be the following day on April 27, 2017.

Paul Oesterman, Chair: That is the tentative next DUR Board meeting.

Mary Griffith: I think that is right. That should be implemented the next day. I don't anticipate any problems with that. It is just getting everything ready for the public meeting. We do have another pharmacy person, Heather Labonte, she wasn't able to attend today. She will be able to help out with the pharmacy items going forward. That is all I have for updates.

4. Board Actions

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria for all prescription drugs for Hospice Program recipients.

Paul Oesterman, Chair: We will start with the Board actions. The first is the discussion and possible adoption of updated prior authorization criteria for all prescription drugs for Hospice Program recipients.

Do we have any comment from the public? Seeing none, lets looks at the revised criteria.

Carl Jeffery: The sheet you have is separate from the binder is the most recent we have. Right now the criteria is for members only over 21 years old. We talked about including the under 21 population, but the way it was on the agenda, we were stuck with just over 21. Look at the trends in your binder starting on page 27. You can see a significant drop off on page 28 of when we implemented this last month in December. Requiring a prior authorization has drastically reduced the number of claims we were seeing. Before, a pharmacy could enter an override code without a PA. The hospice agencies were making the call on what they will cover. I haven't heard any complaints about it. We wanted to see about rolling out to kids as well. There are some restrictions with the under 21 members, where we still have to provide medications pursuant to the Affordable Care Act, and EPSDT.

Mary Griffith: Typically members on hospice waive their right to any curative treatment. But because of children, the ACA and the SSA says we cannot restrict children under the age of 21 from being on hospice and seeking curative treatment. So we have that caveat for children under the age of 21. The other consideration is that it isn't that Medicaid won't pay for this treatment, it is just saying that Hospice should be paying. We are not denying services.

Dave England: You are saying, if they are under 21 there is no hospice?

Mary Griffith: If they are under 21, they can get palliative care and a curative treatment. If they needed chemotherapy, they could still get that paid by Medicaid, but anything palliative like pain medications would be covered by hospice. We found we were way over paying for drugs for palliative treatments, so we have to do this to get a handle on it.

Paul Oesterman, Chair: I think the evidence is the significant reduction in the over 21 members.

Mary Griffith: The over 21 went up, and the under 21 went down, so hopefully we will get a handle on it for next time.

Paul Oesterman, Chair: We have the updated proposed guidelines for both age groups. We need a motion and second.

Dave England: So moved.

James Marx: Second.

Voting: Ayes across the board, the motion carries.

b. **For Possible Action:** Discussion and possible adoption of updated criteria for the Controlled Substance Pharmacy Lock-In program.

Paul Oesterman, Chair: Our second Board action includes the discussion and possible adoption of updated criteria for the controlled substance pharmacy lock-in program. Is there any public comment on this topic?

Seeing none in the room or on line.

Mary Griffith: Originally we put it on for a reason, then we found out we should just leave it as is. By that time it was too late to change the agenda. But we left it on for general comment. Currently we have about 1000 people on lock-in. They're put on for drug seeking behavior, we could have many more, but we have to devote more time to it. Maybe with the new person in the office, we can get some more help with it. There are several more people that we could have on this program. We keep them on indefinitely.

James Marx: How do these members get filtered? I have two members that are on it, and neither meet this criteria.

Mary Griffith: They must have met it in the past, we are looking at ER visits and number of prescriptions in 60 days. We are looking for 10 or more within 60 days. That includes ER visits. But they are also looking for diagnosis. If they have a diagnosis of addiction, that is a red flag. We have a nurse that reviews this list of people every month. They also look at diagnosis.

James Marx: Does it look at just controlled substances or all drugs?

Carl Jeffery: Just controlled substances.

Paul Oesterman, Chair: I would like to see something added to be able to take people off the list. It might lighten the load and be able to include other patients.

Mary Griffith: Right, there is some hesitation. People that have addiction will have that forever, but there are some people that could come off. We just haven't figured out the right way.

Carl Jeffery: We have talked about this before. There was a big push to get some behavior therapy and treatment as well for people with addiction.

James Marx: These patients were not addiction patients. I don't know how that criteria was met. They don't use emergency rooms. They may have 10 controlled substances in 60 days.

Mary Griffith: They don't have to meet all of them.

Shannon Sprout: In general, if you find something that is outside of the written policy, you can reach out to Mary and we can look at those recipients. There may be something coming from claims that you have not seen. But we can look at these if you can send the member details.

James Marx: Generally it isn't a problem, but there was one patient the pharmacy that refused to order medications. They changed pharmacies and things are better now. The other patient died. It has never really been a problem, just more of an enigma of why they are locked in.

Mary Griffith: We don't want someone with chronic conditions, we look at other reasons why they may need so much medication~~s~~. It isn't a perfect system. If there is someone that shouldn't be on, we can take a look. What we have found is that that is more of the exception than the rule.

James Marx: I think it is a good program, I just want to make sure we are using it appropriately.

Mary Griffith: We send letters to the doctors too so they are aware.

Dave England: If you look at E, section 1, D – The recipient has been ~~diagnosis~~ **diagnosed** with a drug dependence addiction. It seems even if they didn't meet the other criteria, this alone would be enough to lock them in. The initial event is 10 scripts, but what if it was 8 or 9, but they have drug dependency and the prescriber is trying to keep them under control, the patient could fall through the cracks. I think we may want to look at a lower criteria. Using "or" instead of "and" criteria. I think we may be missing some that should probably be locked in.

Mary Griffith: We can change how we filter the people to get them on the list. We also look at other behaviors and diagnosis.

Dave England: Looking at line number 3 on page 32 in our handout, recipients can change the lock-in pharmacy at any time by contacting the district office. Can the physician make the call to Medicaid to request a change of pharmacy?

James Marx: There are some conditions that allow a pharmacy to request an override. But they have to know to do that and there are some pharmacies that don't know about it.

Paul Oesterman, Chair: I think we are talking two different things. Dr. Marx I think you are talking about a onetime exception, Dave, I think you are talking about a permanent change.

James Marx: The problem is these issues happen on weekends and holidays. The district office has to be open and answering the phone, so there are some conditions that need to be met.

Dave England: Can we change it to recipients or providers can make the change to the lock-in pharmacy. The provider can arrange the pharmacy for the recipient instead of just the recipient.

Mary Griffith: Typically it is the recipient because they choose which pharmacy to change to. As long as the recipient is aware that the pharmacy is going to change, it shouldn't matter where it comes from.

Beth Slamowitz: Either way, it is going to have to come through Medicaid for the change.

James Marx: Could there be some way to notify the recipient they have the ability for an override?

Mary Griffith: Is it on the NOD?

Carl Jeffery: Yes, I think it is on the Notice of Decision.

Paul Oesterman, Chair: What I'm hearing at this point is a recommendation or comment on point number 1, instead of "if" we have an "or" for each of these criteria. Also the second provision would be for number 3, the recipients that are locked in to one pharmacy can change by contacting the district office or the provider can contact the district office. Does that cover what we discussed?

Dave England: Yes that covers what I was talking about.

Carl Jeffery: By provider, do you mean prescriber and pharmacy?

Paul Oesterman, Chair: I would leave it open to both pharmacy and prescriber.

Dave England: That would allow a pharmacy to change the member if they are having trouble.

Mary Griffith: Would that work systematically?

Carl Jeffery: The change is coming from the case workers, so nothing is going to change from our side. We will still get the change form.

Mary Griffith: But on weekends, the district office isn't open.

Beth Slamowitz: If it doesn't make a difference, it still has to come through Medicaid to make the change regardless of who is making the request.

Dave England: I'm not worrying just about nights and weekends.

Beth Slamowitz: During regular business hours to open to the pharmacy and prescriber to request the request is fine.

Dave England: But we should at least give them the option to do that. If it is an emergency situation, they can get an emergency override, the patient should not be without.

Mary Griffith: If the pharmacy is out of stock or the member is out of town are some exceptions to the lock-in requirement. We also have the 96 hour emergency override.

Dave England: The provider has the option to have them go somewhere else.

Beth Slamowitz: Does the 96-hour override work if they are locked in?

Carl Jeffery: The call center can enter overrides if the pharmacy is out of stock.

Mary Griffith: It would be the same situation if the pharmacy is closed, they would still call the call center for the 96 hour override, so it is the same thing.

Carl Jeffery: For the case workers, do they need authorization from the recipient for the provider to work on the recipient's behalf?

Beth Slamowitz: Like a release?

James Marx: I don't think you would have any objection from the recipient. I think another thing coming up with the DEA reduced allocation, this is the first month, after the 25th there may be some shortages all over the place. That will be another can of worms.

Paul Oesterman, Chair: I tried to order some morphine today and they told me my allocation was up. I called and got an override.

Chris Shea: For the 96 hour override, how does the pharmacy know if another pharmacy could help them? Is there an override code they can transmit?

Carl Jeffery: They have to call the call center.

Chris Shea: I asked someone if we accepted a lock-in recipient into a nursing home, we will get a rejection. She said it can take a couple days to get payment and a lot of times the facilities will pay for it until we can get it done. It doesn't sound like the pharmacies are getting a response about who to call for a change.

Carl Jeffery: The override would be immediate if they call.

Paul Oesterman, Chair: To recap, we have proposed revision to the lock-in criteria where we are adding the "or" to points for number 1, and number 3 we will include the provider has the ability to contact the district office to change the pharmacy.

James Marx: Can the call center initiate the request? It is much easier getting the call center than the district office.

Beth Slamowitz: The call center can add a onetime override, where the district office would still need to make the change.

James Marx: I'm not sure we are going to spend the time calling the district office.

Mary Griffith: Is it possible to change the messaging that goes to the pharmacy where they can get a message to call the call center for an override? The pharmacy would be more aware of the options.

Carl Jeffery: I would have to look to see what the message is now, but we can customize the message.

Paul Oesterman, Chair: We need a motion and second to approve the revised policy in regards to lock-in.

James Marx: Was there no formal procedure?

Paul Oesterman, Chair: I think we changed the "if"s to the "or"s and added the provider to change the pharmacy.

Dave England: It is more inclusive and can be changed by various methods.

James Marx: Ok.

Dave England: So moved.

James Marx: Second.

Voting: Ayes across the board, the motion carries.

5. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for the medication class Incretin Mimetics.

Paul Oesterman, Chair: We are moving into our clinical presentations. If people wish to speak, there is a limit of five minutes. The first is the discussion and possible adoption of updated prior authorization criteria and/or quantity limits for the medication class incretin mimetics. Do we have any public comment from the audience?

Hearing none, we will go ahead and look at the proposed criteria.

Carl Jeffery: We have criteria for this class already, but it only includes Bydureon, Byetta and Victoza. There are a couple new agents in the class and some approved but not available yet. The criteria is the same, we just added the new products and updated the quantity limits. The P&T just voted to make all the available products as preferred. Right now a member can get Tanzeum or Trulicity without any restriction. These are pretty mainstream medications, should they still require prior authorization? Could the Board consider removing the PA criteria?

Paul Oesterman, Chair: With the number of co-morbid complications we see with our diabetic population, anything we can do to enhance the patient's access to their medications would be beneficial. I like the idea of removing the criteria completely.

Dave England: Would there be a possibility of having two different agents?

Carl Jeffery: The DUR and pharmacies should catch that.

Dave England: Otherwise, it is part of the treatment, insulin and metformin just don't cut it any more. As long as it is in the mix, that is one less call to make.

Paul Oesterman, Chair: This is standard of care now.

Darrell Faircloth: Did the P&T add any criteria for those that are preferred?

Carl Jeffery: No, the P&T doesn't add any criteria, they just decide what is preferred and non-preferred. They have some authority to add tweaks here and there. But they don't add clinical criteria.

Shannon Sprout: They send that information back to the DUR Board to evaluate the PA criteria.

Dave England: If this is part of the treatment criteria and includes best-practices, and the DUR criteria catches a duplicate, I could see dropping the PA.

Carl Jeffery: The Victoza has a sister drug indicated for weight loss, so maybe requiring a diagnosis related to diabetes, that way you wouldn't get these used for weight loss.

Chris Shea: Patients like Byetta because they lose a lot of weight on it. I could see some weight loss clinics writing for this.

Dave England: Do we want to leave the PA criteria to limit for diabetes?

Carl Jeffery: You could use any of them for weight loss.

Dave England: The PA would validate for diabetes and not for weight loss.

Beth Slamowitz: If you wanted to remove the PA, you could still require a diagnosis submitted on the claim.

Carl Jeffery: On the proposed criteria, it would remove number 3, the step for metformin or sulfonylurea. You're essentially removing that and adding criteria to submit the code.

Paul Oesterman, Chair: That would be better**.**

Beth Slamowitz: You're saying still have the PA and just submit the forms, but you would still have to do it through a PA. It might be a little easier for the pharmacy to submit the diagnosis.

Carl Jeffery: From the system standpoint, it would still deny for PA if for some reason there was no diagnosis on the claim.

Chris Shea: It kicks that back and says it is missing a diagnosis.

Carl Jeffery: The doctor would still need a PA if they didn't write the diagnosis on the prescription.

Paul Oesterman, Chair: It looks like we want to remove the prior authorization process for the incretin mimetics, but the prescription would require a diagnosis code of type two diabetes. Do we have a motion to remove the incretin memetic prior authorization process as it currently stands?

Dave England: So moved**.**

James Marx: Second**.**

Voting: Ayes across the board, the motion carries.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria for Lumacaftor-Ivacaftor (Orkambi®).

Paul Oesterman, Chair: The second possible action is the discussion and possible adoption of updated prior authorization criteria for Lumacaftor-Ivacaftor, Orkambi. Do we have any public comment?

Seeing none, we will go ahead and review the revised criteria.

Carl Jeffery: This is easy**. t**They have an indication down to six years old from 12.

Paul Oesterman, Chair: The use looks pretty consistent, about four claims per month. I think this is straight forward. Do we have a motion and a second?

Dave England: So moved**.**

Chris Shea: Second**.**

Voting: Ayes across the board, the motion carries.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria for medications used for the treatment of opioid dependence.

Paul Oesterman, Chair: The next item is the discussion and possible adoption of updated prior authorization criteria for buprenorphine/naloxone and buprenorphine. We have one person here to speak.

John DiMuro: Good afternoon, I'm Doctor John DiMuro, I'm the Chief Medical Officer for the State of Nevada and I have been working with the senior behavior mental health policy person and Stephanie Woodard as well with Shannon and Mary with DHCFP. A significant barrier to treatment with these patients with substance abuse is the ability to get the Suboxone or buprenorphine to them right away. I feel we need to allow physicians to prescribe these drugs and have the drugs up to 7 days for the patient at the time they are prescribed in the event we are unable to get a prior authorization. We see this is a huge barrier to getting patient treatment immediately and if they don't have the drug right away, they are more apt to not take the drug. After working with Shannon and Mary and Dr. Woodard, we feel this is a significant issue we would like the Board to take into account and allow physicians to prescribe and the prescriptions

filled without the prior authorization for up to 7 days. I prefer seven days over three, it looks like Dr. Marx is the only prescriber here, I'm dual board certified in anesthesiology and pain medicine, always Thursday and Friday, and patients will have issues with their medications. That will also be the time they are considering moving to a buprenorphine drug. If this happens before a holiday, a three day window would not work. So Shannon, Mary, myself and Dr. Woodward feel seven days would be appropriate. We all agree a seven day window would best benefit the patients.

Paul Oesterman, Chair: Does anyone on the Board have questions?

James Marx: As a Suboxone prescriber and addiction specialist, I would take ~~not~~ no exception to seven days, the 72 hour override has worked out fairly well in the past. Some of the manufacturers supply a 15 pill pack and for most that is enough for 3 to 5 days and that is usually enough to get a PA in. I think the seven day is quite reasonable. The problem we see frequently is patients come from acute detox without any prescription for buprenorphine or given an appointment for ten days. I think it is a great idea.

Paul Oesterman, Chair: We do have the proposed criteria with the initial seven day supply. Carl, do you want to recap?

Carl Jeffery: I wasn't at the public hearing a few weeks ago where this was discussed?

Mary Griffith: There was not a lot of people there because of the snow storm.

Carl Jeffery: We met with Dr. DiMuro to refine a seven day supply recommendation. Essentially how the process works is: a patient new to therapy would present the prescription to the pharmacy, it would reject initially, but give a message to use an override code from the pharmacy to allow the seven day fill. There is no phone call involved or anything, the pharmacy gets a paid claim for seven days. It is also the understanding that the pharmacy is responsible to follow up with the prescriber to get the PA submitted. That is part of the criteria too. But this allows an immediate seven day supply to start therapy right away. The rest of the criteria has not changed.

Paul Oesterman, Chair: With these patients, they go off treatment and then want to restart. If you have a PA on file that has elapsed, but now they come to request another seven days, how will that be addressed?

John DiMuro: What we discussed in order to make a Suboxone naïve patient, is if the patient goes seven days without taking the medication, that would make them a naïve patient again. Dr. Marx, I'm not sure if you have any input.

James Marx: I think that is reasonable. I'm not sure any amount of time is reasonable.

John DiMuro: This is important for us to define what a new prescription would be.

James Marx: Usually the lapse would not be that short of a period of time, it is usually several months or years. I don't think it is very likely you are going to see someone lapse for one week.

Beth Slamowitz: To clarify, from a system perspective, once the prior authorization goes into the system, it is good for a year, regardless of how much of a lapse, they could come back six months later and get the medication again. It would only be after the PA has expired.

Paul Oesterman, Chair: Ok, good, that is what I was looking for. Thank you. We have the proposed criteria for the initial seven day supply, the pharmacy submits the PA type and number. Having not worked retail, are most prescriptions for this coming into the pharmacy with an ICD code on it?

Carl Jeffery: I'm not sure.

James Marx: We will write for pain if not for an indication of opioid dependence. This brings up criteria number three. We had a member on Belbuca, he was a pain patient, and he actually preferred Suboxone to oxycodone. He lost his job and was given Medicaid. We wanted to continue Suboxone, but it wasn't allowed because it was being used for pain. He was on 900mcg of Belbuca instead, but the Suboxone was denied. Belbuca has no contraindication to concurrent use of conventional opioid agonists for breakthrough pain, but the Suboxone does. We have other treatments with buprenorphine that are effective for the treatment of pain.

Mary Griffith: So you're saying it is not FDA indicated for pain?

James Marx: Buprenorphine is approved for pain, but not the Suboxone, the Belbuca is. It is a little ironic that we have two opposing philosophies here. One that is more cost effective than the other. There are some other positive features as well, even though there is a diversion potential for Suboxone. It has become a popular drug, particularly in correctional institutions. It think this has become very complex.

Paul Oesterman, Chair: We have the proposed criteria, the prior auth would still be for a year, and the initial seven days would be authorized. Do we have a motion?

James Marx: What would be the impact of deleting criteria number 3, the diagnosis of chronic pain will not be approved. This would allow the use for chronic pain.

Beth Slamowitz: Suboxone would have to have an FDA approved indication for pain in order for Medicaid to pay for it.

Carl Jeffery: The Belbuca is not normally included in this class. It is buprenorphine, but it is not included in this category.

Dave England: If this is needed to be used for pain, could the physician go through the call center to get it approved for something off-label? We have discussed this in the past, as long as there is some documentation.

James Marx: If the doctor wants to, they can bend the criteria. For someone with pain, you could make the case they are opioid dependentee. I have to say I have done that once or twice.

Beth Slamowitz: You said you have some patients you use to treat pain and on short acting for breakthrough. tThe system may catch that.

James Marx: It doesn't and it didn't.

John DiMuro: I agree that Suboxone can be used for pain. My experience is that patients will use Suboxone for pain, and still take other opioids. I would support a rule that would be by the book. Suboxone is not indicated for pain. I think if we are going to make a rule, then we should stick with what is FDA approved.

Paul Oesterman, Chair: Do we have a motion to approve the updated criteria for buprenorphine and combo products.

James Marx: So moved.

Dave England: Second.

Voting: Ayes across the board, the motion carries.

6. Public Comment on any DUR Board Requested Report

7. DUR Board Requested Reports

Paul Oesterman, Chair: At this point, is there any public comment on the DUR Board requested reports? Seeing none. The first report is the detailed utilization of the top utilizers of opioids. Carl can you explain this report?

Carl Jeffery: This is a carryover from the last meeting. We had a list of top utilizing members for opioids. The Board requested a drill down into that data so we can see what those members are using. I did as much as I could without disclosing any HIPPA data. The encrypted ID is A through J.

Paul Oesterman, Chair: The encrypted ID is the member, and they are letters.

Carl Jeffery: The prescribers are defined with a number, one through 23. This is where it gets confusing because it is not the number of prescribers. It is an identifier. Patient C, has 6 differen~~ce~~t prescribers. That is how those numbers are used. There was a patient that was on large amounts of methadone. We wanted to see what else they were getting. The column is count of date of fill, I can't list the actual date of fill because that may give a clue who the member is. This is a 13 month period. Patient A, hydromorphone, they had 26 fills in 13 months. Sum of the quantity is how many units they have received, the sum of days supply and sum of pharmacy paid.

Paul Oesterman, Chair: Let's look at number A, hydromorphone has 715 total days supply.

Carl Jeffery: It combines different strengths. So if they were on two different strengths, it is the same with the hydrocodone/acetaminophen. You would have to break it down even more to see the different strengths.

Paul Oesterman, Chair: It would be interesting to see if any of these patients are in the lock-in program.

Carl Jeffery: My intent with the prescriber numbers is to compare prescribers across patients. G. is the one with huge amounts of methadone, almost 3800 units of methadone.

Paul Oesterman, Chair: It would be interesting, this report is based on initial slice of patients, it would be interesting to see the top 10 prescribers the next time.

Carl Jeffery: We have looked at prescribers before. We can look at that again.

Chris Shea: Is this cross referenced to the PMP?

Carl Jeffery: I don't have access to the PMP, but it might be interesting to see what else these members are getting.

Paul Oesterman, Chair: A possible action item for next time would be ~~is~~ to request further evaluation or propose criteria. At this point, I don't see any criteria we could implement, other than looking at the lock-in for these recipients.

Carl Jeffery: We can pull out the lock-in people to see. These members could also be in lock-in. They just go to one pharmacy.

Paul Oesterman, Chair: On patient C, a fair number of products were filled only once or twice. The oxycodone seems to be consistent. There are 13 fills from two different providers. That seems to be a red flag. We need a motion to request further reports to get the top ten prescribers for next time.

Mary Griffith: Do you want to further drill down on this report?

Paul Oesterman, Chair: I don't know what ability we have to do that while still complying with HIPPA.

Mary Griffith: These don't include any benzos or anything else do they?

Carl Jeffery: No, these are only opioids.

Mary Griffith: Would it be a benefit to drill down to what else is being prescribed?

Beth Slamowitz: You could cross reference the top 10 prescribers with the top recipients to see if there are any connectors. Then you can look for maybe problem prescribers.

Paul Oesterman, Chair: We are going to look at the top 10 prescribers with a cross reference to the top recipients. We are looking for maybe some additional lock-in patients and prescribers that may need some education.

Chris Shea: The PMP will tell you all this information already and it defines how the patient pays. You may want to talk to the Board of Pharmacy because they track all this already. They are changing tracking to identify prescribers. Can you collaborate with the Board of Pharmacy?

James Marx: I'm not sure that is true, there are filters to track prescribers.

Chris Shea: They were not tracking prescribers is what I was told.

James Marx: It would identify prescribers that were over the normal. There ~~were~~ was always a list of the top prescribers.

Chris Shea: But that information is there, it might make sense to collaborate with them?

Dave England: Can these databases be interrelated? Can the task force and the Medicaid data be combined?

Beth Slamowitz: The difference is Optum will pull the claims data for fee for service. The PMP should be able to pull the same thing, but it would include other payers if they can do that.

Dave England: But we still have to ask the question to compare.

James Marx: It would have to be done in tandem.

Beth Slamowitz: If they have the same fields available, they should be able to run the same report.

Paul Oesterman, Chair: Does the Board itself have access to PMP data?

Carl Jeffery: I think we would be ok to ask for an aggregate report. We wouldn't report certain doctors or patients.

Dave England: You would just do the same like this report with the identifiers.

Paul Oesterman, Chair: Our next step ~~are~~ is to request the top ten providers to see if we can get PMP data cross referencing the existing report we have today. Is there anything else we want? We have a motion on the floor, and Chris has seconded.

Voting: Ayes across the board, the motion carries.

Paul Oesterman, Chair: Our next topic is utilization of agents used for the treatment of opioid induced constipation.

John DiMuro: Can I make a comment on that last section? I wanted to apprise the Board of some news. The controlled substance bill sponsored by the Governor will address everything we have discussed here. When it comes to the data, there are significant areas that lack, and I want to point those out to you. Number one is the providers you are going to research**.** We do not break down to pain specialist, addiction specialist, oncologist, primary care in the rural areas. So don't let the numbers fool you when looking at the top ten prescribers. Number two, you mentioned before, some patients filled 23 prescriptions in 12 months. That is ok if the provider has them on a two week plan. For some patients, it may be necessary for appropriate care to see that patient every two weeks. The high doses may be inherited from other providers. The other thing is what are we going to do with this data**?** If the DO Board had a problem with an osteopath, they can send a document and the physician has to write back and the case can be closed. In the case of the MD Board, if they asked for a response in a letter, it was a formal

investigation. Working with the Board of Pharmacy, we are going to make all the boards equal, so the boards can question the licensees. It will be up to the boards to hold the licensees responsible. Why would a patient receive so many doses from a prescriber? Because there are no flags in the PDMP. The PDMP is not working like it should. Dr. Rand was performing a service. I had a wait of three months to see me, so it falls on these primary care physicians to prescribe controlled substances. I can't blame the physician for that. We have to use our technology better. We need to put flags in the PDMP to catch prescribers. I don't want to prohibit a physician for being scared to write a prescription because we know the illicit will go up. The State of Vermont is going to see that with what they are writing in their bill. So what we are writing is getting buy in from all the groups including oncology. In one way, I want to let you know we have addressed everything you are talking about. In the other way, when you get that data, I ask you peel it apart. I asked the boards that when physicians renew their license, they indicate their area of specialty. I have recommended your level of training be your level of specialty. When we put the flags in the PDMP, now we can see if they are a family practice or someone else. If the flags are correct, we will be able to catch physicians.

James Marx: In the last two months**,** I have patients coming from oncologists that refuse to write for pain medications. It is a sad situation when a cancer patient can't get pain meds because their oncologist is afraid of making them an addict.

John DiMuro: I have not seen that. That is a shame.

Paul Oesterman, Chair: Over the years, I have seen a pendulum with prescribing of opioids. It sounds like the bill will address some of this. I appreciate you pointing out that we really need to look closely at the data. I would expect most of the prescribers to be pain specialists.

John DiMuro: You would expect that, but you may not be able to get that data. You are going to have to go to the boards or the individual to get that information. This is what I have run into while drafting this legislation. I didn't want the Board to go out of the way to get information that won't mean much.

James Marx: Which bill are you referring to?

John DiMuro: The governor's bill**.** We don't have a number yet. It is called controlled substances for pain. It is not just an opioid bill. It is all controlled substances for pain. Benzos are often used for pain, but we want to keep it open for other indications.

Paul Oesterman, Chair: We will ask for any public comment on the opioid induced constipation. Hearing none. For our opioid induced constipation, we requested this report.

Carl Jeffery: We put some PA criteria a few meetings ago, the criteria was enacted in October. Movantik's utilization dropped significantly. This report is a follow up. There is another new agent, so we will likely see this again.

Paul Oesterman, Chair: Does anyone on the Board have any further information on this? The evidence of the PA impact is on the graph. No additional action there. Item 7c, the gastroenterology studies are not available. Can we defer that to the next meeting? The utilization of codeine containing cough suppressants, we have the utilization data. Looking at the data, the

days supply per member seems reasonable. The usage appears to be seasonal which is to be expected. We have a number of different products that are in the breakdown that are a combination of guaifenesin and codeine. I don't know how they are listed as brand or generic.

Carl Jeffery: They have a different name, so they fall in the report as a separate product.

Paul Oesterman, Chair: The big one is still the promethazine with codeine.

Carl Jeffery: The column second from the right is the most telling. There is nothing out of line here, between 100 and 200 mls per prescription.

8. Public Comment on any Standard DUR Report

9. Standard DUR Reports

Paul Oesterman, Chair: I don't see anything we need to review further on this, anyone else on the Board?

The next ~~is~~ item is any public comment on any standard DUR report? Seeing none. We have our prescribing/program trends. Looking at Q3 and Q4 is identical, it looks like someone did a copy and paste. One of them is not right. On the top 10 drug by claim, quarter 4 of the classes are in the same order as quarter 2, but the pharmacy paid amounts are different. Q3, the ulcer drugs jumped into the fray. It is interesting to see a good trend, the opioid analgesics show a gradual decline.

Carl Jeffery: The hepatitis agents, on page 91, appear to be stabilizing. I still don't know how to manage hemophilia agents. Those are going to take some specific case management.

Paul Oesterman, Chair: Anyone on the Board have any comments on these reports? Seems like the quantities are all reasonable for these medications.

Carl Jeffery: Speaking of maintenance, we are going to start February 20, a mandatory maintenance medications. After the first fill**,** will require a three months supply minimum.

Mary Griffith: We do not include long term care claims.

James Marx: What is the intended, compliance or cost?

Carl Jeffery: A little of both, our dispensing fee is $10. If we can eliminate two dispensing fees**…**

Paul Oesterman, Chair: Would we see a report at the next meeting to see how that is progressing?

Chris Shea: Are you going to require that? Part D has short cycle drugs and 30 day supplies. If you require 90 days of a branded drug of an expensive drug, for the cheap drugs makes sense, but for high dollar drugs…

Carl Jeffery: We set a threshold of $500 per month, because some of the antidiabetics are expensive, but none of the agents hit $500 per month with the normal dose.

Beth Slamowitz: I think after some time, we can change the threshold, but we needed a starting point. A lot is access to care, especially in the rural areas. Many pharmacies may not know about the ability to get a 90 day supply.

Chris Shea: I think it makes sense for a lot of medications. Every time you touch a prescription**,** it costs money. I just thought for the high dollar drugs, it may not make sense.

Beth Slamowitz: We looked at that list, and that threshold may change.

Carl Jeffery: It doesn't take too many lost prescriptions before we lose any benefit.

Mary Griffith: If they have a primary insurance, then we should not require this.

Carl Jeffery: Right, we follow the rules of the primary when they have one.

Paul Oesterman, Chair: We have our pro-DUR and Retro-DUR, Carl, do you want to give us an update**?**

Carl Jeffery: For the retro-DUR, we will have something next meeting, we are in a transition. The Pro-DUR is just more of the same. I don't see anything that stands out on this one.

Paul Oesterman, Chair: These include physician administered claims because there is a lot of midazolam**.**

Carl Jeffery: Right, we process the physician administered drug claims and we use this edit to catch duplicates.

Darrell Faircloth: Do all physician administered drugs come into the pharmacy system?

Carl Jeffery: Yes.

Mary Griffith: These DUR edits, on NVPAD claims, who gets the message**?**

Carl Jeffery: If a pharmacy runs it, they will see the message. The only ones we really apply to the PAD claims ~~is~~ **are** the duplicates, and that is how we edit that. It is a hard stop, messages don't go anywhere. A pharmacy would see it if the PAD claim came in before they ran it.

9. Closing Discussion

Paul Oesterman, Chair: Any comments on these reports? Is there any other public comments?

Our next meeting is April 27, 2017. We should have a discussion of the time of the meeting, is this time ok?

Chris Shea: This time works for me.

Paul Oesterman, Chair: Ok, we will keep it at 5:15. The meeting is adjourned.

Meeting adjourned: 7:08 PM

Symlin Utilization

4/1/2016 - 3/31/2017

Year/Mo Filled	Product Name	Count of Members	Count of Claims	Qty Total	Days Supply	Pharm Paid
201610	SYMLINPEN 60	1	1	15	83	$ 3,578.78
201701	SYMLINPEN 60	2	2	21	113	$ 5,016.40

J. Pramlinitide Injection (Symlin®)

Therapeutic Class: Antihyperglycemic, Amylin Analog-Type
Last Reviewed by the DUR Board: September 21, 2006

Pramlinitide injection is subject to prior authorization and age restriction:

1. Coverage and Limitations (For recipients 15 years or older)

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

a. Diagnosis of Type 1 or Type 2 Diabetes Mellitus;

b. Documentation that recipient has not achieved desired HbA1c despite optimal insulin therapy;

c. Documented HbA1c<9%;

d. Patient is competent and has received diabetic education, able to self-administer drug, and willing to perform blood glucose monitoring;

e. Approval period of six months; and

f. Exclusion criteria:

1. HbA1c>9%;

2. Confirmed diagnosis of gastroparesis;

3. Use of drugs that alter GI motility;

4. Presence of hypoglycemia unawareness; and

5. Use of alpha-glucosidase inhibitors (e.g. acarbose, miglitol).

2. Prior Authorization Guidelines

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

Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects approximately 29.1 million people in the United States (U.S.), which is approximately 9.3% of the population (American Diabetes Association [ADA] Diabetes Basics, 2017).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (ADA Diabetes Basics, 2017).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (ADA, 2017).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, and lixisenatide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (SAXENDA®) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ADLYXIN™ (lixisenatide)	Sanofi-Aventis	07/27/2016	-
BYETTA® (exenatide)	AstraZeneca	04/28/2005	-
BYDUREON® (exenatide ER)	AstraZeneca	01/27/2012	-
SYMLIN® (pramlintide)	AstraZeneca	03/16/2005	-
TANZEUM® (albiglutide)	GlaxoSmithKline	04/15/2014	-
TRULICITY® (dulaglutide)	Eli Lilly	09/18/2014	-
VICTOZA® (liraglutide)	Novo Nordisk	01/25/2010	-

(DRUGS@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ADLYXIN (lixisenatide)	BYETTA (exenatide)	BYDUREON (exenatide ER)	SYMLIN (pramlintide)	TANZEUM (albiglutide)	TRULICITY (dulaglutide)	VICTOZA (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✔			
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✔			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✔	✔	✔		✔	✔	✔
Limitations of Use							
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔		✔	✔	✔
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔		✔	✔	✔
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔	✔	✔		✔	✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.					✔	✔	
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔						
Not studied in combination with prandial/short-acting insulin.	✔	✔			✔		✔
Use with insulin has not been studied and is not recommended.			✔				

(Prescribing information: BYETTA, 2015; BYDUREON, 2015; SYMLIN, 2015; VICTOZA, 2016; TANZEUM, 2016; TRULICITY, 2017)

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

CLINICAL EFFICACY SUMMARY

Albiglutide

- The approval of albiglutide was based on 8 pivotal trials involving over 5000 patients as a part of the HARMONY phase 3 program (TANZEUM FDA Medical Review, 2014; TANZEUM prescribing information, 2016). The majority of the trials were multicenter (MC), randomized, double-blind (DB), placebo-controlled (PC) or active control (AC) studies in adult patients with inadequately controlled T2DM (HbA1c 7% to 10%); however, 3 trials were open-label (OL). The primary outcome in each trial was the change in HbA1c from baseline at 26 to 104 weeks.
- HARMONY 1 demonstrated that albiglutide 30 mg once weekly was superior to placebo in patients taking concurrent pioglitazone with or without metformin at 52 weeks, with a mean reduction in HbA1c of 0.8% (Reusch et al, 2014).
- HARMONY 2 compared both albiglutide 30 mg and 50 mg once weekly to placebo in patients treated with diet and exercise alone and found that both were superior to placebo at 52 weeks. The least squares mean difference from placebo in HbA1c was -0.84% with the 30 mg dose and -1.04% with the 50 mg dose (Nauck et al, 2016).
- HARMONY 3 demonstrated that albiglutide 30 mg to 50 mg once weekly was superior to placebo, sitagliptin 100 mg once daily, and glimepiride 2 to 4 mg daily in patients taking concurrent metformin at 2 years, with a mean reduction in HbA1c of 0.6% (Ahren et al, 2014).
- HARMONY 4 was an OL trial comparing albiglutide (30 mg to 50 mg once weekly) to protocol titrated insulin glargine in patients taking concurrent metformin with or without an SFU. In this study, albiglutide demonstrated noninferiority to insulin glargine in HbA1c improvement at 52 weeks (Weissman et al, 2014).
- HARMONY 5 compared albiglutide (30 mg to 50 mg once weekly) to placebo and pioglitazone (30 mg to 45 mg per day) in patients taking concurrent metformin and glimepiride. At week 52, albiglutide did not meet the pre-specified noninferiority margin compared to pioglitazone; however, it was superior to placebo and had a mean reduction in HbA1c of 0.6% (Home et al, 2015).
- HARMONY 6, another OL trial, demonstrated that albiglutide 30 mg to 50 mg once weekly was noninferior to insulin lispro 3 times daily in patients taking concurrent pioglitazone with or without metformin at 26 weeks, with a mean reduction in HbA1c of 0.8% (Rosenstock et al, 2014a).
- HARMONY 7 was an OL study comparing albiglutide 50 mg once weekly to liraglutide 1.8 mg daily in patients taking concomitant metformin, TZD, SFU, or a combination of the medications. At week 32, the mean model adjusted change in HbA1c was -0.78% with albiglutide and -0.99% with liraglutide. Albiglutide failed to meet noninferiority (P=0.085) (Pratley et al, 2014).
- HARMONY 8 demonstrated that albiglutide 30 mg to 50 mg was superior to sitagliptin 25 to 100 mg in patients with impaired renal function on concurrent agents or lifestyle treatment at 26 weeks, with a mean reduction in HbA1c of 0.8% compared to a reduction of 0.5% with sitagliptin (Leiter et al, 2014).

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
- AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (Wysham et al, 2014).
- AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (Giorgino et al, 2015).
- AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (Umpierrez et al, 2014).
- AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro (P=0.005 and P=0.015 for dulaglutide 1.5 mg and 0.75 mg, respectively) (Blonde et al, 2015).
- AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline (P<0.001 for all comparisons) (Nauck et al, 2014; Weinstock et al, 2015).

- AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (Dungan et al, 2014).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 PC, 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo (P<0.001, P<0.002, and P<0.0001, respectively) (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (Blonde et al, 2006; Buse et al, 2007; Klonoff et al, 2008; Ratner et al, 2006; Riddle et al, 2006).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c (P<0.001), fasting plasma glucose (FPG) (P<0.001), and body weight (P<0.001) compared to placebo (Zinman et al, 2007).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) (P<0.001 for both), whereas the SFU caused significant increases in both (P<0.05 for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; P<0.001 for all; glyburide; P<0.001 for all). Only exenatide significantly improved insulin resistance (P<0.01) and β-cell function (P<0.05) (Derosa et al, 2010).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; P=0.002) (Gallwitz et al, 2012).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (Bunck et al, 2009; Bunck et al, 2010; Davies et al, 2009; Heine et al, 2005; Nauck et al, 2007; Secnik et al, 2006). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was “superior” in decreasing FPG (P value not reported and P<0.0001), while in another trial there was no difference between the 2 treatments (P=0.689). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (Bunck et al, 2009; Heine et al, 2005; Nauck et al, 2007). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores (P=0.93 for both) (Secnik et al, 2006).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (Inagaki et al, 2012).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (Bergenstal et al, 2010; Blevins et al, 2011; Diamant et al, 2010; Drucker et al, 2008; Russell-Jones et al, 2012). Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide (P<0.005), sitagliptin (P<0.0001), pioglitazone (P=0.0165), and insulin therapy (P=0.017), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was “superior” compared to sitagliptin (P=0.0002) and pioglitazone (P<0.0001), and similar compared to exenatide (P=0.89) (Bergenstal et al, 2010; Blevins et al, 2011; Drucker et al, 2008). As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs. 35.0%) and vomiting (4.7% vs. 8.9%), and higher incidences of diarrhea (9.3% vs. 4.1%) and injection site-related AEs (13% vs. 10%) (Blevins et al, 2011).
- In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was “superior” compared to sitagliptin (P<0.001) and similar compared to metformin (P=0.62) and pioglitazone (P=0.328). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving “superiority” compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (Diamant et al, 2010).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (Bergenstal et al, 2013).

- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (Buse et al, 2013).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
- In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo (P<0.0001 for all), with only higher doses achieving "superiority" compared to rosiglitazone (P<0.001 for both) (Marre et al, 2009).
- In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo (P<0.01) and the SFU (P<0.001) (Nauck et al, 2009). Results of an 18-month OL extension trial were consistent with the DB study (Nauck et al, 2013).
- In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was "superior" in decreasing HbA1c (P=0.0014 and P<0.0001 for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight (P=0.027) (Garber et al, 2009). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (Garber et al, 2011).
- In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (Russell-Jones et al, 2009; Zinman et al, 2009). When compared to insulin therapy, decreases in HbA1c (P=0.0015) and body weight (P<0.001) and improvements in β-cell function (P=0.0019) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (Russell-Jones et al, 2009).
- LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; P<0.0001), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of <7%. Significant decreases in FPG were also achieved with liraglutide (P<0.0001); however, exenatide significantly decreased PPG after breakfast and dinner (P<0.0001 and P=0.0005) (Buse et al, 2009). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (Buse et al, 2010).

Lixisenatide

- Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
- GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise (P<0.0001) (Fonseca et al, 2012).
- GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs. placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs. -0.72% for the lixisenatide group. The difference vs. placebo was -0.46% (P<0.0001) (Adlyxin prescribing information, 2016; Bolli et al, 2014).
- GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (Yu et al, 2014).
- GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% (P<0.0001) (Adlyxin prescribing information, 2016; Rosenstock et al, 2014b).

- GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% (P<0.0001) (Adlyxin prescribing information, 2016; Pinget al, 2013).
- In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs. placebo (Riddle et al, 2013a).
- In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (Riddle et al, 2013b; Seino et al, 2012).
- GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs. insulin glulisine 3 times daily was 0.23 (P=0.0002) (Adlyxin prescribing information, 2016; Rosenstock et al, 2016).
- GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs. exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs. exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs. exenatide was 0.17% (P=0.0175) (Adlyxin prescribing information, 2016; Rosenstock et al, 2013).

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials with exenatide (EXSCEL, results expected in 2018), albiglutide (results expected in 2019), and dulaglutide (REWIND, results expected in 2019) (ClinicalTrials.gov, 2016).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs. the placebo group (14.9%) (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs. the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs. the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; P=0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (Marso et al, 2016a).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs. placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo (P<0.001), but did not demonstrate superiority (P=0.81).The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (Pfeffer et al, 2015).
- Semaglutide, a once-weekly GLP-1 receptor agonist in the pipeline, demonstrated reduced CV risks in the SUSTAIN-6 trial when compared to placebo. A larger confirmatory trial is planned by Novo Nordisk, which is also expected to gather additional data on retinopathy complications reported in earlier studies (Marso et al 2016b, Skydsgaard 2016).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (Wang et al, 2013; Shyangdan et al, 2011; Sun et al, 2015).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight

loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (Htike et al, 2016).

- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of CV events (Monami et al, 2014b) or pancreatitis (Monami et al, 2014a) compared to placebo or other antidiabetic agents.

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; P=0.0071) and was also associated with a significant weight loss compared to placebo (P<0.001) (Whitehouse et al, 2002). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs. -0.18%; P=0.012) and pramlintide 60 mcg 4 times daily (-0.39 vs -0.18%; P=0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (P=0.011 and P=0.001 for the 3- and 4 times daily dosing, respectively) (Ratner et al, 2004).
- A meta-analysis of 3 studies assessing the effect of pramlintide as adjunctive therapy in patients with T1DM reported that, compared to placebo, pramlintide resulted in significant reductions in HbA1c and body weight from baseline to week 26 (0.3% and 1.8 kg, respectively; both P≤0.0009) (Ratner et al, 2005).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N=930; 16 to 52 weeks duration) and 4 obesity studies (N=686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; P=0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤7% than patients in the control group; however, this difference was not significant (P=0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; P<0.00001) (Singh-Franco et al, 2011).

Clinical Guidelines

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines state that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (ADA, 2017; Garber et al, 2017; Inzucchi et al, 2015).

SAFETY SUMMARY

- Contraindications:
  - o Hypersensitivity to the drug or any of its components.
  - o BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide) are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
  - o SYMLIN (pramlintide): Gastroparesis and hypoglycemia unawareness.
- Boxed warnings:
  - o BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide) and VICTOZA (liraglutide)
    - Cause thyroid C-cell tumors in rats and mice. It is unknown if they cause thyroid C-cell tumors including MTC in humans.
    - They are contraindicated in patients with a personal or family history of MTC or in patients with MEN 2.
  - o SYMLIN (pramlintide)
    - Use with insulin has been associated with an increased risk of severe hypoglycemia, particularly in patients with T1DM.
- Warnings/Precautions:

- o ADLYXIN (lixisenatide), BYETTA (exenatide), BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide)
  - Pancreatitis – There have been reports of fatal and nonfatal hemorrhagic or necrotizing pancreatitis. Consider other therapies in patients with a history of pancreatitis.
  - Hypoglycemia – Risk is increased when used with insulin or insulin secretagogue.
  - Renal impairment – There have been post-marketing reports of altered renal function including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation.
- o BYETTA (exenatide), BYDUREON (exenatide ER), and TRULICITY (dulaglutide)
  - Severe GI disease – Use is not recommended.
- o ADLYXIN (lixisenatide), BYETTA (exenatide), and BYDUREON (exenatide ER)
  - Immunogenicity – Patients can develop antibodies; glycemic control may be lost. Consider other therapies if there is worsening of glycemic control or failure to achieve the glycemic target.
- o ADLYXIN (lixisenatide), BYETTA (exenatide), SYMLIN (pramlintide), and VICTOZA (liraglutide)
  - Pens should never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.
- o SYMLIN (pramlintide)
  - Hypoglycemia – Risk is increased when used with insulin or insulin secretagogue.

- Adverse events:
  - o The most common AEs seen with these agents are nausea and vomiting which generally decrease over time.
- Drug Interactions:
  - o Orally administered drugs – Absorption of oral drugs can potentially be delayed. If absorption is critical to an oral drug's effectiveness, it should be given 1 hour before ADLYXIN (lixisenatide) or BYETTA (exenatide), and 1 hour before or 2 hours after SYMLIN (pramlintide).
  - o Insulin – Mixing SYMLIN (pramlintide) and insulin can alter the pharmacokinetics of both products, leading to inadequate glucose control or hypoglycemia. They should never be mixed.
- Risk Evaluation and Mitigation Strategy (REMS) programs:
  - o TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide)
    - The REMS programs for these agents include a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC.
  - o SYMLIN (pramlintide)
    - The REMS program includes a communication plan informing healthcare providers of the risk of severe hypoglycemia when this agent is used in combination with insulin as well as the importance of proper patient selection for treatment with this drug.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ADLYXIN (lixisenatide)	Injection (50 mcg/mL): 3 mL prefilled pen (14 pre-set doses; 10 mcg per dose) Injection (100 mcg/mL): 3 mL prefilled pen (14 pre-set doses; 20 mcg per dose)	Initiate at 10 mcg subcutaneously (SC) once daily for 14 days; on day 15, increase dosage to 20 mcg once daily	--	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
BYETTA (exenatide)	Injection (250 mcg/mL): 1.2 mL prefilled pen, 5 mcg per dose, 60 doses 2.4 mL prefilled pen, 10 mcg per dose, 60 doses	Initiate at 5 mcg SC twice daily; increase to 10 mcg twice daily after 1 month based on clinical response.	--	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to morning and evening meals (or

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
				before the 2 main meals of the day, approximately 6 hours or more apart).
BYDUREON (exenatide ER)	Injection tray: Single-dose vial containing 2 mg exenatide powder and 1 prefilled syringe delivering 0.65 mL diluent Pen injection: Single-dose pen containing 2 mg exenatide per 0.65 mL diluent	Administer 2 mg SC once every 7 days (weekly).	If a dose is missed, administer as soon as noticed as long as the next dose is due at least 3 days later.	Inject in the thigh, abdomen, or upper arm. Administer at any time of day with or without meals. Administer immediately after the powder is suspended.
SYMLIN (pramlintide)	Injection (1,000 mcg/mL): 1.5 mL disposable multidose SYMLINPen® 60 pen-injector for 15, 30, 45, and 60 mcg doses; 2.7 mL disposable multidose SYMLINPen 120 pen-injector for 60 and 120 mcg doses	T1DM 15 mcg SC immediately prior to major meals. Increase the dose to the next increment (30 mcg, 45 mcg, or 60 mcg) when no clinically significant nausea has occurred for at least 3 days. T2DM 60 mcg SC immediately prior to major meals. Increase dose to 120 mcg when no clinically significant nausea has occurred for 3 days.	Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (70/30) by 50%. Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. Dose should be decreased If significant nausea persists.	Inject in the thigh or abdomen. Bring to room temperature prior to injecting. Administer immediately prior to each major meal (≥250 kcal or containing ≥30 g of carbohydrate).
TANZEUM (albiglutide)	Single-use pen for injection: 30 mg, 50 mg	30 mg SC once weekly; dose may be increased to 50 mg once weekly if the glycemic response is inadequate.	If a dose is missed, administer as soon as possible if within 3 days and resume dosing on usual day of administration. If it is more than 3 days after the missed dose, skip dose, and administer at next regularly scheduled weekly dose.	Inject in the thigh, abdomen, or upper arm. Administer on the same day each week. Day may be changed if necessary, so long as the previous dose was administered ≥4 days prior. Wait 15 minutes for the 30-mg pen and 30 minutes for the 50-mg pen after the

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
				lyophilized powder and diluent are mixed to ensure reconstitution.
TRULICITY (dulaglutide)	Single-dose pen or prefilled syringe: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL	0.75 mg SC once weekly; dose can be increased to 1.5 mg once weekly for additional glycemic control.	If a missed dose occurs and there are at least 3 days (72 hours) until the next scheduled dose, administer the dose. If less than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day.	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. The day of weekly administration may be changed if necessary as long as the last dose was administered 3 or more days before.
VICTOZA (liraglutide)	Injection (6 mg/mL): 3 mL pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	0.6 mg SC once daily for 1 week, then increase the dose to 1.2 mg once daily. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg once daily.	The initial dose is intended to reduce GI symptoms during initial titration, and is not effective for glycemic control.	Inject in the thigh, abdomen, or upper arm. Administer once daily at any time of day, independently of meals. If VICTOZA is stopped for more than 3 days, start at 0.6 mg per day again.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ADLYXIN (liraglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment, but close monitoring for AEs and for changes in	No pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of ADLYXIN.	There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			renal function is recommended. Clinical experience in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) is extremely limited; patients should be closely monitored for GI AEs and for changes in renal function. There is no therapeutic experience in patients with end-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m^2); it is not recommended to use ADLYXIN in this population.		these drugs are excreted in human milk.
BYETTA (exenatide)	No differences in safety or efficacy were observed between elderly and younger patients; however, because elderly patients are more likely to have decreased renal function, caution is advised when initiating these drugs in the elderly.	Safety and efficacy have not been established.	BYETTA is not recommended for use in patients with ESRD or severe renal impairment (creatinine clearance [CrCL] <30 mL/min). Caution should be applied when initiating or escalating doses from 5 to 10 mcg in patients with moderate renal impairment (CrCL 30 to 50 mL/min).	Hepatic dysfunction is not expected to affect blood concentrations.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.
BYDUREON (exenatide ER)	No differences in safety or efficacy were observed between elderly and younger patients; however, because elderly patients are more likely to have	Safety and efficacy have not been established.	BYDUREON is not recommended for use in patients with ESRD or severe renal impairment (CrCL <30 mL/min). Caution is advised in patients with	Hepatic dysfunction is not expected to affect blood concentrations.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	decreased renal function, caution is advised when initiating these drugs in the elderly.		renal transplantation or moderate renal impairment (CrCL 30 to 50 mL/min).		agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.
SYMLIN (pramlintide)	No consistent differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended.	Use has not been studied in patients with hepatic impairment.	Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
TANZEUM (albiglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is required in mild, moderate, or severe renal impairment. Experience in patients with severe renal impairment is limited. In clinical trials, GI AEs increased as renal function decreased.	No clinical trials were conducted to examine the effects of mild, moderate, or severe hepatic impairment on the pharmacokinetics of TANZEUM. Therapeutic proteins such as TANZEUM are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of TANZEUM.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk. Consider stopping at least 1 month before a planned pregnancy due to the long washout period.
TRULICITY (dulaglutide)	No overall differences in safety or efficacy have been detected in	Safety and efficacy have not been established.	There is limited clinical experience in patients with severe renal impairment or	There is limited clinical experience in patients with mild, moderate,	Pregnancy category C* There are no adequate and

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients 65 years of age and older. However, greater sensitivity of some older individuals cannot be ruled out.		ESRD. TRULICITY should be used with caution, and if these patients experience GI AEs, renal function should be closely monitored.	or severe hepatic impairment. Therefore, this drug should be used with caution in these patient populations.	well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.
VICTOZA (liraglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended for patients with renal impairment. The safety and efficacy of VICTOZA was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m^2). There is limited experience with this drug in patients with severe renal impairment, including ESRD. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Caution should be used in patients who experience dehydration.	There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, caution is advised in this patient population. No dose adjustment is recommended for patients with hepatic impairment.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The GLP-1 receptor agonists, or incretin mimetics, exenatide (BYETTA), exenatide ER (BYDUREON), albiglutide (TANZEUM), dulaglutide (TRULICITY), liraglutide (VICTOZA), and lixisenatide (ADLYXIN) are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Pramlintide (SYMLIN) is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. BYETTA is administered twice daily (60 minutes prior to meals); VICTOZA is administered once daily (independent of meals); and ADLYXIN is administered once daily (1 hour prior to the first meal of the day). BYDUREON, TANZEUM, and TRULICITY are administered once weekly. SYMLIN is available as a SC injection to be administered immediately prior to each major meal. These agents are currently available as branded products only.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial demonstrated reduced CV risk with liraglutide vs. placebo (Marso et al, 2016a), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs. placebo (Pfeffer et al, 2015). Results of the SUSTAIN-6 trial for semaglutide, an agent which has not yet been FDA approved, have also been published (Marso et al, 2016b).
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of ADLYXIN and BYETTA, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. TANZUEM, TRULICITY, and VICTOZA have REMS programs which include a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another in the general treatment algorithm; however, the ADA guidelines recommend that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. For T1DM, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (ADA, 2017; Garber et al, 2017; Inzucchi et al, 2015).

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Nevada Medicaid
EXONDYS 51 (eteplirsen)
Pharmacy Coverage Guideline

Brand Name	Generic Name
EXONDYS 51	eteplirsen

CRITERIA FOR COVERAGE/NONCOVERAGE

EXONDYS 51™ (eteplirsen) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Diagnosis of Duchenne muscular dystrophy (DMD) **AND**
2. Documentation of a confirmed mutation of the dystrophin gene amenable to exon 51 skipping **AND**
3. Prescribed by or in consultation with a neurologist who has experience treating children **AND**
4. Dose will not exceed 30 milligrams per kilogram of body weight once weekly

Initial Authorization: 6 months

Reauthorization Duration:

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

1. One of the following:
- **1.1.** All of the following:
  - **1.1.1.** Patient has been on therapy for less than 12 months **AND**
  - **1.1.2.** Patient is maintaining ambulatory status **AND**
  - **1.1.3.** Patient is tolerating therapy **AND**
  - **1.1.4.** Dose will not exceed 30 milligrams per kilogram of body weight once weekly **AND**
  - **1.1.5.** Prescribed by or in consultation with a neurologist who has experience treating children

OR

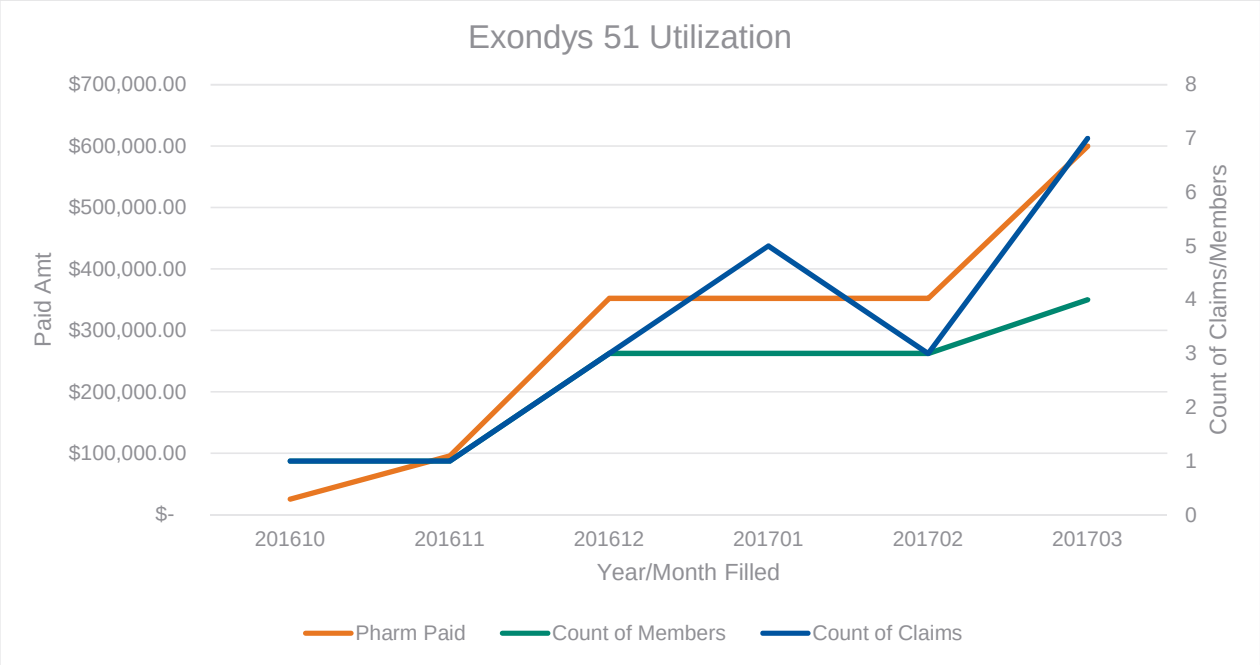
- **1.2.** All of the following:

1.2.1. Patient has been on therapy for 12 months or more **AND**
1.2.2. Patient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients) **AND**
1.2.3. Patient is maintaining ambulatory status **AND**
1.2.4. Patient is tolerating therapy **AND**
1.2.5. Dose will not exceed 30 milligrams per kilogram of body weight once weekly **AND**
1.2.6. Prescribed by or in consultation with a neurologist who has experience treating children

Exondys 51 Utilization

4/1/2016 - 3/31/2017

Year/Mo Filled	Product Name	Count of Members	Count of Claims	Qty Total	Days Supply	Pharm Paid
201610	EXONDYS 51	1	1	32	28	$ 25,610.17
201611	EXONDYS 51	1	1	120	28	$ 96,010.17
201612	EXONDYS 51	3	3	440	84	$352,030.51
201701	EXONDYS 51	3	5	440	140	$352,050.85
201702	EXONDYS 51	3	3	440	84	$352,030.51
201703	EXONDYS 51	4	7	750	154	$600,071.19



Therapeutic Class Overview
EXONDYS 51 (Agent for Duchenne Muscular Dystrophy [DMD])

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is an X-linked, recessive neuromuscular disorder caused by mutations of the dystrophin gene (Food and Drug Administration [FDA] Summary Review, 2016). These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells (FDA Summary Review, 2016).
    - Dystrophin is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation (FDA Summary Review, 2016). Absence of dystrophin leads to muscle damage, with replacement by fat and collagen (FDA Summary Review, 2016).
    - The first symptoms of DMD typically emerge between 2 and 5 years of age and include frequent falls; difficulty with walking, standing, and balancing; difficulty in getting up from a lying or sitting position; trouble with running or jumping; waddling gait; and development of large calf muscles (Exondys 51 Formulary Submission Dossier, 2016; Muscular Dystrophy Association [MDA] Web site).
    - DMD patients progressively lose the ability to perform activities independently and often require use of a wheelchair by their early teens (MDA Web site). With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary (FDA Summary Review, 2016; MDA Web site).
- DMD occurs in approximately 1 out of every 3500 to 5000 male infants worldwide (Exondys 51 Formulary Submission Dossier, 2016). While DMD primarily affects boys, in rare cases, female carriers can exhibit a wide range of clinical severity and may have comorbidities including muscle weakness, difficulty walking, and cardiac abnormalities (Exondys 51 Formulary Submission Dossier, 2016).
- Treatment for DMD has been largely supportive and utilizes glucocorticoids such as prednisone, which are widely believed to delay the loss of ambulation and respiratory decline by several years. Another glucocorticoid, which has been widely available outside of the United States for many years, Emflaza (deflazacort), recently garnered FDA approval for treatment of DMD (FDA Summary Review, 2016; Gloss et al, 2016; UpToDate, 2016[b]).
    - Although the time of steroid initiation in ambulatory boys with DMD varies by individual, most guidelines generally agree that glucocorticoids can be offered to patients ≥ 4 years of age whose motor skills have plateaued or are declining (Bushby et al, 2010; UpToDate, 2016[b]).
- On September 19, 2016, the FDA announced the approval of Sarepta Therapeutics' Exondys 51 (eteplirsen), an orphan drug for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The FDA additionally granted eteplirsen priority review status, fast track status, and rare pediatric disease designation (FDA Web site; Sarepta Therapeutics News Release, 2016).
    - This indication received accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.
    - A clinical benefit of eteplirsen has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
- Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA (FDA Summary Review, 2016). Theoretically, by restoring the mRNA reading frame, a truncated but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, thereby delaying disease progression.
    - Eteplirsen is specific for exon 51 mutations, a subset of the mutations that cause DMD in ~13% of the overall DMD patient population.
- Under accelerated approval provisions, an effect on a surrogate marker that is determined by the FDA to be reasonably likely to predict clinical benefit can support approval, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments (FDA Advisory Committee Meeting Minutes, 2016). An effect on an intermediate clinical endpoint (ie, a clinical endpoint that can be measured earlier than irreversible morbidity or mortality [IMM] and that is reasonably likely to predict an effect on IMM or other clinical benefit) can also serve as a basis for accelerated approval (FDA Advisory Committee Meeting Minutes, 2016).
    - In the case of eteplirsen, dystrophin production (measured by changes in the percentage of dystrophin-positive fibers assessed by immunohistochemistry [IHC] and/or by changes in the dystrophin protein levels

quantified by Western Blot) served as the primary surrogate endpoint in the clinical trials, while the change from baseline in the 6-minute walk test (6MWT) distance was the primary clinical outcome.

- Medispan Class: Muscular Dystrophy Agents

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EXONDYS 51™ (eteplirsen)	Sarepta Therapeutics, Inc.	09/19/2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	EXONDYS 51 (eteplirsen) Sarepta Therapeutics, Inc.
• Eteplirsen is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. o This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen. • A clinical benefit of eteplirsen has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.	✔

(EXONDYS 51 Prescribing Information, 2016)

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

CLINICAL EFFICACY SUMMARY

Clinical trials

- The clinical development program for eteplirsen (also referred to as AVI-4658) in male patients with DMD included the 2 early phase Studies 33 and 28, pivotal Phase 2b Study 201 and its extension Study 202, ongoing Phase 2 Studies 203 and 204 (both with no data yet available), and the ongoing, confirmatory Phase 3 PROMOVI Study (Study 301).
- Study 33 was a Phase 1/2, single-blind (SB), non-randomized, placebo-controlled (PC), dose-escalation, proof-of-concept, safety and efficacy study in 7 patients with varying degrees of ambulation and with deletions amenable to exon 51 skipping (Kinali et al, 2009).
    - Patients received a single intramuscular (IM) dose of eteplirsen (low-dose, 0.09 mg [n = 2]; high-dose, 0.9 mg [n = 5]) in the extensor digitorum brevis (EDB) muscle of one foot and an IM dose of normal saline placebo in the EDB muscle of the opposite foot.
    - Open biopsies of both EDB muscles were conducted 3 to 4 weeks following the injection to assess the safety and tolerability of eteplirsen (primary endpoint), as well as its biochemical efficacy (ie, its ability to restore dystrophin protein production by exon skipping) [secondary endpoint].
    - No adverse events (AEs) related to eteplirsen administration were reported.
    - Both patients who received low-dose eteplirsen showed little expression of dystrophin. IM injection of the higher dose resulted in increased dystrophin expression in all treated EDB muscles, although the immunostaining results were not uniform.

  - Review of Study 33 data by the FDA found that while an increase in dystrophin expression was reported adjacent to the needle track, it was not clear whether, or to what degree, this might reflect the activity of eteplirsen when given by the intravenous (IV) route, which does not produce similar high local concentrations or mechanical effects (FDA Briefing Document, 2016).
- Study 28 was a 12-week, Phase 1b/2a, open-label (OL), dose-escalation study conducted in 19 ambulatory patients with deletions amenable to exon 51 skipping (Cirak et al, 2011).
  - Patients were assigned to 6 cohorts that varied by dose (0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg, 10 mg/kg, and 20 mg/kg) and received an IV infusion of eteplirsen once weekly for 12 weeks. The safety and tolerability of eteplirsen were the primary endpoints, while the biochemical efficacy and pharmacokinetic (PK) parameters of eteplirsen were the secondary endpoints.
  - Eteplirsen was well tolerated with no drug-related serious adverse events (SAEs).
  - Eteplirsen induced exon 51 skipping in all cohorts and new dystrophin protein expression in a significant dose-dependent ($p = 0.0203$), but variable manner in boys from cohort 3 (dose 2 mg/kg) and onwards.
  - Seven patients responded to treatment (1 patient in cohort 3 [2 mg/kg], 3 patients in cohort 5 [10 mg/kg], and 3 patients in cohort 6 [20 mg/kg]), in whom the mean dystrophin fluorescence intensity increased from 8.9% (95% confidence interval [CI]: 7.1 to 10.6) to 16.4% (95% CI: 10.8 to 22.0) of normal control after treatment ($p = 0.0287$).
  - The 3 patients with the greatest responses to treatment (1 each from cohorts 3, 5, and 6) had 21%, 15%, and 55% dystrophin-positive fibers after treatment and these findings were confirmed with Western blot, which showed an increase after treatment of protein levels from 2% to 18%, from 0.9% to 17%, and from 0% to 7.7% of normal muscle, respectively.
  - Review by the FDA found that the results of Study 28 did not appear to be interpretable due to concerns about the reliability of the methods and procedures used during the study (FDA Briefing Document 2016).
    - Western blot bands were too saturated to allow for the reliable quantification of dystrophin.
    - The sponsor reported that repeating and re-analysis of assays when unblinded to treatment may have increased the risk of bias and false positive findings.
- Study 201 was a 24-week, Phase 2b, double-blind (DB), PC, randomized controlled trial (RCT) in 12 ambulatory patients 7 to 13 years of age with deletions amenable to exon 51 skipping; all 12 patients rolled over into the ongoing, Phase 2, OL, multi-dose, long-term extension Study 202 for an additional 212 weeks. Data from these studies supported the eteplirsen new drug application (NDA); results were published by Mendell et al (2013).
  - Patients were randomized 1:1:1 to receive once weekly IV infusions of eteplirsen 30 mg/kg/week ($n = 4$), 50 mg/kg/week ($n = 4$), or placebo ($n = 4$) (ie, Cohorts 1, 2, and 3, respectively) for the first 24 weeks.
  - During Weeks 25 to 28, the 4 patients originally treated with placebo were switched to the eteplirsen 30 mg/kg or 50 mg/kg groups ($n = 2$ in each group); patients remained on these doses throughout the OL extension study. All patients underwent biceps biopsies at baseline and deltoid biopsies at Week 48 for analysis of the percentage of dystrophin-positive fibers assessed by immunohistochemistry (IHC) (surrogate endpoint). Additional biceps biopsies were obtained at Week 12 (from 4 patients in Cohort 2 and 2 patients in Cohort 3) or Week 24 (from 4 patients in Cohort 1 and 2 patients in Cohort 3). The 6MWT was the primary functional outcome measure and was performed pre-treatment and post-treatment through Week 48 (every 4 weeks through Week 36; then at Week 48).
  - Once weekly treatment with eteplirsen 30 mg/kg for 24 weeks resulted in a 22.9% (range: 15.9% to 29%) mean increase in dystrophin-positive fibers from baseline compared to the combined placebo group ($p \leq 0.002$). Once weekly treatment with eteplirsen 50 mg/kg for 12 weeks did not result in an increase of dystrophin-positive fibers compared to baseline and was not statistically different compared to the placebo groups. The within-cohort comparison of the percentage of dystrophin-positive fibers (Week 24 vs. baseline for the 30 mg/kg group and Week 12 vs. baseline for the 50 mg/kg group) resulted in a statistically significant difference for the 30 mg/kg group ($p \leq 0.004$), but not for the 50 mg/kg group, or the combined placebo groups.
  - At Week 48, the 30 and 50 mg/kg groups showed statistically significant ($p \leq 0.001$) increases in the percentage of dystrophin-positive fibers (mean = 47.3%, range = 29.8% to 60.3%).
  - The adjusted mean changes for the 6MWT distance from baseline to Week 24 were as follows: placebo: -25.8 m (± 30.6 m); 30 mg/kg: -128.2 m (± 31.6 m); and 50 mg/kg: -0.3 m (± 31.2 m).
  - Adjusted mean changes from baseline to Week 48 on the 6MWT distances were the following: placebo/delayed group: -68.4 m (± 37.6 m); 30 mg/kg: -153.4 m (± 38.7 m); and 50 mg/kg: +21 m (± 38.2 m).

- In a post hoc analysis by Mendell et al (2016), the disease progression of the 12 eteplirsen-treated patients originally recruited for Studies 201 and 202 was compared to 13 external controls that were matched on exon 51 skipping genotype, age, corticosteroid use, and the existence of sufficient longitudinal data to allow for the identification of baseline and follow-up visits.
    - Eteplirsen-treated patients demonstrated a statistically significant advantage of 151 m ($p < 0.01$) on the 6MWT and experienced a lower incidence of loss of ambulation in comparison to matched historical controls amenable to exon 51 skipping. The authors concluded that over 3 years of follow-up, eteplirsen-treated patients showed a slower rate of decline in ambulation assessed by the 6MWT compared to untreated matched historical controls.
- FDA review of the entirety of data captured from Studies 201 and 202 identified several technical and operational issues, alongside methodological flaws in study design that cast doubt on the reliability and interpretation of the results (FDA Briefing Document, 2016; FDA Summary Review, 2016).
    - The original data from Nationwide Children's Hospital submitted to the FDA showed that immunostaining for dystrophin appeared to increase markedly in all groups with time, with some 50 to 60% of fibers staining positive for dystrophin at 48 weeks. The results of an FDA-recommended re-analysis with independent masked readers failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen-treated patients. Results at Week 180 in the blinded re-analysis showed an increase of only 17%.
        - Analyses based on IHC can overestimate the amount of dystrophin in tissue sections because a muscle fiber can be considered "positive" if it exhibits any staining at all, even if the level of dystrophin is very low.
        - The publication by Mendell et al (2013) that claimed a remarkable treatment effect was therefore considered to be misleading and the FDA has since called for its retraction.
    - Western blot analyses, required by the protocol and used to more accurately quantify dystrophin levels, were confounded by comparisons of biopsied tissue from different muscles at baseline (biceps) and at Weeks 48 and 180 (deltoid). Archived pre-treatment muscle biopsy samples were available for re-analysis from only 3 patients in Studies 201/202; additional samples were obtained from 6 patients, selected externally. Biopsy samples from controls were also obtained from different muscle groups than the eteplirsen-treated patients. For these reasons, the control value of 0.08% dystrophin in untreated patients was considered uncertain, making the relative change in dystrophin difficult to estimate.
    - Contrary to the Mendell et al (2016) post hoc analysis, the FDA found that the clinical course of eteplirsen patients over more than 3.5 years of treatment with eteplirsen had been generally similar to the expected natural history of patients provided with intensive supportive care.
- Study 203 is an ongoing, 96-week, Phase 2, OL, SB, non-randomized study in ambulatory patients aged 4 to 6 years with DMD and deletions amenable to exon 51 skipping (estimated enrollment N = 40) (ClinicalTrials.gov Web site). Twenty patients in the treatment arm will receive eteplirsen IV 30 mg/kg once weekly and an untreated group of 20 patients with deletions not amenable to exon 51 skipping will serve as controls. The number of patients with treatment-emergent adverse events (TEAEs) is the primary outcome, while the change from baseline in the percentage of dystrophin-positive skeletal muscle fibers is the secondary outcome.
- Study 204 is an ongoing, 96-week, Phase 2, OL, single-arm, safety study in patients aged 7 to 21 years with advanced DMD (ie, non-ambulatory or incapable of walking ≥ 300 m on the 6MWT) and deletions amenable to exon 51 skipping (estimated enrollment N = 20) (ClinicalTrials.gov Web site). All patients will receive eteplirsen 30 mg/kg IV once weekly. The number of patients with TEAEs is the primary outcome. Clinical laboratory or vital sign/electrocardiogram (ECG) abnormalities and changes in pulmonary function tests are among the secondary outcome measures.
- Study 301 [PROMOVI] is an ongoing, 96-week, Phase 3, OL, multi-center (MC) confirmatory study whose objective is to provide evidence of efficacy for eteplirsen in ambulatory DMD patients 7 to 16 years of age with deletions amenable to exon 51 skipping (ClinicalTrials.gov Web site; Exondys 51 Formulary Submission Dossier, 2016; FDA Summary Review, 2016). The estimated enrollment is 160 patients, 80 of whom will receive eteplirsen 30 mg/kg IV once weekly, while the remaining 80 patients with deletions not amenable to exon 51 skipping will be recruited to the untreated group. All patients will receive 1 biopsy at baseline and then will be randomized to receive a second muscle biopsy at either Weeks 24, 48, 72, or 96. The change from baseline in the 6MWT distance is the primary endpoint, while dystrophin levels assessed by Western blot and the percentage of dystrophin-positive fibers assessed by IHC are among the key secondary endpoints.

  - In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, the FDA requested an interim analysis of a subset of samples.
  - At the time of this request, 13 patients (mean age of 8.9 years) had been treated with OL eteplirsen for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. An FDA inspection team observed the performance of the Western blot assays and considered the results to be reliable.
  - Of the 12 patients with evaluable results, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change > 1%. The sponsor used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant ($p < 0.05$).
  - At the FDA, members of the review team disagreed on whether the increase in dystrophin production observed in eteplirsen-treated patients would be reasonably likely to predict a clinical benefit (FDA Summary Review, 2016).
- In a decisional memo dated July 14, 2016, the Director for the Center for Drug Evaluation and Research (CDER) concluded that the data submitted met the standard for accelerated approval based on the surrogate endpoint of increased dystrophin protein production, which she believed was reasonably likely to predict a clinical benefit. An appeal of this decision from the Director of the Office of Drug Evaluation I (ODE-1) convened the Agency Scientific Dispute Process Review Board, whose Chair ultimately agreed with the conclusions of the ODE-1 Director against accelerated approval. On September 16, 2016, the FDA Commissioner set forth a final decision that deferred to the CDER Director's judgment and authority to make the decision to approve eteplirsen under the accelerated approval pathway. The FDA has additionally called for the retraction of Mendell et al (2013), a publication that numerous officials claim is based on unreliable assay measures which greatly overstated the degree of dystrophin protein expression, thereby leading to unrealistic expectations and hope for DMD patients and their families.
- Due to the number of methodological flaws and limitations in study designs of the eteplirsen pivotal trials, final approval of eteplirsen for DMD in patients with deletions amenable to exon 51 skipping was based on the following data permitted by the FDA and detailed in the product's prescribing information:
  - Studies 201 and 202: The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. There was no significant difference in change in the 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Study 202 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group.
  - Confirmatory Phase 3 Study 301 [PROMOVI]: In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation [SD]) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Treatment Guidelines

- Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management (Bushby et al, 2010):
  - Diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation.
  - Suspicion of the diagnosis of DMD should be considered irrespective of family history and is usually triggered in 1 of 3 ways: (1) most commonly, the observation of abnormal muscle function in a male child; (2) the detection of an increase in serum creatine kinase tested for unrelated indications; or (3) after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells).
  - Initial symptoms might include delayed walking, frequent falls, or difficulty with running and climbing stairs. Although DMD is typically diagnosed at around 5 years of age, the diagnosis might be suspected much earlier because of delays in attainment of developmental milestones, such as independent walking or language.
  - The key tests done on the muscle biopsy for DMD are immunocytochemistry and immunoblotting for dystrophin, and should be interpreted by an experienced neuromuscular pathologist. A muscle biopsy can provide information on the amount and molecular size of dystrophin, as long as the protein is present. Differentiating total and partial absence of dystrophin can help to distinguish DMD from a milder dystrophinopathy phenotype. Electron microscopy is not required to confirm DMD. Genetic testing after a

positive biopsy diagnosis of DMD is mandatory. A muscle biopsy is not necessary if a genetic diagnosis is secured first, particularly as some families might view the procedure as traumatic.
    - The genetic tests commonly used to identify dystrophin mutations are multiplex PCR, multiplex ligation-dependent probe amplification, single-condition amplification/internal primer, and multiplex amplifiable probe hybridization. Multiplex PCR is widely available and the least expensive, but only detects deletions and does not cover the whole gene, so that a deletion might not always be fully characterized. Multiplex ligation-dependent probe amplification and amplifiable probe hybridization will detect deletions and duplications and cover all exons, and single-condition amplification/internal primer will detect deletions and provide sequence data. None of these techniques is universally available.
    - Glucocorticoids are the only medication currently available that slows the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Cardiac function might also improve, with limited data to date indicating a slower decline in echocardiographic measures of cardiac dysfunction, although these measures are not necessarily predictive of the delay in cardiac symptoms, signs, or cardiac-related mortality.
    - The goal of the use of glucocorticoids in the ambulatory child is the preservation of ambulation and the minimization of later respiratory, cardiac, and orthopedic complications, taking into account the well-described risks associated with chronic glucocorticoid administration. Particular care needs to be taken with such patients in deciding which glucocorticoid to choose, when to initiate treatment, and how best to monitor the child for any problems.
    - No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an ambulatory boy with DMD. The panel's opinion is that the timing of initiation of glucocorticoid therapy must be an individual decision, based on functional state and also considering age and pre-existing risk factors for adverse side-effects. Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age.
    - The typical boy with DMD continues to make progress in motor skills until approximately age 4 to 6 years, albeit at a slower rate than his peers. The eventual use of glucocorticoids should be discussed with caregivers at this stage, in anticipation of the plateau in motor skills and subsequent decline. Once the plateau phase has been clearly identified, usually at age 4 to 8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for side-effects) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended, but might be of more limited benefit.
- American Academy of Neurology (AAN) Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy (Gloss et al, 2016)
    - In children with DMD, prednisone should be offered for improving strength and pulmonary function.
    - Prednisone may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age.
    - Deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4 to 2.5 years.
    - Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5 to 15 years of follow-up.
    - Deflazacort and prednisone may be equivalent in improving motor function.
    - Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort.
    - Deflazacort may be associated with a greater risk of cataracts than prednisone.
    - The preferred dosing regimen of prednisone is 0.75 mg/kg/day. Over 12 months, prednisone 10 mg/kg/weekend is equally effective, with no long-term data available. Prednisone 0.75 mg/kg/day is associated with significant risk of weight gain, hirsutism, and cushingoid appearance.

SAFETY SUMMARY

- EXONDYS 51 has no contraindications or warnings and precautions. The most common adverse reactions were balance disorder and vomiting.

Table 3. Adverse reactions in DMD patients treated with eteplirsen 30 or 50* mg/kg/week with an incidence at least 25% more than placebo in Study 201 (ie, Study 1)

Adverse reactions	Eteplirsen (n = 8)	Placebo (n = 4)
Balance disorder	38%	0%
Vomiting	38%	0%
Contact dermatitis	25%	0%

* 50 mg/kg/week = 1.7 times the recommended dosage

(EXONDYS 51 Prescribing Information, 2016)

- In the 88 patients who received ≥ 30 mg/kg/week of eteplirsen for up to 208 weeks in clinical studies (201/202, 203, 204, and 301), the following events were reported in ≥ 10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.
- There have been reports of transient erythema, facial flushing, and elevated temperature occurring on the days of eteplirsen infusion.
- Risk Assessment and Medical Reviews by the FDA (2016) reported the following:
    - No patients died during the eteplirsen clinical development program.
    - Nonfatal SAEs were reported in 6 patients in the safety population. The SAEs included wound infection, vomiting, ankle fracture, femur fracture, decreased oxygen saturation, and viral lymphadenitis. These events were considered by the clinical reviewers as unrelated to treatment.
    - Nine AEs occurring in 6 patients were assessed as severe. The events included incision site hemorrhage, hemorrhoids, back pain, nasal congestion, bone pain, loss of balance, viral lymphadenitis, femur fracture, and cardiomyopathy with left ventricular dysfunction. All of the events were judged by the investigator and clinical reviewers to be unrelated except for cardiomyopathy, which was considered by the investigator as possibly related; a review of echocardiograms for this patient, a 10-year-old boy, showed that he had pre-existing cardiomyopathy. The boy discontinued treatment due to a decrease in left ventricular ejection fraction after having received 7 once-weekly doses of eteplirsen 4 mg/kg.
    - As the placebo-controlled experience is extremely limited for eteplirsen (ie, 8 patients on drug vs. 4 patients on placebo treated for 24 weeks in Study 201), most of the safety experience comes from OL studies, which greatly limits the interpretability of data, in particular considering the various events and complications that are expected as DMD progresses.
    - In Studies 201/202, which have been ongoing for nearly 4 years, with most of the experience without a concurrent control, the clinical reviewer describes that infections were noted, including an increase in respiratory infections, which is expected in that population. The clinical reviewer also noted some AEs related to neuromuscular symptoms and hypersensitivity-related events in the later part of these studies.
    - In the other OL trials, AEs expected in the DMD population were observed, and the lack of a concurrent control makes it impossible to determine whether their incidence was increased by eteplirsen treatment.
    - Various laboratory test changes of unclear clinical significance in eteplirsen-treated patients were described, but no changes of clinical relevance in vital signs or ECGs were noted by the clinical reviewer.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
EXONDYS 51 (eteplirsen)	Injection: IV	30 mg/kg once weekly	Infuse over 35 to 60 minutes; application of a topical anesthetic cream to the infusion site prior to administration may be considered

(EXONDYS 51 Prescribing Information, 2016)

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution			
	Elderly	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
EXONDYS 51 (eteplirsen)	As DMD is largely a disease of children and young adults, there is no geriatric experience with EXONDYS 51.	Not studied	Not studied	No human or animal data are available to assess the use of EXONDYS 51 during pregnancy or its effects on milk production, on breastfed infants, or the presence of eteplirsen in milk.

(EXONDYS 51 Prescribing Information, 2016)

CONCLUSION

- EXONDYS 51 (eteplirsen) is an orphan drug indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The FDA granted eteplirsen priority review status, fast track status, and rare pediatric disease designation (FDA Web site; Sarepta Therapeutics News Release, 2016).
    - This indication received accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.
    - A clinical benefit of eteplirsen has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
- Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA (FDA Summary Review, 2016). Theoretically, by restoring the mRNA reading frame, a truncated but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, thereby delaying disease progression.
    - Eteplirsen is specific for exon 51 mutations, a subset of the mutations that cause DMD in ~13% of the overall DMD patient population.
- The clinical development program for eteplirsen in male patients with DMD included the 2 early phase Studies 33 and 28, pivotal Phase 2b Study 201 and its extension Study 202, ongoing Phase 2 Studies 203 and 204, and the ongoing, confirmatory Phase 3 PROMOVI Study (Study 301). Serious methodological flaws in the study design of the pivotal studies led to the exclusion of the majority of data from studies 201 and 202 published by Mendell et al (2013) from the final text of the EXONDYS 51 prescribing information. Results from Studies 201, 202, and 301 that were permitted by the FDA included the following:
    - Studies 201/202 (N = 12): The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. No significant changes in the 6MWD were noted.
    - Study 301 (N = 12 evaluable patients): The pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%.
- The most common adverse reactions with eteplirsen (incidence ≥ 35% and higher than placebo) with eteplirsen use in Studies 201 and 202 were balance disorder (38%) and vomiting (38%).
- The recommended dose of eteplirsen is 30 mg/kg administered as a 35- to 60-minute IV infusion once weekly. Application of a topical anesthetic cream to the infusion site may be considered prior to administration of eteplirsen.
- While the approval of eteplirsen for patients with DMD amenable to exon 51 skipping was an historic milestone for patients and their families, serious methodological flaws in study design brought to light during the FDA review have called into question the ability of eteplirsen to produce dystrophin in high enough amounts that may be reasonably likely to produce a clinical benefit.

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Publication Date:

Nevada Medicaid
SPINRAZA (nusinersen)
Pharmacy Coverage Guideline

Brand Name	Generic Name
SPINRAZA	nusinersen

CRITERIA FOR COVERAGE/NONCOVERAGE

SPINRAZA™ (nusinersen) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Diagnosis of Spinal Muscular Atrophy (SMA) **AND**
2. Prescribed by or in consultation with a neurologist who has experience treating SMA

Initial Authorization: 12 months

Reauthorization Duration:

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

1. One of the following:
- **1.1.** All of the following:
  - **1.1.1.** Patient has been on therapy for less than 12 months **AND**
  - **1.1.2.** Patient is maintaining neurological status **AND**
  - **1.1.3.** Patient is tolerating therapy **AND**
  - **1.1.4.** Prescribed by or in consultation with a neurologist who has experience treating SMA

OR

- **1.2.** All of the following:
  - **1.2.1.** Patient has been on therapy for 12 months or more **AND**
  - **1.2.2.** Patient has experienced a benefit from therapy (e.g., disease amelioration compared to untreated patients) **AND**
  - **1.2.3.** Patient is maintaining neurological status **AND**
  - **1.2.4.** Patient is tolerating therapy **AND**
  - **1.2.5.** Prescribed by or in consultation with a neurologist who has experience treating SMA

Spinraza Utilization

4/1/2016 - 3/31/2017

Year/Mo Filled	Product Name	Count of Members	Count of Claims	Qty Total	Days Supply	Pharm Paid
201703	SPINRAZA	3	3	20	56	$500,030.51

Therapeutic Class Overview
Agent for Spinal Muscular Atrophy: SPINRAZA (nusinersen)

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons in the spinal cord and brainstem, leading to progressive muscular atrophy and weakness (*Genetics Home Reference 2017, Wang et al 2007*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant death (*Markowitz et al 2012*).
- SMA is an autosomal recessive inherited disorder. The overall incidence is between 4 and 10 per 100,000 live births, and 1 person in 50 to 90 is a carrier of a mutation that can cause SMA (*Bodamer 2017, Wang et al 2007*).
- There are several forms of SMA with varying degrees of severity and ages of onset. Please see Table 1 for an overview of the SMA clinical classifications.
- Type 1 SMA is the most common form, affecting approximately 58% of patients. Type 2 and Type 3 occur in approximately 29% and 13% of patients, respectively, and type 4 is less common (< 5%) (*Food and Drug Administration [FDA] medical review 2016*). Mothers may notice a decrease of fetal movement in late pregnancy, and some experts classify prenatal onset as type 0 SMA, which is very rare (*Bodamer 2017, FDA medical review 2016*).

Table 1. Clinical Classification of SMA (*Bodamer 2017, FDA medical review 2016, Markowitz et al 2012, Wang et al 2007*)

SMA Type	Age at Onset	Typical Life Span	Clinical Features
Type 0 (Prenatal)	Prenatal	< 6 months	Mostly unable to achieve motor milestones. Severe weakness at birth and profound hypotonia. Early respiratory failure.
Type 1 (Severe)	0 to 6 months	< 2 years (without respiratory support)	Never sits unsupported. Weakness and hyporeflexia. Weakness of mouth and throat muscles leads to a weak cry, poor suck and swallow reflexes, pooling of secretions, and aspiration. Respiratory failure.
Type 2 (Intermediate)	6 to 18 months	~ 70% alive at age 25 years	Sits independently, but never stands or walks. Proximal weakness, hypotonia and hyporeflexia. Weakness and swallowing difficulties may lead to poor weight gain. Difficulty coughing and clearing secretions. Scoliosis may be present.
Type 3 (Mild)	> 18 months	Almost normal	Stands and walks. Some patients lose the ability to walk in childhood; others in adolescence or adulthood. Swallowing and respiratory difficulties are less common, but may occur. Scoliosis, muscle aching, and joint overuse symptoms are common.
Type 4 (Adult)	> 21 years	Normal	Adult onset of progressive weakness that can lead to eventual loss of ambulation after years. Mild motor impairment; no respiratory or gastrointestinal problems.

- SMA is usually caused by a deletion or mutation in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q. The mutation is most commonly a homozygous deletion involving exon 7 of the gene (*Bodamer 2017*).
- The *SMN1* gene is responsible for the production of SMN protein, and mutations in the *SMN1* gene lead to a shortage of the protein. Without this protein, motor neurons degenerate and nerve impulses are not carried between the brain and muscles. The result is muscle weakness and impaired movement (*Bodamer 2017, Genetics Home Reference 2017*).

- There is also a modifying (or "backup") gene called *SMN2*, which has > 99% similarity to *SMN1*. Although *SMN1* is normally the active gene for SMN protein production, there is a small amount of protein generated by *SMN2* that may modulate the clinical severity of SMA (*FDA summary review 2016, Bodamer 2017*). This backup gene is the target for the mechanism of action of nusinersen.
    - *SMN2* produces several different versions of the SMN protein; however, only one form is full-length and functional (*Genetics Home Reference 2017*). The majority of *SMN2* messenger RNA (mRNA) transcripts do not contain exon 7 and do not generate full-length functional SMN protein (*Finkel et al 2016*).
    - The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have less severe SMA. Most patients with types 0, 1, 2, 3, and 4 SMA have 1, 2, 3, 4, and ≥ 4 copies of *SMN2*, respectively (*FDA summary review 2016*). However, there is variability to this, and predicting the clinical phenotype using *SMN2* copy number is not recommended (*Wang et al 2007*).
- Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to sites within *SMN2* pre-mRNA, promoting inclusion of exon 7 in *SMN2* mRNA transcripts and increasing production of full-length, functional SMN protein (*Finkel et al 2016*).
- Prior to the FDA approval of nusinersen, there were no specific treatments for SMA (*FDA news release 2016*). Treatment has been supportive, focusing on providing nutrition and respiratory assistance and preventing or treating the complications of weakness. Nonpharmacologic treatments include physical therapy, spinal bracing, chest physiotherapy, and respiratory support (*Bodamer 2017*).
- Nusinersen was approved by the FDA in December 2016 as a treatment for SMA. The FDA granted nusinersen fast track designation, orphan drug designation, and priority review (*FDA news release 2016*).
- Nusinersen is available through a limited distribution process. The provider can order the product through CuraScript SD (a specialty distributor) or from Accredo Specialty Pharmacy. Nusinersen will be shipped directly to the practice or facility (*Spinraza reimbursement guide 2016*).
- Medispan Class: Spinal Muscular Atrophy Agents

Table 2. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SPINRAZA™ (nusinersen)	Biogen	12/23/2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 3. FDA Approved Indications

Indication	SPINRAZA (nusinersen)
Treatment of SMA in pediatric and adult patients	✔

(SPINRAZA prescribing information, 2016)

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

CLINICAL EFFICACY SUMMARY

Clinical Trials

- Please see the appendix for a description of key motor function endpoints.
- The pivotal trial leading to FDA approval of nusinersen was the ENDEAR trial, a Phase 3, double-blind, sham-controlled trial (*Finkel et al 2017, Spinraza dossier 2016*). This trial enrolled patients who were 7 months or younger at screening, with onset of clinical signs and symptoms consistent with SMA at ≤ 6 months of age. Patients were treated with 12 mg scaled equivalent intrathecal doses of nusinersen (adjusted based on the patient's age), with loading doses on days 1, 15, 29, and 64, followed by maintenance dosing every 4 months (days 183 and 302). Control patients received a sham procedure (skin prick).
    - At the planned interim analysis after approximately 14 months of follow-up, 78 patients (51 and 27 in the nusinersen and control arms, respectively) had reached a 6-month evaluation and were included in the interim efficacy set. Of these patients, 1 patient in each group had voluntarily withdrawn from the study, and

21 patients had died (11 of 51 [21.6%] in the nusinersen group and 10/27 [37.0%] in the control group); thus, 55 patients were included in the interim efficacy set for motor milestone change assessments.
    - The primary endpoints were 1) the proportion of motor milestone responders, based on the Hammersmith Infant Neurological Examination (HINE) section 2 (HINE-2), and 2) event-free survival: time to death or permanent ventilation (≥ 16 hours ventilation/day for > 21 days or tracheostomy).
        - The proportion of patients achieving a motor milestone response was 41% in the nusinersen group and 0% in the control group (p = 0.000027). Positive changes in motor milestones were observed for most patients who received nusinersen, whereas most patients who received the control had no change or a decline from baseline.
        - Patients treated with nusinersen had significantly greater event-free survival (61%) than control patients (32%) (hazard ratio [HR], 0.53; p = 0.0046).
    - Secondary endpoints supported the primary results.
    - Based on positive results at the interim analysis, the study was suspended prior to its planned end.
- The CHERISH trial, which was another Phase 3, double-blind, sham-controlled trial, evaluated the use of nusinersen in later-onset SMA (*Biogen Medical Information 2016, Spinraza dossier 2016*). It enrolled patients aged 2 to 12 years with an onset of SMA at > 6 months of age. Patients received nusinersen 12 mg intrathecally (n = 84 at interim analysis) or sham-control (n = 42 at interim analysis) on days 1, 29, 85, and 274.
    - Key endpoints to be assessed (each after 15 months of treatment) included the change in the Hammersmith Functional Motor Scale – Expanded (HFMSE) score (a measurement of ability to perform activities) (primary endpoint), achievement of motor milestones, and the upper limb module (ULM) (an assessment of upper limb functional abilities).
    - The length of follow-up was approximately 16 months.
    - In a pre-planned interim analysis, there was a difference of 5.9 points in the HFMSE at 15 months between the nusinersen and control groups (p = 0.0000002). Patients in the nusinersen group experienced a mean improvement of 4.0 points, and patients in the control group experienced a mean decline of 1.9 points.
    - Results for other endpoints were consistent with a favorable response to nusinersen compared to control (specific results not yet reported).
- Additional open-label, single-arm, phase 1 and 2 studies offer further support for the use of nusinersen in SMA patients.
    - A phase 2 study (CS3A), evaluating 20 patients at the interim analysis, enrolled patients aged 3 weeks to ≤ 7 months with SMA symptom onset between 3 weeks and 6 months (*Finkel et al 2016, Spinraza dossier 2016*). The interim analysis was conducted approximately 18 months after the last patient was enrolled. In 16 of 19 patients treated with nusinersen, incremental improvement in HINE-2 motor milestones was demonstrated compared to baseline. Secondary endpoints, including an additional motor function scale and an analysis of death or permanent ventilation, supported the effectiveness of nusinersen when compared to a natural history case series.
    - A phase 2 study (NURTURE), evaluating 17 patients at the interim analysis, enrolled pre-symptomatic patients aged ≤ 6 weeks with genetic documentation of SMA (*Bertini et al 2016, Spinraza dossier 2016*). Patients were identified based on an affected sibling, newborn screening, or prenatal screening. At the time of the interim analysis, 13, 10, and 5 patients had reached days 64, 183, and 302 of the study, respectively. No patients receiving nusinersen met the endpoint of death or respiratory intervention. Improvement in HINE motor milestones were achieved by 12 of 13 patients at day 64, 10 of 10 patients at day 183, and 5 of 5 patients at day 302, indicating achievement of age-appropriate motor development. Secondary motor function endpoints supported the primary endpoint.
    - An additional report evaluated 28 patients aged 2 to 15 years who had been enrolled in a Phase 1/2a study (CS2) and followed into a phase 1 extension study (CS12) (*Darras et al 2016, Spinraza dossier 2016*). The primary objective of these studies was to assess the safety and tolerability of nusinersen in patients with type 2 or 3 SMA; efficacy endpoints were considered exploratory. The length of follow-up was approximately 8 months in study CS2 and 24 months in study CS12. In patients with type 2 SMA, improvements were observed in motor function over time based on results of the HFMSE and the ULM. In patients with type 3 SMA, HFMSE scores were stable and increases were observed in the 6-minute walk test (6MWT).
- Although nusinersen has not been studied in adults or patients with type 4 SMA, its indication is for the treatment of SMA in pediatric and adult patients. The FDA medical review noted that the underlying cause of SMA (a shortage of

SMN protein) is common to patients with all SMA types, and it is reasonable to expect that nusinersen should provide clinical benefits in all types of SMA. Open-label studies included patients 2 to 17 years of age with 2 to 5 *SMN2* copies and symptom onset corresponding to types 2 and 3 SMA; these results plus the initial summary of the sham-controlled trial in later-onset patients support the conclusion that nusinersen provides clinical benefits to patients with types 2 and 3 SMA and allow reasonable extrapolation to these populations. Given the invasive nature of nusinersen administration, patients with milder forms of SMA (type 4) may need to weigh potential benefits, risks and discomfort, and relative symptom severity to make individual treatment decisions (*FDA medical review 2016*).

Guidelines

- Consensus guidelines from participants of the International Conference on SMA Standard of Care describe supportive care relating to pulmonary complications, gastrointestinal issues/nutrition, and orthopedics/rehabilitation (*Wang et al 2007*). Key features of supportive care include airway clearance, noninvasive ventilatory support, assessment and treatment of feeding difficulties, nutritional supplementation, posture management, orthotics, and assistive equipment. The guidelines have not been updated to include drug treatment with nusinersen.

SAFETY SUMMARY

- Contraindications
    - None
- Warnings/precautions
    - Thrombocytopenia and coagulation abnormalities
        - Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. In a clinical study, 6 of 56 (11%) nusinersen-treated patients with normal or above normal platelet levels at baseline developed a platelet level below normal, compared to 0 of 28 control patients. No patient had a platelet count < 50,000/mcL and no patient developed a sustained low platelet count despite continued drug exposure.
        - Patients may be at increased risk of bleeding complications. A platelet count and coagulation laboratory testing should be conducted at baseline, prior to each nusinersen dose, and as clinically needed.
    - Renal toxicity
        - Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides.
        - Nusinersen is present in and excreted by the kidney. In a clinical study, 17 of 51 (33%) nusinersen-treated patients had elevated urine protein, compared to 5 of 25 (20%) control patients. In a group of later-onset SMA patients, 36 of 52 (69%) had elevated urine protein. No elevations in serum creatinine or cystatin C were observed in these studies.
        - Quantitative spot urine protein testing should be conducted at baseline and before each nusinersen dose. If the urinary protein concentration is > 0.2 g/L, repeat testing and further evaluation should be considered.
- Adverse effects
    - In the controlled study in infants with symptomatic SMA, the most common adverse events (AEs) that occurred, in ≥ 20% of nusinersen-treated patients and at least 5% more frequently than in control patients, were lower respiratory infection (43% vs 29%), upper respiratory infection (39% vs 34%), and constipation (30% vs 22%). Serious AEs of atelectasis were more frequent in nusinersen-treated patients than control patients (14% vs 5%).
    - Other reported AEs included teething, upper respiratory tract congestion, aspiration, ear infections, scoliosis, severe hyponatremia, rash, and reduction in growth.
    - In the open-label studies in later-onset patients, the most common AEs included headache (50%), back pain (41%), and post lumbar puncture syndrome (41%).
    - Because patients in the controlled study were infants, AEs that would be verbally reported could not be assessed.
- Immunogenicity

- The immunogenic response to nusinersen was determined in 126 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADAs). Five patients (4%) developed treatment-emergent ADAs, of which 3 were transient and 2 were considered to be persistent. There are insufficient data to evaluate an effect of ADAs on clinical response, AEs, or pharmacokinetics.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
SPINRAZA (nusinersen)	Injection for intrathecal use	12 mg (5 mL); 4 loading doses (first 3 at 14-day intervals, then a fourth dose 30 days after the third dose); maintenance dosing every 4 months	To be given by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; administered as an intrathecal bolus over 1 to 3 minutes; sedation should be considered as indicated by the clinical condition of the patient; ultrasound or other imaging techniques should be considered to guide administration, particularly in younger patients

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
SPINRAZA (nusinersen)	No experience; SMA is largely a disease of children and young adults	Safety and effectiveness established for pediatric patients from newborn to 17 years	No data available	No data available	No adequate data on developmental risk associated with use in pregnant women Unknown whether excreted in breast milk; risks and benefits should be considered

CONCLUSION

- Nusinersen is the first medication to be FDA-approved for the treatment of SMA, a serious neuromuscular disease that is the most common genetic cause of infant death and can also affect older children and adults.
- Initial results from randomized trials have demonstrated the efficacy of nusinersen in improving motor function and improving event-free survival, and small single-arm trials provided supportive evidence in several different patient types.
    - A pivotal trial, ENDEAR, was a Phase 3, double-blind, sham-controlled trial enrolling patients 7 months or younger who had an onset of SMA symptoms at ≤ 6 months of age (*Finkel et al 2017, Spinraza dossier 2016*). At the interim analysis, a higher proportion of patients treated with nusinersen had a motor milestone response than those in the control group (41% vs 0%). A co-primary endpoint of event-free survival also favored nusinersen (61%) compared to control (32%).
    - Another Phase 3, double-blind, sham-controlled trial, CHERISH, was conducted in patients aged 2 to 12 years with later-onset SMA (*Biogen Medical Information 2016, Spinraza dossier 2016*). In a pre-planned interim analysis, there was a difference of 5.9 points in the HFMSE at 15 months between the nusinersen and control groups ($p = 0.0000002$). Results for other endpoints were consistent with a favorable response to nusinersen compared to control (specific results not yet reported).
    - Additional open-label, single-arm, Phase 1 and 2 studies offer further support for the use of nusinersen in SMA patients, including patients with symptom onset between 3 weeks and 6 months of age, pre-symptomatic

patients with genetically-diagnosed SMA, and patients aged 2 to 15 years with type 2 or 3 SMA (*Bertini et al 2016, Darras et al 2016, Finkel et al 2016, Spinraza dossier 2016*).

- Nusinersen has generally been well tolerated in clinical trials. Key warnings/precautions include:
  - Thrombocytopenia and coagulation abnormalities – a platelet count and coagulation laboratory testing should be conducted at baseline, prior to each nusinersen dose, and as clinically needed.
  - Renal toxicity – quantitative spot urine protein testing should be conducted at baseline and before each nusinersen dose.
- In the controlled study in infants with symptomatic SMA, the most common AEs that occurred, in ≥ 20% of nusinersen-treated patients and at least 5% more frequently than in control patients, were lower respiratory infection, upper respiratory infection, and constipation. Serious AEs of atelectasis were more frequent in nusinersen-treated patients than control patients (14% vs 5%).
- In conclusion, nusinersen provides the first FDA-approved treatment option for SMA, and has been demonstrated to have beneficial effects on clinically relevant endpoints including achievement of motor milestones and event-free survival. Nusinersen is administered by intrathecal injection in healthcare settings.

APPENDIX

- **Hammersmith Functional Motor Scale – Expanded (HFMSE)** (*Spinraza dossier 2016*)
  - Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment.
  - Consists of 33 items evaluating the child's ability to perform activities. Each item is scored on a 3-point scale, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
  - The total score can range from 0 (all activities failed) to 66 (all activities achieved).
  - A clinically meaningful change was estimated to be a 3-point change at 6 months (in a previous study of other treatments in patients with type 2 or type 3 SMA).
- **Hammersmith Infant Neurological Examination (HINE)** (*De Sanctis 2016, Spinraza dossier 2016, FDA Medical Review 2016, Together in SMA 2016*)
  - Measures functional ability and achievement of motor milestones.
  - Contains 26 items; total possible score is 78. Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months. At 9 or 12 months, scores ≥ 73 are regarded as optimal.
    - Section 1 is based on the neurological exam (postures, cranial nerve function, reflexes, tone, and movements)
    - Section 2 (HINE-2) evaluates development of motor function based on 8 items (head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking); each item is scored between 0 and 2 to 4, for a maximum score of 26.
    - Section 3 evaluates the state of behavior (consciousness, social orientation, and emotional state).
- **Six-Minute Walk Test** (*Spinraza dossier 2016*)
  - Evaluates functional exercise capacity by measuring the maximum distance a person can walk in 6 minutes over a 25 meter linear course.
  - Has been accepted by regulatory agencies as a clinically meaningful endpoint in other neurologic disorders.
- **Upper Limb Module (ULM)** (*Spinraza dossier 2016*)
  - Designed to assess upper limb functional abilities in patients with SMA, including young children and patients with severe contractures in the lower limbs.
  - Consists of 9 upper limb performance items that reflect activities of daily living.
  - The total score ranges from 0 to 18 points, with higher scores indicating greater functional abilities.
  - An increase of ≥ 2 points is considered clinically meaningful.
  - A revised version of the ULM consists of 20 upper limb performance items.

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Nevada Medicaid
Psychotropic Medication Utilization in Children

Four or more psychotropics require prior authorization.

The chart below shows the count of recipients under the age of 18 receiving 4 or more psychotropic agents:

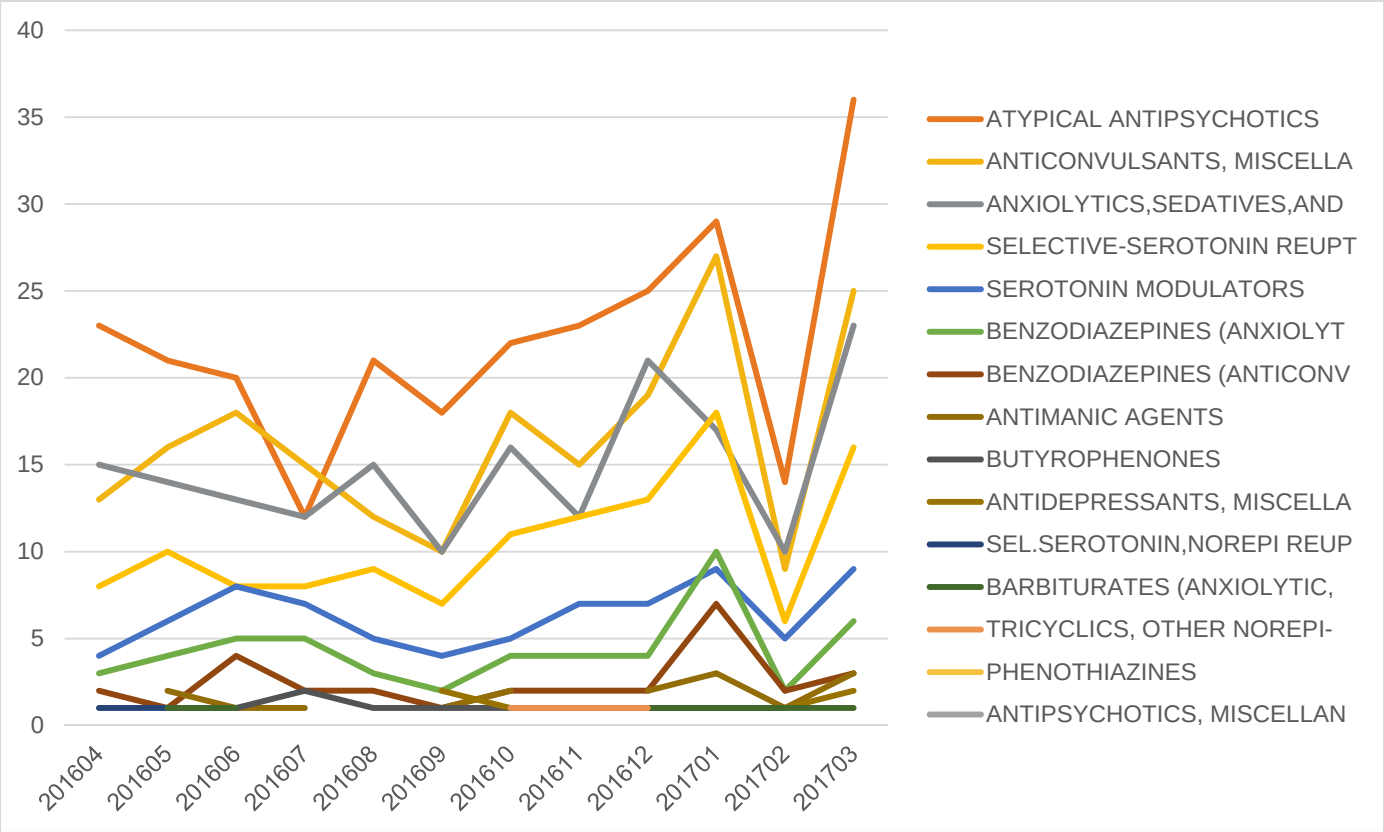
Year/Month	Count of Members
201604	10
201605	13
201606	12
201607	10
201608	11
201609	9
201610	12
201611	12
201612	14
201701	18
201702	8
201703	19

Of those recipients, the chart below breaks down the products most commonly used:

Drug Group	AHFS Description	Product Name	Count of Members
57	**ANXIOLYTICS,SEDATIVES,AND**	BUSPIRONE HCL	30
		HYDROXYZINE HCL	42
		HYDROXYZINE PAMOATE	91
	BENZODIAZEPINES (ANXIOLYT	ALPRAZOLAM	3
		DIAZEPAM	3
		LORAZEPAM	35
58	**ANTIDEPRESSANTS, MISCELLA**	BUPROPION HCL ER	1
		BUPROPION HCL SR	1
		BUPROPION HCL XL	6
		MIRTAZAPINE	2
	SEL.SEROTONIN,NOREPI REUP	PRISTIQ	4
		VENLAFAXINE HCL ER	5
	SELECTIVE-SEROTONIN REUPT	CITALOPRAM HYDROBROMIDE	2
		ESCITALOPRAM OXALATE	15
		FLUOXETINE HCL	46
		SERTRALINE HCL	63
	SEROTONIN MODULATORS	TRAZODONE HCL	76
	TRICYCLICS, OTHER NOREPI-	IMIPRAMINE HCL	4
59	**ANTIMANIC AGENTS**	LITHIUM CARBONATE	6

		LITHIUM CARBONATE ER	10
	ANTIPSYCHOTICS, MISCELLAN	LOXAPINE SUCCINATE	1
	ATYPICAL ANTIPSYCHOTICS	ABILIFY	57
		ARIPIPRAZOLE	44
		GEODON	7
		LATUDA	11
		OLANZAPINE	31
		OLANZAPINE ODT	1
		QUETIAPINE FUMARATE	35
		REXULTI	2
		RISPERIDONE	41
		SAPHRIS	2
		SEROQUEL XR	6
		VRAYLAR	4
		ZIPRASIDONE HCL	23
	BUTYROPHENONES	HALOPERIDOL	10
		HALOPERIDOL LACTATE	1
	PHENOTHIAZINES	PROCHLORPERAZINE EDISYLAT	4
60	**ANXIOLYTICS,SEDATIVES,AND**	ZOLPIDEM TARTRATE	15
	BARBITURATES (ANXIOLYTIC,	PHENOBARBITAL	7
	BENZODIAZEPINES (ANXIOLYT	ESTAZOLAM	4
72	**ANTICONVULSANTS, MISCELLA**	CARBAMAZEPINE	9
		CARBAMAZEPINE ER	3
		DIVALPROEX SODIUM	1
		DIVALPROEX SODIUM DR	15
		DIVALPROEX SODIUM ER	23
		EPITOL	9
		FYCOMPA	1
		GABAPENTIN	12
		LAMOTRIGINE	56
		LEVETIRACETAM	2
		LEVETIRACETAM ER	1
		LYRICA	1
		OXCARBAZEPINE	37
		SABRIL	4
		TOPIRAMATE	13
		TOPIRAMATE ER	4
		VIMPAT	3
		ZONISAMIDE	3
	BENZODIAZEPINES (ANTICONV	CLONAZEPAM	18
		CLONAZEPAM ODT	8
		ONFI	4
	BENZODIAZEPINES (ANXIOLYT	DIASTAT ACUDIAL	1
		DIAZEPAM	6

The chart below shows the number of recipients over the past year receiving four or more psychotropic medications.



Two or more medications within the same class require prior authorization.

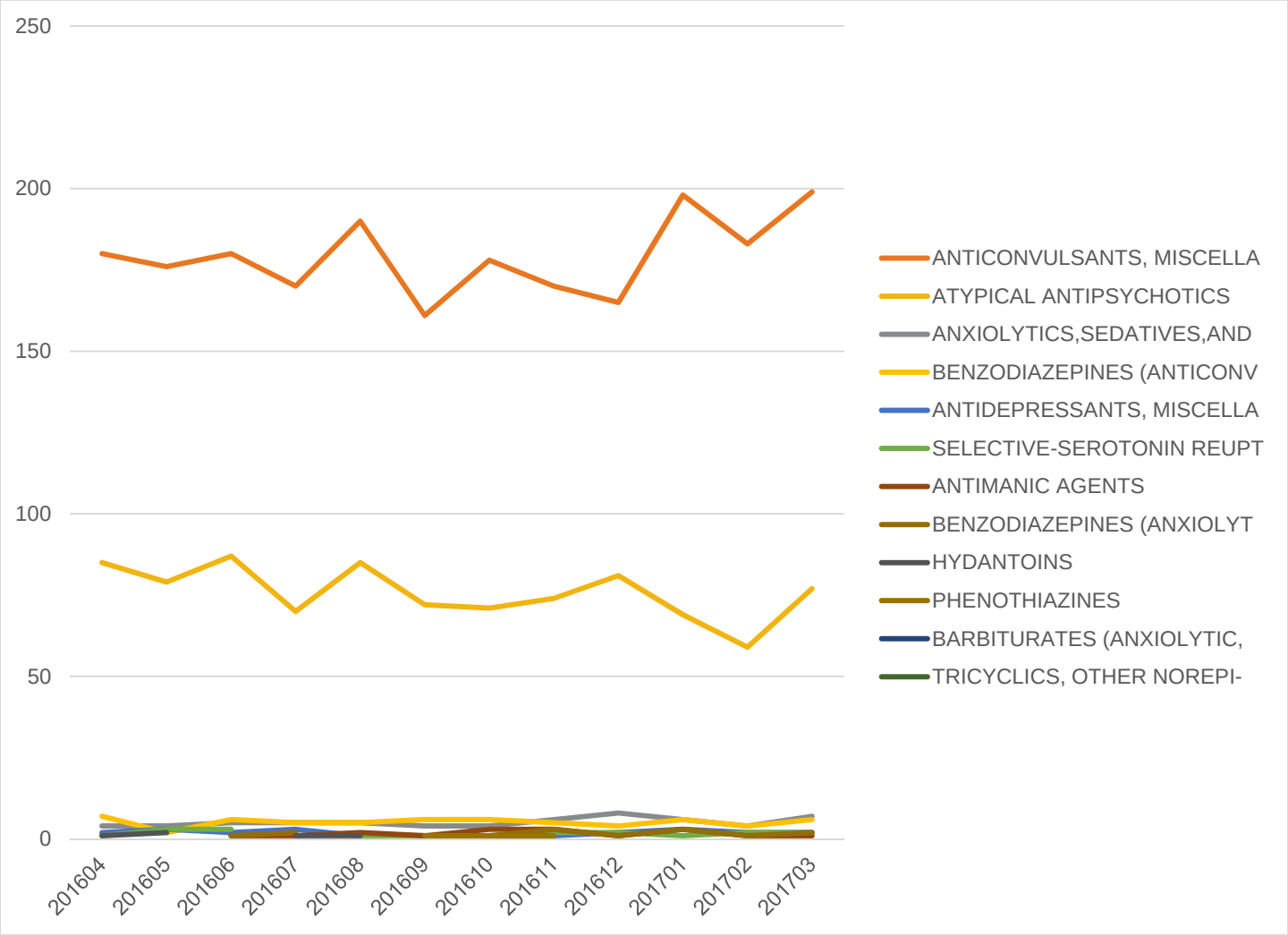
The chart below shows the members under the age of 18 receiving more than one agent per class.

Row Labels	Count of MemberID
201604	280
201605	269
201606	285
201607	258
201608	290
201609	247
201610	266
201611	265
201612	264
201701	289
201702	258
201703	296
Grand Total	**3267**

The chart below breaks down the type of medications members are taking as duplicates.

Drug Group	AHFS Description	Count Of Product Names	Count of Members
57	**ANXIOLYTICS,SEDATIVES,AND**	2	61
		3	1
	BENZODIAZEPINES (ANXIOLYT	2	14
58	**ANTIDEPRESSANTS, MISCELLA**	2	22
	SELECTIVE-SEROTONIN REUPT	2	19
	TRICYCLICS, OTHER NOREPI-	2	1
59	**ANTIMANIC AGENTS**	2	17
	ATYPICAL ANTIPSYCHOTICS	2	877
		3	31
		5	1
	PHENOTHIAZINES	2	5
60	**BARBITURATES (ANXIOLYTIC,**	2	1
72	**ANTICONVULSANTS, MISCELLA**	2	1799
		3	326
		4	25
	BENZODIAZEPINES (ANTICONV	2	62
	HYDANTOINS	2	5

The chart below shows the number of members under the age of 18 on multiple agents within the same class.



N. Psychotropic Medications for Children and Adolescents

Therapeutic Class: Psychotropic Agents
Last Reviewed by the DUR Board: September 3, 2015

Psychotropic medications for children and adolescents are subject to prior authorization based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for billing information.

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

1. Coverage and Limitations

The Division of Health Care Financing and Policy (DHCFP) requires prior authorization approval for children and adolescents for the psychotropic therapeutic classes below and medication combinations considered to be poly-pharmacy. The DHCFP has adopted the following practice standards to strengthen treatment outcomes for our children and adolescents.

a. The psychotropic therapeutic classes subject to this policy are:

2. Antipsychotics

2. Antidepressants

3. Mood Stabilizers (including lithium and anticonvulsants used for behavioral health indications.)

4. Sedative hypnotics

5. Antianxiety agents

b. For all children under 18 years of age, the following must be documented in the medical record for authorization.

1. For psychotropic medications in this age group, when possible, be prescribed by or in consultation with a child psychiatrist.

2. Psychotropic medication must be part of a comprehensive treatment plan that addresses the education, behavioral management, living home environment and psychotherapy.

3. Physician and/or prescriber monitoring is required while the recipient is utilizing any psychotropic medication.

a. For recipients who are in initial treatment (have not received any doses previously) or are continuing therapy but are considered unstable (has had a dose change in the last three months), medical documentation must support a monthly or more frequent visit with the physician and/or precsriber. If the recipient was discharged from an institution on the medication, the follow-up visit(s) can be with their treating physician and/or prescriber.

b. For recipients who are considered stable in their medication therapy, medical documentation must support visits with the treating physician at least every three months.

c. Poly-pharmacy: Each psychotropic medication prescribed must be independently treating a specific symptom and/or diagnosis.

1. Poly-pharmacy (intra-class) is defined as more than one drug within the same therapeutic class within a 60-day time period.

a. Prior authorization approval is required for two or more drugs in the same therapeutic class within a 60-day period.

2. Poly-pharmacy (inter-class) is defined as more than one drug across different therapeutic classes within a 60-day time period.

a. Prior authorization approval is required for four or more drugs across all psychotropic therapeutic classes listed in this policy within a 60-day time period.

3. Approval for poly-pharmacy may be given in situations where the requested medication(s) will be used for cross tapering and situations where the recipient will be discontinuing the previously prescribed agent. A 30-day cross-taper will be allowed.

4. Approval for poly-pharmacy may be given for a medication to augment the effect of another psychotropic medication as long as the purpose of the poly-pharmacy is clearly documented in the recipient's medical record and each agent is supported by individual authorizations.

5. The recipient must have a trial of each individual medication alone. The reasons for an inadequate response must be documented in the medical record.

6. For intra-class and inter-class poly-pharmacy, all psychotropic medications must be utilized for a medically accepted indication as established by the Food and Drug Administration (FDA), and/or peer reviewed literature.

d. For children under six years of age, in addition to the Coverage and Limitation requirements, all psychotropic medications require a prior authorization approval and must be utilized for a medically accepted indication as established by the FDA and/or peer-reviewed literature.

e. Continuity of Care. In an effort to improve recipient safety and quality of care:

1. For recipients under 18 years of age, who have been discharged from an institutional facility, they will be allowed to remain on their discharge medication regimen for up to six months to allow the recipient time to establish outpatient mental health services. The initial prior authorization after discharge must document the name of the discharge institution and the date of discharge.

2. For all other recipients under the age of 18, a six month prior authorization will be granted to cover current medication(s) when it is documented that the recipient has been started and stabilized. This will allow the recipient time to establish services if necessary and to transition to medication(s) per Nevada Medicaid policy.

2. Exceptions to this criteria for Anticonvulsants and ADD/ADHD medications:

a. Treatment for seizure disorders with anticonvulsants are not subject to this policy. The ICD Codes for Epilepsy and/or Convulsions will bypass the prior authorization requirement at the pharmacy POS if the correct ICD Code is written on the prescription and transmitted on the claim. Or the prior authorization requirement will be overridden for anticonvulsant medications when the prescriber has a provider specialty code of 126, neurology or 135, pediatric neurology, in the POS system.

b. The current policy for treatment of ADD/ADHD is to be followed. Refer to this Chapter's Appendix A.

3. Prior Authorization Guidelines:

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

Therapeutic Class Overview
Atypical Antipsychotics

INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (Miyamato et al, 2005).
- Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with schizophrenia (Farah, 2005).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D_2 and other neuroreceptors: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (SGAs) (Miyamato et al, 2005).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include autism, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents –GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA®, RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (Weissman and Bridgemohan, 2016).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the United States report a prevalence of 14.6 per 1,000 children at age 8 in 2012 (Morbidity and Mortality Weekly Report [MMWR], 2016).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component which alters brain development (Augustyn, 2016).
  - Overall treatment goals include maximization of functioning, improvement in quality of life and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies, and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances and depression (Weissman and Bridgemohan, 2016).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be approximately 1%, although the true prevalence is uncertain (Stovall, 2016[a]).
  - Genetics, in addition to environmental factors, appears to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (Stovall, 2016[b]).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (Gelenberg et al, 2010).
  - For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed

mood or (2) loss of interest or pleasure. The goal of treatment is full remission (Diagnostic and Statistical Manual of Mental Disorders [DSM] V, 2013).
    - Based on data from 2006 to 2008, approximately 9% of US adults meet the criteria for current depression, including 3.4% who have MDD. Women are more likely to experience major depression in their lifetime as compared to men (11.7 vs 5.6%), and major depression is most prevalent in patients aged 45 to 64 years old (CDC, 2013; MMWR, 2010).
- Schizophrenia
    - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain (Lehman et al, 2004).
    - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (DSM V, 2013; Lehman et al, 2004).
    - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a one-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include one of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (DSM V, 2013).
    - The prevalence of schizophrenia is approximately 0.3 to 0.66%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (McGrath et al, 2008; van Os et al, 2009).
- Tourette's disorder
    - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (Murphy et al, 2013).
    - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least one year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
    - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
    - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school age children having had tics in the previous year.
- The agents included in this review are listed in Table 1 by brand name. Since there are multiple branded agents that contain the same generic component the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.

Table 1. Medications Included Within Class Review

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
Single Entity Agents				
ABILIFY® (aripiprazole)	tab; sol	Otsuka (brand); various (generic)	11/15/2002 (tab) 12/12/2004 (sol)	✔
ABILIFY® DISCMELT™ (aripiprazole)	ODT	various (generic)	06/07/2006	✔
CLOZARIL® (clozapine)	tab	Heritage (brand); various (generic)	09/26/1989	✔
FANAPT® (iloperidone)	tab; titrate pack	Vanda and Inventia (brand)	05/06/2009	-*
FAZACLO® (clozapine)	ODT	Jazz (brand); various (generic)	02/09/2004	✔
GEODON® (ziprasidone hydrochloride)	cap	Pfizer (brand); various (generic)	02/05/2001	✔
GEODON® (ziprasidone mesylate)	inj (short-acting)	Pfizer	06/21/2002	-

Drug	Formulation	Manufacturer	FDA Approval Date	Generic
INVEGA® (paliperidone)	tab	Janssen (brand); various (generic)	12/19/2006	✔
LATUDA® (lurasidone)	tab	Sunovion	10/28/2010	-
REXULTI® (brexpiprazole)	tab	Otsuka	07/10/2015	-
RISPERDAL® (risperidone)	tab; sol	Janssen (brand); various (generic)	12/29/1993	✔
RISPERDAL® M-TAB® (risperidone)	ODT	Janssen (brand); various (generic)	04/02/2003	✔
SAPHRIS® (asenapine)	SL tab	Forest Pharma	08/13/2009	-
SEROQUEL® (quetiapine)	tab	AstraZeneca (brand); various (generic)	09/26/1997	✔
SEROQUEL XR® (quetiapine extended-release)	tab	AstraZeneca	05/17/2007	✔
VERSACLOZ® (clozapine)	susp	Jazz	02/06/2013	-
VRAYLAR™ (cariprazine)	cap; titrate pack	Allergan	09/17/2015	-
ZYPREXA® (olanzapine)	tab; inj (short-acting)	Eli Lilly (brand); various (generic)	09/30/1996 (tab) 03/29/2004 (inj)	✔
ZYPREXA ZYDIS® (olanzapine)	ODT	Eli Lilly (brand); various (generic)	04/06/2000	✔
Long-Acting Injectable Products				
ABILIFY MAINTENA® (aripiprazole extended-release)	inj	Otsuka	02/28/2013	-
ARISTADA™ (aripiprazole lauroxil extended-release)	inj	Alkermes	10/5/2015	-
INVEGA SUSTENNA® (paliperidone palmitate)	inj	Janssen	07/31/2009	-
INVEGA TRINZA® (paliperidone palmitate)	inj	Janssen	05/18/2015	-
RISPERDAL CONSTA® (risperidone microspheres)	inj	Janssen	10/29/2003	-
ZYPREXA RELPREVV® (olanzapine pamoate)	inj	Eli Lilly	12/11/2009	-
Combination Products				
SYMBYAX® Olanzapine/ fluoxetine	cap	Eli Lilly (brand); various (generic)	12/24/2003	✔

Abbrv: cap = capsule; inj = injection; ODT = oral disintegrating tablet; SL = sublingual; sol = solution; susp = suspension; tab = tablet; titrate pak = titration pack

*Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products. Currently, Inventia is only manufacturing the Fanapt titration pack (ME staff press release, 2016).

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

INDICATIONS

- The following summarizes all FDA-approved indications:
  - Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
  - Bipolar disorder: All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder.
    - Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
  - Depression: Aripiprazole, REXULTI, and SEROQUEL XR are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine when prescribed in combination with fluoxetine is indicated for treatment resistant depression.
  - Schizophrenia: All agents in class are indicated for use in schizophrenia with the exception of the combination agent, SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia.
    - Aripiprazole, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
  - Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Table 2 highlights FDA-approved indications at a high level. Please refer to Tables 4 and 5 for a detailed explanation of indications by agent, age, formulation, and use as an adjunct or monotherapy.

Table 2. Food and Drug Administration Approved Indications

Agent	Autism	Bipolar Disorder: manic/mixed	Bipolar Disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder
Oral Products									
aripiprazole	✔ *	✔ *	-	-	✔	-	✔ *	-	✔ *
asenapine	-	✔ *	-	-	-	-	✔	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-
clozapine	-	-	-	-	-	✔	✔	✔	-
iloperidone	-	-	-	-	-	-	✔	-	-
lurasidone	-	-	✔	-	-	-	✔	-	-
olanzapine	-	✔ *	-	-	✔ †	-	✔ *	-	-
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-
ziprasidone	-	✔	-	-	-	-	✔	-	-
Long-Acting Injectable Products									
aripiprazole ER	-	-	-	-	-	-	✔	-	-
aripiprazole lauroxil ER	-	-	-	-	-	-	✔	-	-
paliperidone palmitate (SUSTENNA)	-	-	-	-	-	✔	✔	-	-
paliperidone palmitate (TRINZA)	-	-	-	-	-	-	✔	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-
olanzapine pamoate	-	-	-	-	-	-	✔ ‡	-	-

*FDA-approved indications for pediatric patients; †Extended-release formulation; ‡ Patients must be observed by a health care professional for 3 hours post-dose administration

(Prescribing information: ABILIFY, 2016; ABILIFY MAINTENA, 2016; ARISTADA, 2016; CLOZARIL, 2016; FANAPT, 2016; FAZACLO, 2015; GEODON, 2015; INVEGA, 2016; INVEGA SUSTENNA, 2016; INVEGA TRINZA, 2016; LATUDA, 2013; REXULTI, 2016; RISPERDAL, 2016; RISPERDAL CONSTA, 2016; SAPHRIS, 2017; SEROQUEL, 2013; SEROQUEL XR, 2016; SYMBYAX, 2016; VERSACLOZ, 2015; VRAYLAR, 2016; ZYPREXA, 2016; ZYPREXA RELPREVV, 2016)

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SR), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted a SR of literature on the safety and efficacy of antipsychotics in children and adolescents. The review included studies of atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone), conducted in patients 24 years of age or younger, used for the following FDA-approved and off-label indications: pervasive developmental disorder, attention deficit hyperactivity disorder/disruptive behavior disorders, bipolar disorder, schizophrenia, psychosis, Tourette's syndrome, OCD, post-traumatic stress disorder, anorexia nervosa, and miscellaneous behavioral issues. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome. No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons. The risks of weight gain (weight gain, 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain. Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data). Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder in patients, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy and only one low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (Owen et al, 2009). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 for placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points for 5 mg/day, 2.5 for 10 mg/day, and 2.5 for 15 mg/day compared with 3.3 for placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (Marcus et al, 2009).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; P < 0.00001), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; P = 0.004) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; P = 0.02) (Hirsch et al, 2016).
- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (McCracken et al, 2002; Shea et al, 2004). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-

daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (McCracken et al, 2002; Shea et al, 2004). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (RISPERDAL prescribing information, 2014). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group (P < 0.001) (McCracken et al, 2002). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (Shea et al, 2004). Somnolence was the most frequently reported adverse event (72.5 vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 vs 1 kg), pulse rate, and systolic blood pressure.

- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase (P = 0.02) (McDougle et al, 2005).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients per trial. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (Aman et al, 2008; Capone et al, 2008; Gagliano et al, 2004; Gencer et al, 2008; Luby et al, 2006; Miral et al, 2008; Nagaraj et al, 2006).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean baseline ABC-I subscale was not statistically different (P = 0.06), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (Ghanizadeh et al, 2014).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and SAPHRIS (asenapine) have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 11 trials measured efficacy and safety in adolescents with bipolar disorder. Compared to placebo, aripiprazole, olanzapine, ziprasidone, quetiapine and risperidone were associated with greater improvements in response rates in analysis of 7 trials with 1,006 patients (RR, 1.76; 95% CI, 1.46 to 2.13); number needed to treat [NNT], 3 to 7). Increased remission rates were observed with atypical antipsychotic use in 6 trials with 976 patients (RR, 2.4; 95% CI, 1.5 to 3.83; NNT, 2 to 12); however, significant heterogeneity was noted across trials. Comparing olanzapine to risperidone, olanzapine was associated with significantly smaller improvement in Young Mania Rating Scale (YMRS) score and a non-significant lower response rate (RR, 0.72; 95% CI, 0.5 to 1.03) in analysis of 2 trials with 92 patients. Risperidone significantly improved YMRS score vs ziprasidone in 1 trial with 84 patients. Overall, atypical antipsychotics may improve remission rates compared to placebo in adolescents with bipolar disorder (Seida et al, 2012[a]; Seida et al, 2012[b]).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo, asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in YMRS score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5mg, -3.2; P = 0.0008 vs 5mg, -5.3; P < 0.001 vs 10mg, -6.2; P < 0.001). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group (P < 0.05). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (P = not reported). Overall, asenapine was well tolerated and showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (Findling et al, 2015).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($P < 0.001$), with no difference between groups (19 vs 20; $P = 0.89$). All other efficacy measures were not statistically different from placebo (DelBello et al, 2009). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $P = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (P = not reported) (Findling et al, 2014).
- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $P = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($P = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $P < 0.001$), as well as increase in fasting total cholesterol, LDL cholesterol and triglycerides (all $P < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($P < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($P = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (Detke et al, 2015).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- Based on a 2012 AHRQ SR of 81 trials evaluating typical and atypical antipsychotics, a total of 23 randomized trials and 2 cohort studies measured efficacy and safety in adolescents with schizophrenia. Clozapine, olanzapine, and risperidone were associated with greater improvements compared to haloperidol in Brief Psychiatric Rating Scale (BPRS) score in analysis of 3 trials with 71 patients. Risperidone significantly improved Positive and Negative Syndrome Scale (PANSS) score in 1 trial with 8 patients. There was no significant difference in PANSS score comparing olanzapine vs haloperidol in 1 trial with 19 patients. Overall, clozapine, olanzapine, and risperidone may be more effective than haloperidol in adolescents with schizophrenia (Seida et al, 2012[a]; Seida et al, 2012[b]).
- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in BPRS scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and higher glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (Kumar et al, 2013).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible dose trial. There is minimal evidence of safety and efficacy in this population.

- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66 vs 45%, respectively (Yoo et al, 2013).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 in placebo (ABILIFY prescribing information, 2015).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (ABILIFY prescribing information, 2015). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (Gulisano et al, 2011).

ADULTS

- The AHRQ conducted a SR of literature on the safety and efficacy of antipsychotics in adults comparing first- (typical antipsychotics) and second-generation (atypical antipsychotics). The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (Abou-Setta et al, 2012).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI (brexpiprazole). The following summarizes direct comparative evidence and recent MAs and SRs.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 11 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes when compared to aripiprazole, olanzapine, and risperidone, and difference in Montgomery-Asberg Depression Rating Scale (MADRS) score compared to aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (Abou-Setta et al, 2012).
- One SR of 9 RCTs (N = 1,289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short term trials lasting 3 to 6 weeks ($P < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($P < 0.001$) (Muralidharan et al, 2013).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 5 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (McIntyre et al, 2009[a];

McIntyre et al, 2010[a]; McIntyre et al, 2009[b]; McIntyre et al, 2010[b]; Szegedi et al, 2011). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (McIntyre et al, 2010[b]). A meta-analysis of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (Cipriani et al, 2011). The most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (McIntyre et al, 2009[b]).

- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible dose, DB, PC 3-week trials (Calabrese et al, 2015; Durgam et al, 2015[a]; Sachs et al, 2014). A total of 1,047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (FDA/CBER summary review, 2015). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (Calabrese et al, 2015; Durgam et al, 2015[a]; Sachs et al, 2014). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, the steady state was not achieved in trials (FDA/CBER summary review, 2015). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to pooled analysis (n = 1,940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7 vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (Perlis et al, 2006[a]).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (Calabrese et al, 2005; Corya et al, 2006; McElvoy et al, 2010; Loebel et al, 2014[a]; Loebel et al, 2014[b]; Shelton et al, 2005; Suppes et al, 2010; Thase et al, 2007; Young et al, 2010).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (Tohen et al, 2003; Brown et al, 2009). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (Tohen et al, 2003). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (Chiesa et al, 2012; Young et al, 2010).
- MAs have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (Fornaro et al, 2016; Silva et al, 2013; Taylor et al, 2014; Vieta et al, 2010). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

<u>Major Depressive Disorder (MDD)</u>

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, REXULTI (brexpiprazole), and SEROQUEL XR (quetiapine ER) are indicated for the treatment of MDD as adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One meta-analysis, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics treatment in combination with a SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (9.1 vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (Wen et al, 2014).
- Another meta-analysis evaluated 14 trials in patients with current MDD and an inadequate response to at least one course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher NNT compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (Spielmans et al, 2013).

Adjunctive treatment for MDD

- Aripiprazole, REXULTI, and SEROQUEL XR are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (Berman et al, 2007; Marcus et al, 2008). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (Marcus et al, 2008). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients, 50 to 67 years and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (Steffens et al, 2011). Other trials have demonstrated similar results (Kamijima et al, 2013; Papakostas et al, 2005). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29 %; P = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (Lenze et al, 2015).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (Thase et al, 2015; FDA briefing document, 2015). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (Correll et al, 2015; Kane et al, 2015[a]; Thase et al, 2015).
- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; P < 0.01; NNT, 9) dose significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but the quetiapine fumarate 150 mg/day

(53.7%; P = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; P < 0.001; NNT, 8) and 150 mg/day dose (35.6%; P < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo treatment, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (Bauer et al, 2010).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in class indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (Corya et al, 2006; Shelton et al, 2005; Thase et al, 2007). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (Corya et al, 2006). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (Corya et al, 2006; Shelton et al, 2005).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (P < 0.001) (Thase et al, 2007). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (Corya et al, 2006). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (Shelton et al, 2005).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic agents in class are indicated for use in schizophrenia with the exception of combination agent SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder. The following summarizes recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, Iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms vs aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1,701 patients in 3 trials, risperidone for 4,043 patients in 20 trials, and olanzapine-treatment for 3,742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1,405 patients in 6 trials and olanzapine provided better response rates for 4,099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (Abou-Setta et al, 2012).
- One large, recent Bayesian meta-analysis of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approve agents indicated that EPS was lowest for clozapine and highest for

haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the meta-analysis had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (Leucht et al, 2013).

- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2,881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30 to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There is limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (Khanna et al, 2014).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5,971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provides evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (Asmal et al, 2013).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (Lieberman et al, 2005; Stroupe et al, 2006; Stroupe et al, 2009). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to one year (Kane et al, 2011; Kane et al, 2010[a]; Potkin et al, 2007; Schoemaker et al, 2010). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (Kane et al, 2011). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (Shoemaker et al, 2010). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (Potkin et al, 2007).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (Correll et al, 2015; Kane et al, 2015[a]). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (Correll et al, 2015; Kane et al, 2015[a]; Thase et al, 2015). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients (P < 0.0001) and time to impending relapse was statistically significantly lower (Hazard ratio [HR], 0.34; P = 0.0008). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (Fleischhacker et al, 2016).
- The efficacy and safety of cariprazine in schizophrenia was based on 3 DB, randomized, PC 6-week trials (Durgam et al, 2014; Durgam et al, 2015[b]; Kane et al, 2015[b]). A total of 1,792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible dose study with no active comparator. In the flexible dose study, the mean daily dose ranged from 5 to 8 mg per day (Kane et al, 2015[b]). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (FDA/CBER summary review, 2015). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1,317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (FDA/CBER summary review, 2015). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (Durgam et al, 2014; Durgam et al, 2016[b]). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95%CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; P < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (Durgam et al, 2016[a].)
- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (Potkin et al, 2008). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (Cutler et al, 2008). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (Citrome et al, 2011; Citrome et al, 2012). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in a meta-analysis that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The meta-analysis found the long-term efficacy of Iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (P = 0.85), with a more favorable long-term safety profile (Kane et al, 2008). Moreover, another meta-analysis designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS

was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (Weiden et al, 2008). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; P < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (P < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (Weiden et al, 2016).

- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone dosed 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (Meltzer et al, 2011; Nakamura et al, 2009). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (Harvey et al, 2011; Potkin et al, 2011). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (P = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (Potkin et al, 2011). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day), or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (P = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (Tandon et al, 2016).

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperidone long-acting injection is the only long-acting injection FDA-approved for bipolar I disorder as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (Mcfadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (Quiroz et al, 2010; Vieta et al, 2012). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (Mcfadden et al, 2009). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (P = 0.001) (Vieta et al, 2012). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (Mcfadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007).

Schizophrenia

- All 6 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include ABILIFY MAINTENA (aripiprazole ER), ARISTADA (aripiprazole lauroxil), ZYPREXA

RELPREVV (olanzapine pamoate), INVEGA SUSTENNA (paliperidone palmitate once-a-month injection), INVEGA TRINZA (paliperidone palmitate once-every-3-months injection), and RISPERDAL CONSTA (risperidone microspheres). INVEGA SUSTENNA is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.

- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One meta-analysis of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (P = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (P < 0.001) and oral antipsychotics (P = 0.048) (Fusar-Poli et al, 2013).
- One SR and meta-analysis of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; P = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (P = 0.02) and in preventing hospitalization (P = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (P = 0.65) (Kishimoto et al, 2013).
- One meta-analysis compared outcomes for once-monthly long acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (Nussbaum et al, 2012).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (Gentile et al, 2013).
- Two additional long-acting injectable agents were approved in 2015, ARISTADA (aripiprazole lauroxil) and INVEGA TRINZA (paliperidone palmitate once-every-3-months injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly intramuscular (IM) injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo (P < 0.001 for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (Meltzer et al, 2015).
  - The FDA-approval of INVEGA TRINZA, the 3-month IM paliperidone palmitate injection, was based on one PC, OL/DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were

then administered the once every 3 month injection. Paliperidone palmitate once every 3 months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($P < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), weight increased (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (Berwaerts et al, 2015).

SAFETY SUMMARY

- All atypical antipsychotic agents have a boxed warning of increased mortality in elderly patients with dementia-related psychosis. Those agents (ie., ABILIFY, LATUDA, REXULTI, SEROQUEL, SEROQUEL XR, and SYMBYAX) indicated for depressive episodes carry a boxed warning of an increased risk of suicidal thoughts and behaviors. ZYPREXA RELPREVV has a boxed warning of incidences of post-injection delirium and/or sedation syndrome. Lastly, clozapine-containing agents (ie., CLOZARIL, FAZACLO, and VERSACLOZ) have boxed warnings of severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- GEODON is contraindicated in patients with recent acute myocardial infarction (MI), history of QT prolongation or with drugs that prolong QT, and uncompensated heart failure (HF). LATUDA is contraindicated for concomitant use with strong CYP3A4 inducers and/or inhibitors. Lastly, SAPHRIS is contraindicated in patients with severe hepatic impairment.
- Clozapine-containing products and ZYPREXA RELPREVV are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling is required as part of both programs. Clozapine products also require certain laboratory levels prior to prescribing. ZYPREXA RELPREVV requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is unknown (FDA safety communication [clozapine], 2016).
- A vast number of Warnings and Precautions are assigned to the atypical antipsychotic agents. The following outlines the most recent FDA safety communications:
    - In May 2016, the FDA warned that impulse-control problems had been associated with the use of aripiprazole. Uncontrollable urges to gamble, binge eat, shop, and have sex were reported. New warnings were added to the drug labels and patient Medication Guides (FDA safety communication [aripiprazole], 2016).
    - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (FDA safety communication [clozapine], 2015).
    - In March 2015, the FDA concluded their study after 2 unexplained deaths were reported as a result of high plasma drug concentrations after the appropriate doses of ZYPREXA RELPREVV were administered. Study results were inconclusive; therefore, the FDA did not make recommendations to change treatment (FDA safety communication [ZYPREXA RELPREVV], 2015).
    - In May 2016, the FDA warned that olanzapine can cause a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). In December 2014, 6 patients reported incidences of DRESS with GEODON use. If DRESS is suspected, use should be discontinued immediately. As a result, DRESS was added as a Warning and Precaution to both products (FDA safety communication [olanzapine], 2016; FDA safety communication [ziprasidone], 2014).
    - In September 2011, 52 cases of Type I hypersensitivity reactions were reported with SAPHRIS use. A Warning and Precaution of hypersensitivity reactions was added to the SAPHRIS prescribing information (FDA safety communication [asenapine], 2011).
    - In February 2011, a safety warning for all atypical antipsychotics was communicated after increases in the risk of EPS and withdrawal symptoms were observed in newborns whose mothers were administered antipsychotics in the third trimester of pregnancy (FDA safety communication, 2011).
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative Adverse Event Risk Observed in Trials for Atypical Antipsychotic Agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	Moderate	Moderate	Moderate	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Low to moderate	Low	Low to moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low to moderate
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	Moderate	Moderate	Moderate	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Low	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate

Abbrv: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(Altinbas et al, 2013; FDA/CBER summary review [VRAYLAR], 2015; Jibson et al, 2016)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
Aripiprazole (ABILIFY,†† ABILIFY DISMELT, ABILIFY MAINTENA)	Orally disintegrating tablet: 10 mg 15 mg Oral Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg Long-acting injection (vial or syringe): 300 mg 400 mg Oral Solution: 1 mg/mL	Bipolar disorder – manic or mixed episodes: Oral formulations and monotherapy: initial, 15 mg PO daily; recommended dose, 15 mg PO daily; max, 30 mg PO daily tablet Adjunct to lithium or valproate (oral formulations): initial dose may range from 10 mg to 15 mg PO daily Schizophrenia: Oral formulations: initial or target, 10 to 15 mg PO daily; max, 30 mg PO daily tablet; dose increases should generally not be made before 2 weeks; daily doses > 15 mg were not shown to be more efficacious than 15 mg PO daily Long-acting injection: initial or maintenance, 400 mg IM once a month; max, 400 mg/month; take 14 days of concurrent oral aripiprazole (10 to 20 mg) or current oral antipsychotic in conjunction with the first injection Adjunctive treatment of major depressive disorder: Oral formulations: initial, 2 to 5 mg PO daily; recommended dose, 2 to 15 mg (or 5 to 10 mg) PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Dosing of oral solution: May be substituted for tablets on an mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.	Bipolar mania – manic or mixed episodes as monotherapy or as adjunct to lithium or valproate (10 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days Schizophrenia (13 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 10 mg PO daily; max, 30 mg PO daily tablet; titrate every 2 days; daily doses of 30 mg daily were not shown to be more efficacious than 10 mg daily Autistic disorder with irritability (6 to 17 years): Oral formulations: initial, 2 mg PO daily; target dose, 5 to 15 mg PO daily; max, 15 mg PO daily; dose adjustments up to 5 mg/day should occur at intervals of ≥ 1 week. Tourette's Disorder (6 to 18 years): Oral formulations: initial, 2 mg PO daily; recommended dose, 5 mg PO daily for patients < 50 kg and 10 mg PO daily for patients ≥ 50 kg; max, 10 mg PO daily for patients < 50 kg and 20 mg PO daily for patients ≥ 50 kg; dose adjustments should occur gradually at intervals of ≥ 1 week.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers.*	Oral formulations should be administered once daily without regard to meals. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. Long-acting injection may be administered in the deltoid or gluteus by a healthcare professional only.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
			Dosing of oral solution: May be substituted for tablets on a mg-per-mg basis up to 25 mg. Tablet doses of 30 mg should receive 25 mg of solution.		
Aripiprazole lauroxil (ARISTADA)	Long-acting injection (pre-filled syringe): 441 mg 662 mg 882 mg	Schizophrenia: Initial or maintenance, 441 mg, 662 mg, or 882 mg IM once a month or 882 mg IM once every 6 weeks; take 21 days of concurrent oral aripiprazole in conjunction with the first injection	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or in patients taking concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers for more than 2 weeks.*	Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections. The 441 mg dose can be injected into the deltoid or gluteal muscle, but the 662 mg and 882 mg doses can only be administered in the gluteal muscle by a healthcare professional.
Asenapine (SAPHRIS)	Sublingual tablet: 2.5 mg 5 mg 10 mg	Bipolar disorder– manic or mixed episodes: Acute and maintenance monotherapy: initial, target and max dose, 10 mg SL twice daily; dose can be decreased to 5 mg SL twice daily if adverse effects occur. Adjunct to lithium or valproate: initial dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily Schizophrenia: Acute treatment: initial, 5 mg SL twice daily; target dose, 5 mg SL twice daily; max dose, 10 mg SL twice daily; the safety	Bipolar disorder– manic or mixed episodes (10 to 17 years): Initial, 2.5 mg SL twice daily; target dose, 2.5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily; titrate 2.5 to 5 mg every 3 days	Pediatric patients appear to be more sensitive to dystonia with initial dosing when the recommended titration schedule is not followed.	Do not swallow sublingual tablets. Sublingual tablets should be placed under the tongue and left to dissolve completely. The sublingual tablet will dissolve in saliva within seconds. Eating and drinking should be avoided for

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		of doses above 10 mg SL twice daily has not been evaluated Maintenance treatment: initial, 5 mg SL twice daily; target dose, 5 to 10 mg SL twice daily; max dose, 10 mg SL twice daily			10 minutes after administration.
Brexpiprazole (REXULTI)	Oral Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	Adjunctive treatment of major depressive disorder: Initial, 0.5 to 1 mg PO once daily; maintenance, 2 mg once daily; max, 3 mg once daily Schizophrenia: Initial, 1 mg PO once daily; maintenance, 2 to 4 mg once daily; max, 4 mg once daily	Not FDA-approved	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers.*	Take with or without food
Cariprazine (VRAYLAR)	Capsule: 1.5 mg 3 mg 4.5 mg 6 mg Titration pack: 1.5 mg and 3 mg	Schizophrenia: Initial, 1.5 mg PO once daily; maintenance, 1.5 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily. Bipolar disorder – manic or mixed episodes: Initial, 1.5 mg PO once daily; maintenance, 3 to 6 mg PO once daily; titrate by 1.5 to 3 mg once daily to target dose; max, 6 mg once daily.	Not FDA-approved	Due to the long half-life, dose changes may not be reflected for several weeks. Monitor for adverse events and response for several weeks. Dose adjustments are recommended with concomitant CYP3A4 inhibitors.*	Take with or without food Discontinuation of treatment may not be immediately reflected in the patient. No data addressing switching patients to another treatment is available.
Clozapine (CLOZARIL, FAZACLO, VERSACLOZ)	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet:	Treatment-resistant schizophrenia: Initial, 12.5 mg PO once or twice daily;* target dose, 300 to 450 mg daily (in divided doses); max, 900 mg PO daily; titrate by 25 to 50 mg daily to target dose by the end of 2 weeks, after 2 weeks then may titrate by ≤ 100 mg no more frequently than once or twice weekly.	Not FDA-approved	In the event of planned termination of therapy, gradual reduction in dose is recommended over a 1 to 2 week period. Dose adjustments are recommended in patients with	Prior to initiating, a baseline ANC must be ≥ 1,500/µL (≥ 1,000/µL for patients with Benign Ethnic Neutropenia [BEN]). To continue treatment, ANC must be monitored regularly.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	25 mg 50 mg 100 mg 200 mg Suspension: 50 mg/mL	Reduce the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder: Same dosing as above. Mean dose is ~300 mg daily.		renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.*	Shake oral suspension for 10 seconds prior to each use.
Iloperidone (FANAPT)	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	Schizophrenia: Initial, 1 mg twice daily; maintenance, increase to reach the target dose range of 6 to 12 mg twice daily with daily dosage adjustments not to exceed 2 mg twice daily; max, 12 mg twice daily	Not FDA-approved	Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.*	Control of symptoms may be delayed during the first 1 to 2 weeks. Some adverse effects are dose related.
Lurasidone (LATUDA)	Tablet: 20 mg 40 mg 60 mg 80 mg 120 mg	Schizophrenia: Initial, 40 mg PO once daily;† max, 160 mg PO once daily Bipolar disorder - depressive episodes: Monotherapy or as adjunct to lithium or valproate: initial, 20 mg PO once daily; maintenance 20 to 120 mg once daily; max, 120 mg once daily; in the monotherapy study, daily doses of 80 to 120 mg were not shown to be more efficacious than 20 to 60 mg daily.	Not FDA-approved	Recommended starting dose is 20 mg and the max dose is 80 mg with concomitant use with a moderate CYP3A4 inhibitor, or moderate to severe hepatic or renal impairment.	Administer with food (≥ 350 calories).
Olanzapine (ZYPREXA, ZYPREXA ZYDIS, ZYPREXA RELPREVV)	Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg	Schizophrenia: Oral formulations: initial, 5 to 10 mg PO daily; maintenance, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Long-acting injection: initial (during the first 8 weeks), 210 to 300 mg IM every 2 weeks	Schizophrenia (13 to 17 years): Oral formulations: initial, 2.5 to 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg.	Lower starting dose recommended in debilitated or pharmaco-dynamically sensitive patients or patients with predisposition to	Be aware that there are 2 olanzapine injectable formulations with different dosing schedules.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg Short-acting injection (vial): 10 mg Long-acting injection (vial): 210 mg 300 mg 405 mg	or 405 mg IM every 4 weeks depending upon target oral olanzapine dose; maintenance (after the first 8 weeks of ZYPREXA RELPREVV), 150 to 300 mg IM every 2 weeks or 300 to 405 mg IM every 4 weeks depending upon target oral olanzapine dose; doses > 405 mg every 4 weeks or > 300 mg every 2 weeks have not been evaluated.* <u>Bipolar disorder– manic or mixed episodes:</u> Monotherapy (oral formulations): initial, 10 or 15 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily; adjust in increments of 5 mg daily. Adjunct to lithium or valproate (oral formulations): initial, 10 mg PO daily; maintenance, 5 to 20 mg PO daily; max, 20 mg PO daily. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine):</u> Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 12.5 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated. <u>Agitation associated with schizophrenia and bipolar I mania</u>: Short-acting injection: initial, 2.5 to 10 mg IM up to every 2 hours; target dose, 10 mg IM (lower dose to 5 to 7.5 mg when clinical factors warrant); max, 30 mg IM daily	<u>Bipolar disorder– manic or mixed episodes (13 to 17 years):</u> Oral formulations: initial, 2.5 or 5 mg PO daily; target, 10 mg PO daily; max, 20 mg PO daily; adjust in increments of 2.5 to 5 mg. <u>Bipolar disorder - depressive episodes (in combo with fluoxetine) (10 to 17 years)</u>: Oral formulations: initial, 2.5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 2.5 to 12 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 12 mg olanzapine with 50 mg of fluoxetine have not been evaluated.	hypotensive reactions, or with potential slowed metabolism. Recommended dosing for the powder for injection is based on correspondence to oral olanzapine doses.	Administer ZYPREXA without regard to meals. ZYPREXA RELPREVV is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Establish tolerability with oral olanzapine prior to initiating therapy with ZYPREXA RELPREVV.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		Treatment-resistant depression (in combo with fluoxetine): Oral formulations: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5 to 20 mg PO daily in combination with fluoxetine 20 to 50 mg PO daily; doses > 18 mg olanzapine with 75 mg of fluoxetine have not been evaluated.			
Olanzapine/ fluoxetine (SYMBYAX)	Capsule: 3/25 mg 6/25 mg 6/50 mg 12/25 mg 12/50 mg	Bipolar disorder - depressive episodes and treatment-resistant depression: Initial, 6/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 18/75 mg have not been evaluated	Bipolar disorder - depressive episodes (10 to 17 years): Capsule: initial, 3/25 mg once daily in the evening; maintenance, adjust dosage according to efficacy and tolerability; max, doses > 12/50 mg have not been evaluated	Discontinue treatment gradually.	Neonates exposed to SSRIs late in the third trimester have required prolonged hospitalizations, respiratory support, and tube feeding. Consider tapering dose for pregnant women during the third trimester.
Paliperidone (INVEGA, INVEGA SUSTENNA, INVEGA TRINZA)	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Long-acting injection: Once-a-month (INVEGA SUSTENNA): 39 mg 78 mg 117 mg 156 mg 234 mg Once every 3 months	Schizophrenia: Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg, increases > 6 mg should occur at intervals > 5 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 117 mg (range, 39 to 234 mg) administered once monthly; max, 234 mg administered once monthly. Long-acting injection (INVEGA TRINZA): To be initiated only after 4 months of INVEGA SUSTENNA. INVEGA TRINZA dose depends on INVEGA SUSTENNA dose; INVEGA SUSTENNA 78 mg, 117	Schizophrenia (12 to 17 years) weighing < 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 6 mg PO daily; max, 6 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study, daily doses of 6 mg were not shown to be more efficacious. Schizophrenia, adolescents (12 to 17 years) weighing ≥ 51 kg: Oral formulation:† initial, 3 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg at intervals > 5 days and only after reassessment; in one study,	For patients who have never taken oral paliperidone or oral or injectable risperidone, tolerability should be established with oral paliperidone or risperidone prior to initiating treatment with long-acting injectable paliperidone.	Tablets should be swallowed whole and should not be chewed, divided, or crushed. Administer the first 2 INVEGA SUSTENNA doses in the deltoid muscle. Following the second INVEGA SUSTENNA dose, doses can be administered in either the deltoid or gluteal muscle.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	(INVEGA TRINZA): 273 mg 410 mg 546 mg 819 mg	mg, 156 mg, or 234 mg doses administered once monthly should be converted to INVEGA TRINZA 273 mg, 410 mg, 546 mg, or 819 mg doses administered once every 3 months, respectively; conversion from the INVEGA SUSTENNA 39 mg dose has not been studied. Schizoaffective disorder (monotherapy or adjunct to mood stabilizers or antidepressants): Oral formulation:† initial, 6 mg PO daily; maintenance, 3 to 12 mg PO daily; max, 12 mg PO daily; titrate by 3 mg in increments of > 4 days and only after reassessment. Long-acting injection (INVEGA SUSTENNA): initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 78 to 234 mg administered once monthly; max, 234 mg administered once monthly; the 39 mg dose has not been studied.	daily doses of 12 mg were not shown to be more efficacious.		
Quetiapine (SEROQUEL, SEROQUEL XR)	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Immediate-release tablet: 25 mg 50 mg 100 mg 200 mg	Bipolar disorder - depressive episodes: Immediate-release tablet: initial, 50 mg PO once daily at bedtime; maintenance, 300 mg PO daily*; max, 300 mg PO daily Extended-release tablet: initial, 50 mg PO once daily; maintenance, 300 mg once PO daily*; max, 300 mg PO daily Bipolar disorder - manic episodes: Immediate-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 50 mg PO twice daily; maintenance,	Bipolar disorder - manic episodes (10 to 17 years): Immediate-release tablet (monotherapy): initial, 25 mg PO twice daily; maintenance, 200 to 300 mg PO twice daily*; max, 600 mg PO daily Extended-release tablet (monotherapy): initial, 50 mg PO daily; recommended, 400 to 600 mg PO daily*; max, 600 mg PO daily	Dose titration is required.	Extended-release tablets should be swallowed whole and not split, chewed, or crushed. Administer extended-release tablets without food or with a light meal. Extended-release tablets should be administered once

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	300 mg 400 mg	400 to 800 mg PO daily*; max, 800 mg PO daily Bipolar disorder – manic or mixed episodes: Extended-release tablet (monotherapy or as an adjunct to lithium or divalproex): initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily Major depressive disorder: Extended-release tablet (as an adjunct to antidepressants): initial, 50 mg PO once daily; maintenance, 150 to 300 mg PO once daily*; max, 300 mg PO daily Schizophrenia: Immediate-release tablet: initial, 25 mg PO twice daily; maintenance, 150 to 750 mg PO daily*; max, 750 mg PO daily for acute treatment (≤ 6 weeks) and 800 mg PO daily for maintenance dosing Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400 to 800 mg PO once daily*; max, 800 mg PO daily	Schizophrenia (13 to 17 years): Immediate-release tablet: initial, 25 mg PO twice daily; recommended, 200 to 400 mg PO twice daily*; max, 800 mg PO daily Extended-release tablet: initial, 50 mg PO daily; recommended, 400 to 800 mg PO daily*; max, 800 mg PO daily		daily, preferably in the evening. Administer immediate-release tablets without regard to food.
Risperidone (RISPERDAL, RISPERDAL CONSTA, RISPERDAL M-TAB)	Orally disintegrating tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Solution: 1 mg/mL	Bipolar – manic or mixed episodes:‡: Oral formulations: initial, 2 to 3 mg PO daily; target, 1 to 6 mg PO daily; max, 6 mg PO daily Long-acting injection (monotherapy or as an adjunct to lithium or valproate): 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every 2 weeks; max, 50 mg IM every 2 weeks Schizophrenia:	Bipolar – manic or mixed episodes (10 to 17 years): Oral formulations: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 2.5 mg PO daily; no additional benefit was seen above 2.5 mg PO	For the treatment of bipolar mania in adults, there is no clinical data supporting maintenance dosing. For the treatment of bipolar mania in children and adolescents, no	For the treatment of bipolar mania, risperidone should be administered once daily. For the treatment of schizophrenia, risperidone should be administered once or twice daily.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
	Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Long-acting injection: 12.5 mg 25 mg 37.5 mg 50 mg	Long-acting injection: 25 mg IM every 2 weeks; maintenance, 25 to 50 mg IM every 2 weeks; max, 50 mg IM every 2 weeks Oral formulations: initial, 2 mg PO once daily or 1 mg PO twice daily; target, 4 to 16 mg PO per day (divided into once or twice daily dosing); maintenance therapy, 2 to 8 mg PO daily; max, 16 mg PO daily; daily doses of > 6 mg per day for twice daily dosing were not were not shown to be more efficacious than lower doses.	daily; doses higher than 6 mg PO daily were not studied <u>Irritability associated with autistic disorder, children and adolescents aged 5 to 16 years</u>§: Orally disintegrating tablet, oral solution, tablet: initial, 0.25 mg PO daily for patients < 20 kg and 0.5 mg daily for patients ≥ 20 kg; max, 1 mg PO daily in patients < 20 kg, 2.5 mg in patients ≥ 20 kg <u>Schizophrenia, adolescents aged 13 to 17 years:</u> Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 3 mg PO daily; max, 6 mg PO daily	additional benefit was seen with doses > 2.5 mg/day, and doses > 6 mg/day were not evaluated. Titrate the dose of RISPERAL CONSTA no sooner than every 4 weeks; clinical effects are observed ≥ 3 weeks after injection.	Oral RISPERDAL (or another antipsychotic) should be given with the first injection of RISPERDAL CONSTA, and continued for 3 weeks (and then discontinued) to ensure adequate concentrations of RISPERDAL CONSTA.
Ziprasidone (GEODON)	Capsule: 20 mg 40 mg 60 mg 80 mg Short-acting injection: 20 mg/mL	<u>Acute agitation in schizophrenia</u>: Injection: initial, 10 mg IM every 2 hours or 20 mg every 4 hours; max, 40 mg IM daily¶ <u>Bipolar disorder – manic or mixed episodes</u>: Capsule (monotherapy): initial, 40 mg PO twice daily; maintenance (monotherapy), 60 to 80 mg PO twice daily on day 2; maintenance (adjunct to lithium or valproate), 40 to 80 mg PO twice daily <u>Schizophrenia</u>: Capsule: initial, 20 mg PO twice daily; maintenance, 20 to 80 mg PO twice daily;	Not FDA-approved	Not applicable.	Administer capsules with food. Administration of short-acting injection for more than 3 consecutive days has not been studied. If long term therapy is indicated, oral therapy should replace the injection as soon as possible.

Drug	Dosage Form: Strength	Usual Recommended Dose: Adult	Usual Recommended Dose: Pediatric	Other Dosing Considerations	Administration Considerations
		max, 100 mg PO twice daily; no additional benefit for doses > 20 mg twice daily			Coadministration of capsules and injection is not recommended.

Abbrv: ANC = absolute neutrophil count, BEN = Benign Ethnic Neutropenia, CBC = complete blood count, CYP = cytochrome isoenzyme, IM = intramuscularly, PO = orally, SL = sublingually, WBC = white blood count

*Please refer to individual package insert for dose titration and/or tapering guidance.

†Initial dose titration is not required.

‡There is no clinical data supporting maintenance dosing.

§No dosing data is available for children who weighed less than 15 kg.

¶Administration for more than 3 consecutive days has not been studied.

**In combination with fluoxetine 20 mg (adults and children)

††Short-acting injection is FDA-approved and guidance outlined in prescribing information; however, formulation has been discontinued.

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution				
	Elderly	**Pediatrics**	**Renal Dysfunction**	**Hepatic Dysfunction**	**Pregnancy/ Nursing**
Aripiprazole*	No dosage adjustment is recommended for elderly patients. Safety and effectiveness of aripiprazole lauroxil extended-release injection in patients > 65 years of age have not been evaluated.	Safety and effectiveness in pediatric patients < 13 years with schizophrenia, patients < 10 years with bipolar mania, and patients < 6 years with Tourette's or with irritability associated with autism have not been established. PK in patients aged 10 to 17 years was similar to adults. The long-acting injections have not been studied in children.	No dosage adjustment is required in subjects with renal impairment.	No dosage adjustment is required in subjects with hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Asenapine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and efficacy in the treatment of bipolar disorder in patients < 10 years of age, and patients with schizophrenia aged < 12 years have not been evaluated.	No dosage adjustment is required in subjects with renal impairment.	Contraindicated in patients with severe hepatic impairment.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Brexpiprazole*	Has not been studied in patients aged ≥ 65 years; PK studies showed similar results to adults for MDD.	Safety and effectiveness have not been established. Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric patients.	In moderate, severe, or end-stage renal impairment (CrCL < 60 mL/min), the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	In moderate to severe hepatic impairment, the max dose for MDD is 2 mg once daily and in schizophrenia is 3 mg once daily.	May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure; discontinue drug or nursing.
Cariprazine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently	Safety and effectiveness have not been established.	Not recommended in severe renal impairment (CrCL < 30 mL/min).	Not recommended in severe hepatic impairment (Child-Pugh 10 to 15).	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	than younger patients.				of animal models; discontinue drug or nursing.
Clozapine*†	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Elderly are more susceptible to hypotension, tachycardia, anticholinergic effects, and tardive dyskinesia.	Safety and effectiveness in pediatric patients have not been established.	Dose reductions may be needed in patients with renal impairment.	Dose reductions may be needed in patients with hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.
Iloperidone*	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	Renal impairment (CrCL < 30 mL/min) had minimal effect on PK parameters.	Not recommended in severe impairment.	No adequate studies in pregnant women; use only if clearly needed. Drug is present in the milk of animal models; do not breastfeed.
Lurasidone	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients.	Safety and effectiveness in pediatric patients have not been established.	PK bounds varied moderately in mild to severe impairment; dose should not exceed 80 mg/day in patients with CrCL < 50.	In severe impairment AUC was much higher than in mild to moderate impairment; dose reduction to max 40 mg/day recommended.	No adequate studies in pregnant women; use only if benefit outweighs risk. Discontinue drug or nursing.
Olanzapine	Consider a lower starting dose (2.5 mg to 5 mg short-acting injection) for any elderly patient if factors are present that might decrease PK clearance or increase the PD response. Clinical studies did not include sufficient numbers of elderly	Safety and effectiveness in pediatric patients with schizophrenia or manic/mixed bipolar I disorder < 13 years of age and < 10 years in combination with fluoxetine for acute treatment of depressive episodes have not been established.	No dosage adjustment is required in subjects with renal impairment. Has not been studied in long-acting injection formulations.	May reduce clearance; however a small study (N = 6) of cirrhosis patients showed very little PK effects. Has not been studied in long-acting injection formulations.	No adequate studies in pregnant women; use only if benefit outweighs risk. May cause EPS and/or withdrawal symptoms in neonates with third trimester exposure. Drug is present in human milk; do not breastfeed.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	patients in long-acting injection studies to determine whether or not they respond differently than younger patients.	Safety and effectiveness of the long-acting injection have not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.			
Olanzapine/ fluoxetine	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Certain factors might decrease PK clearance or increase PD response; consider a lower starting dose (3/25 mg or 6/25 mg).	Safety and efficacy in pediatric patients with bipolar depression < 10 years have not been established. Safety and efficacy in treatment resistant depression has not been established. Adolescents treated with oral olanzapine are more prone to weight gain, sedation, metabolic changes, prolactin, and AST increases.	No dosing recom-mendations	Consider lower initial doses of SYMBYAX (3/25 mg or 6/25 mg) in hepatic impairment. Caution is advised when using SYMBYAX in patients with diseases or conditions that could affect its metabolism.	No adequate studies in pregnant women; fluoxetine exposure in the first trimester has had inconsistent results and the third trimester have resulted in complications requiring prolonged hospitalizations, respiratory support, and tube feeding. Use only if benefit outweighs risk. Drug is present in human milk; do not breastfeed.
Paliperidone Paliperidone palmitate‡	Because elderly patients may have diminished renal function, dose adjustment may be required according to their renal function status. In general, the recommended dosing for elderly patients with healthy renal function is the same as for younger adult patients with	Safety and effectiveness in pediatric patients with schizophrenia < 12 years of age have not been established. Safety and effectiveness in pediatric patients with schizoaffective disorder and other conditions have not been established.	Adjust dose to 3 to 6 mg once daily in mild renal impairment (CrCL 50 to 80 mL/ min); 1.5 to 3 mg once daily in moderate to severe impairment (CrCL 10 to 50 mL/ min). For mild impairment, SUSTENNA should be dosed at 156 mg on day 1 followed by 117	For patients with mild to moderate hepatic impairment no dose adjustment is recom-mended. Not studied in patients with severe hepatic impairment.	No adequate studies in pregnant women; however, in general neonates with third trimester exposure have EPS and/or withdrawal symptoms with antipsychotic use. Drug is present in human milk; discontinue drug or nursing.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
	healthy renal function.	Safety and effectiveness of the long-acting injection in patients < 18 years of age have not been established.	mg one week later; subsequent dose should be 78 mg every month. TRINZA should be transitioned after stabilized on SUSTENNA. For moderate to severe impair-ment, long-acting injections are not recommended.		
Quetiapine	For elderly patients, consider a slower rate of dose titration and a lower target dose; when indicated, dose escalation should be performed with caution in these patients.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, and bipolar mania < 10 years have not been established. Increases in systolic and diastolic BP occurred in pediatric patients. Safety and effectiveness in bipolar depression have not been established.	Dosage adjustment not needed.	Start at a low dose of 50 mg for extended-release (XR) and 25 mg immediate-release (IR). Increase by 25 to 50 mg for IR and 50 mg for XR formulations.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in human milk; discontinue drug or nursing.
Risperidone‡	Clinical studies did not include sufficient numbers of elderly patients to determine whether or not they respond differently than younger patients. Lower doses may be considered as elderly are susceptible to hypotension and risperidone is highly excreted by the kidneys.	Safety and effectiveness in pediatric patients with schizophrenia < 13 years, bipolar disorder < 10 years, and autistic disorder < 5 years have not been established. Pediatric patients treated with oral risperidone are prone to tardive dyskinesia, weight gain, somnolence,	For severe impairment (CrCL < 30 mL/min), start at 0.5 mg twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	For severe impairment (Child-Pugh C), start at 0.5 mg orally twice daily (see PI for dose titration). Long-acting injection should be initiated after patient is stable on the oral formulation.	Reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding disorder, and corpus callosum were reported in neonates exposed in the third trimester. No data is available in humans with the long-acting injection. Drug is present in human milk;

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy/ Nursing
		and elevated prolactin levels. Safety and efficacy of the long-acting injection in pediatric patients have not been established.			discontinue drug or nursing.
Ziprasidone	Consider a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. Ziprasidone IM has not been studied in this group.	Safety and effectiveness in pediatric patients have not been established.	Caution should be used in renal impairment with administration of IM formulations due to cyclodextrin, which is renally filtered.	Dose adjustments are not required but PK changes have been observed. Ziprasidone IM has not been studied in this group.	Based on animal data, may cause fetal harm. Limited human data; only use if the benefit justifies the risk. Drug is present in the milk of animal models; do not breastfeed.

Abbrv: AST = hepatic aminotransferase, ANC = absolute neutrophil count, AUC = area under the curve, BP=blood pressure, CrCL = creatinine clearance, EPS = extrapyramidal symptoms, IM = intramuscular, MDD = major depressive disorder, NMS = neuroleptic malignant syndrome, PD = pharmacodynamic, PI = prescribing information, PK = pharmacokinetic
*For CYP2D6 poor metabolizers dosage adjustments are recommended.
†For hospice patients (life expectancy ≤ 6 months), consider reducing the ANC monitoring frequency to once every 6 months.
‡Patients with Parkinson's disease or Dementia with Lewy Bodies can have increased sensitivity to long-acting injections, which may result in confusion, EPS, NMS, obtundation, and instability with frequent falls.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called first generation antipsychotics, and atypical antipsychotics, also called second generation antipsychotics (Miyamato et al, 2005).
- There are a number of atypical antipsychotics formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets. FDA-approved indications for the atypical antipsychotics include autism, bipolar disorder, Tourette's disorder, major depressive disorder, schizophrenia, and schizoaffective disorder. FDA-approved atypical agents include (Drugs@FDA, 2017):
  - Generic agents – aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiapine immediate- and extended-release, risperidone, ziprasidone, and olanzapine/fluoxetine
  - Branded agents – GEODON® (short-acting injection only), LATUDA®, REXULTI®, SAPHRIS®, VERSACLOZ® (oral suspension), and VRAYLAR™
  - Long-acting injections – ABILIFY MAINTENA®, ARISTADA™ , INVEGA SUSTENNA®, INVEGA TRINZA® (the only once every 3 months injection), RISPERDAL CONSTA®, and ZYPREXA RELPREVV®
- In terms of the pharmacology of the atypical antipsychotics, different chemical entities have different properties. Most atypical antipsychotics have a fairly long half-life (≥ 24 hours), except lurasidone, quetiapine, and ziprasidone. Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone. The newly FDA-approved agent, cariprazine, has the longest half-life in the oral class (1 to 3 weeks for active metabolite); therefore, delayed adverse events have been reported. Clozapine can be highly toxic; therefore, clinicians should check plasma levels before exceeding a 600 mg dose. For the long-acting injectable agents, drug tolerability should be established prior to initiating the long-acting injectable treatment; a patient's response to an adjusted dose may not be seen for some time due to the long half-life. RISPERDAL CONSTA serum concentrations may not be seen until

approximately 3 weeks after injection. In certain slow metabolizers careful dose adjustment should be made as is the case with iloperidone and CYP2D6 slow metabolizers (Clinical Pharmacology, 2016; Micromedex 2.0, 2016).

- FDA-approved indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in class are indicated for use in schizophrenia with the exception of combination agent SYMBYAX (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding INVEGA TRINZA, are indicated for the treatment of schizoaffective disorder, and clozapine is the only agent in class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, and REXULTI. RISPERDAL CONSTA is the only long-acting injectable indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, REXULTI, and SEROQUEL XR are indicated as adjunctive treatment for major depressive disorder in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression.
- Comparative effectiveness data is most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (Leucht et al, 2013; Lieberman et al, 2005; Stroupe et al, 2006; Stroupe et al, 2009). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (Lehman et al, 2004; Leucht et al, 2013). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include extrapyramidal symptoms (EPS), increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia (with the exception of clozapine), making them a generally better-tolerated treatment option (Abou-Setta et al, 2012; Lehman et al, 2004; Seida et al, 2012[a]; Seida et al, 2012[b]; VA Pharmacy Benefits Management Services, 2012). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (Jibson et al, 2016; Micromedex 2.0, 2016). The following factors may be considered when selecting certain agents in patients:
  - o Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - o EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - o Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in class; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.

- QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
- Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
- Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9 to 25%) and iloperidone (3 to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15 to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, and lurasidone. However, fewer studies have been conducted with the newer agents.
- Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold versus new-onset seizures. Incidences of seizure are most often reported with clozapine (3 to 5%), and to a lesser degree risperidone (0.3%)
- Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49 to 87% of patients versus adults in which incidences range from 1 to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (Serretti et al, 2011).
- Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20 to 52%) and quetiapine (18 to 57%). In class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
- Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias. In 2015, the FDA made changes to the recommended monitoring within the clozapine REMS program around severe neutropenia (FDA Drug Safety Communication [clozapine], 2015).
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. In 2011, the FDA issued an alert on serious allergic reactions after 52 cases of Type I hypersensitivity reactions were reported with asenapine use (FDA Drug Safety Communication [Saphris], 2011).

- Newly FDA-approved agent, cariprazine, has demonstrated safe and effective use in doses ≤ 6mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (Calabrese et al, 2015; Durgam et al, 2015[a]; Durgam et al, 2014; Durgam et al, 2015[b]; FDA/CBER summary review, 2015; Kane et al, 2015[b]; Sachs et al, 2014). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. Although, one 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 to 9 mg daily during maintenance therapy (Durgam et al, 2016[a]; Durgam et al, 2016[b]).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (ABILIFY prescribing information, 2015; Gulisano et al, 2011; Yoo et al, 2013).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval

stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (P = 0.06) (Ghanizadeh et al, 2014). Both agents have demonstrated safe and effective use in placebo controlled trials (Marcus et al, 2009; McCracken et al, 2002; Owen et al, 2009; Shea et al, 2004; McDougle et al, 2005). Based on current data, both agents appear to have similar efficacy and safety.

- For the treatment of major depressive disorder (MDD), aripiprazole, REXULTI (brexpiprazole), and SEROQUEL XR (quetiapine ER) have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (SYMBYAX) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. REXULTI is the newest agent FDA-approved and has not been included in MAs. Primary efficacy results demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (Thase et al, 2015). One meta-analysis found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (Wen et al, 2014). Another meta-analysis concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (Spielmans et al, 2013). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).
- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and SAPHRIS are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. In an AHRQ SR, aripiprazole, olanzapine, ziprasidone, quetiapine, and risperidone were associated with greater improvements in response rates (NNT, 3 to 7) and increased remission rates (NNT, 2 to 12) compared to placebo (Seida et al, 2012[a]; Seida et al, 2012[b]). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (Findling et al, 2014; Detke et al, 2015). In adult patients with bipolar disorder, selection of agents should be based on the adverse event profile and individual patient characteristics as all FDA-approved agents have demonstrated efficacy (Abou-Setta et al, 2012; Muralidharan et al, 2013). RISPERDAL CONSTA is the only long-acting injection agent in class that has demonstrated safe and effective use (McFadden et al, 2009; Quiroz et al, 2010; Vieta et al, 2012; Yatham et al, 2007). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (Fornaro et al, 2016; Silva et al, 2013; Taylor et al, 2014; Vieta et al, 2010).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (Abou-Setta et al, 2012; Asenjo Lobos et al, 2010; Asmal et al, 2013; Cipriani et al, 2011; Citrome et al, 2009; Durgam et al, 2014; Durgam et al, 2015[b]; Glick et al, 2011; Jones et al, 2010; Kane et al, 2015[b]; Khanna et al, 2014; Klemp et al, 2011; Komossa et al, 2009[a], Komossa et al, 2010[a]; Komossa et al, 2009[b]; Komossa et al, 2010[b]; Komossa et al, 2011; Kumar et al, 2013; Leucht et al, 2009[a]; Leucht et al, 2009[b]; Leucht et al, 2013; Lieberman et al, 2005; Perlis et al, 2006[b]; Riedel et al, 2010; Seida et al, 2012[a]; Seida et al, 2012[b]; Stroupe et al, 2006; Stroupe et al, 2009; Tarr et al, 2011; Vieta et al, 2010; Yildiz et al, 2011).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (Hirschfeld et al, 2002; Hirschfeld et al, 2005; VA/DoD, 2010).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (VA/DoD, 2016; Gelenberg et al, 2010).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (Gelenberg et al, 2010).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (Dixon et al, 2009; Lehman et al, 2004; VA Pharmacy Benefits Management Services, 2012).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (Findling et al, 2011).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (Volkmar et al, 2014).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (McClellan et al, 2007).
- Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (McClellan et al, 2013).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (Murphy et al, 2013). The European Society for the Study of Tourette Syndrome guideline recommends risperidone as first-line treatment, aripiprazole for treatment-refractory patients, and clonidine for patients with co-morbid ADHD (Roessner et al, 2011).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

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Top 10 Prescribers
Nevada Medicaid
4/1/2016 - 3/31/2017

Prescriber Identifier	Degree	Specialty	Location	Count of Member ID	Sum of Qty	Sum of Days Supply
Top 10 number of patients						
1	NP	Pain Management	Las Vegas	2,498	231,203	74,006
2	PA	None	Las Vegas	1,794	177,509	50,404
3	PA	None	Las Vegas	1,757	194,922	50,144
4	PA	None	Las Vegas	1,418	127,797	41,991
5	MD	Internal Med, Pain Management	Las Vegas	1,292	118,887	35,468
6	MD	Physical Medicine and Rehab	Reno	1,282	128,193	37,022
7	MD	Physical Medicine and Rehab	Carson City	1,233	110,956	32,034
8	DDS	None	Reno	1,211	21,274	5,229
9	MD	Physical Medicine and Rehab	Reno	1,174	87,406	27,642
10	MD	Internal Med, Critical Care	Fallon	1,066	106,248	18,773
Top 10 by qty						
1	NP	Pain Management	Las Vegas	2,498	231,203	74,006
3	PA	None	Las Vegas	1,757	194,922	50,144
2	PA	None	Las Vegas	1,794	177,509	50,404
6	MD	Physical Medicine and Rehab	Reno	1,282	128,193	37,022
4	PA	None	Las Vegas	1,418	127,797	41,991
5	MD	Internal Med, Pain Management	Las Vegas	1,292	118,887	35,468
7	MD	Physical Medicine and Rehab	Carson City	1,233	110,956	32,034
11	MD	Internal Med, Critical Care, Rehab Therapy	Sparks	683	106,622	19,338
10	MD	Internal Med, Critical Care	Fallon	1,066	106,248	18,773
12	PA	Hematology/Oncology, Ped	Las Vegas	1,004	102,752	28,586
Top 10 by Days Supply						
1	NP	Pain Management	Las Vegas	2,498	231,203	74,006
2	PA	None	Las Vegas	1,794	177,509	50,404
3	PA	None	Las Vegas	1,757	194,922	50,144
4	PA	None	Las Vegas	1,418	127,797	41,991
6	MD	Physical Medicine and Rehab	Reno	1,282	128,193	37,022
5	MD	Internal Med, Pain Management	Las Vegas	1,292	118,887	35,468
7	MD	Physical Medicine and Rehab	Carson City	1,233	110,956	32,034
12	PA	Hematology/Oncology, Ped	Las Vegas	1,004	102,752	28,586
9	MD	Physical Medicine and Rehab	Reno	1,174	87,406	27,642
13	MD	Anesthesiology, Mammography, Pediatrics-Cardiology	Las Vegas	1,016	93,792	27,332

Top 10 Opioid Utilizers - Other Medications
Nevada Medicaid
4/1/2016 - 3/31/2017

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
00000086592	3	13	AMOXICILLIN/CLAVULANATE P	14	7	$ 17.54
00000086592	3	13	PREDNISONE	5	5	$ 9.99
00000086592	3	13	SULFAMETHOXAZOLE/TRIMETHO	14	7	$ 10.99
00000086592	3	47	ADVAIR DISKUS	60	30	$ 338.70
00000086592	3	47	PROAIR HFA	9	25	$ 61.49
00000086592	3	48	HYDROMORPHONE HCL	3,540	670	$ 575.77
00000086592	3	48	HYDROCODONE POLISTIREX/CH	180	18	$ 86.67
00000086592	3	48	OXYBUTYNIN CHLORIDE ER	120	120	$ 125.33
00000086592	3	48	THEREMS-M	30	30	$ 9.99
00000086592	3	48	ADVAIR DISKUS	240	120	$ 1,368.57
00000086592	3	48	SSD	50	14	$ 17.49
00000086592	3	48	BACLOFEN	660	180	$ 246.54
00000086592	3	48	SULFAMETHOXAZOLE/TRIMETHO	40	10	$ 13.51
00000086592	3	48	BUTALBITAL/ACETAMINOPHEN/	150	37	$ 108.93
00000086592	3	48	OXYCODONE HCL	3,240	360	$ 1,261.42
Subtotal				**8,352**	**1,633**	**$ 4,252.93**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
04346000003	18	22	FLULAVAL QUADRIVALENT 201	1	1	$ 23.57
04346000003	9	26	ONETOUCH ULTRA BLUE	700	210	$ 951.23
04346000003	9	26	JANUVIA	240	240	$ 2,916.39
04346000003	9	26	METFORMIN HCL	480	240	$ 97.23
04346000003	9	26	ONETOUCH DELICA LANCETS F	700	180	$ 68.19
04346000003	9	26	PRAVASTATIN SODIUM	270	270	$ 152.95
04346000003	9	26	QUETIAPINE FUMARATE	720	240	$ 169.74
04346000003	9	26	FUROSEMIDE	240	240	$ 73.04
04346000003	9	26	PROVENTIL HFA	40	96	$ 473.90
04346000003	9	26	TAMSULOSIN HCL	210	210	$ 113.25
04346000003	9	26	ADVAIR DISKUS	540	270	$ 3,077.27
04346000003	9	33	LEVOFLOXACIN	10	10	$ 14.37
04346000003	9	45	ONETOUCH ULTRA 2	1	1	$ 17.74
04346000003	18	55	DIAZEPAM	1,440	360	$ 151.44
04346000003	18	55	EVZIO	1	1	$ 3,615.85
04346000003	18	55	METHADONE HCL	5,760	360	$ 846.15
04346000003	18	55	MORPHINE SULFATE ER	1,080	360	$ 1,859.13
04346000003	18	55	GABAPENTIN	1,050	360	$ 167.61
04346000003	18	55	LIDOCAINE	71	60	$ 148.99
04346000003	18	55	MELOXICAM	720	360	$ 137.23
Subtotal				**14,273**	**4,069**	**$ 15,075.27**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
11119297885	5	6	LEVOFLOXACIN	5	5	$ 12.60
11119297885	5	6	PREDNISONE	5	5	$ 11.51
11119297885	7	6	NITROFURANTOIN MONOHYDRAT	20	10	$ 30.95
11119297885	21	8	DOXYCYCLINE HYCLATE	28	14	$ 29.04
11119297885	21	8	IBUPROFEN	15	5	$ 10.89
11119297885	7	11	METRONIDAZOLE	20	10	$ 17.22
11119297885	7	11	LEVOFLOXACIN	10	10	$ 12.34
11119297885	5	15	FLORANEX	30	10	$ 58.92
11119297885	5	15	VANCOMYCIN HCL	56	14	$ 661.96
11119297885	5	15	SPIRONOLACTONE	30	30	$ 12.09
11119297885	7	17	CIPROFLOXACIN HCL	20	10	$ 13.29
11119297885	7	18	CREON	450	57	$ 3,601.29
11119297885	9	18	PANTOPRAZOLE SODIUM	30	30	$ 12.33
11119297885	10	18	TRAMADOL HCL	180	30	$ 13.92
11119297885	12	18	CAPECITABINE	112	21	$ 1,683.71
11119297885	12	18	OXYCODONE HCL	3,240	250	$ 1,129.12
11119297885	12	18	FUROSEMIDE	30	30	$ 9.30
11119297885	12	18	DIPHENOXYLATE/ATROPINE	100	13	$ 23.96
11119297885	12	18	ALPRAZOLAM	120	120	$ 43.27
11119297885	14	18	MINOCYCLINE HCL	20	10	$ 17.54
11119297885	21	18	MORPHINE SULFATE ER	60	30	$ 128.50
11119297885	21	18	ALPRAZOLAM	30	30	$ 10.84

11119297885	21	18	OXYCODONE HCL	840	65	$ 328.37
11119297885	5	19	CEPHALEXIN	120	30	$ 20.93
11119297885	5	19	OXYCODONE HCL	160	13	$ 41.19
11119297885	5	19	FENTANYL	10	30	$ 116.49
11119297885	7	19	CIPROFLOXACIN HCL	14	7	$ 12.38
11119297885	12	19	CAPECITABINE	448	84	$ 7,748.20
11119297885	12	19	ALPRAZOLAM	60	60	$ 21.59
11119297885	12	19	OXYCODONE HCL	720	55	$ 246.44
11119297885	12	19	PROCHLORPERAZINE MALEATE	90	22	$ 18.42
11119297885	14	19	PROCHLORPERAZINE MALEATE	135	45	$ 42.41
11119297885	14	19	ONDANSETRON HCL	6	2	$ 11.70
11119297885	21	19	MORPHINE SULFATE ER	60	30	$ 128.50
11119297885	21	19	ALPRAZOLAM	30	30	$ 10.78
11119297885	21	19	OXYCODONE HCL	720	60	$ 273.73
11119297885	7	23	CEFDINIR	20	10	$ 26.50
11119297885	7	23	FLORANEX	42	14	$ 12.69
11119297885	5	28	METOCLOPRAMIDE HCL	30	10	$ 11.51
11119297885	9	34	HYDROCODONE/ACETAMINOPHEN	20	4	$ 13.77
11119297885	9	34	VANCOMYCIN HCL	30	10	$ 407.99
11119297885	7	37	TAMSULOSIN HCL	30	30	$ 15.63
11119297885	7	37	SULFAMETHOXAZOLE/TRIMETHO	60	30	$ 15.26
11119297885	5	41	DIPHENOXYLATE/ATROPINE	480	60	$ 161.60
11119297885	9	41	DIPHENOXYLATE/ATROPINE	240	30	$ 83.40
11119297885	9	41	CHOLESTYRAMINE	378	30	$ 71.99
11119297885	12	41	DIPHENOXYLATE/ATROPINE	240	30	$ 83.63
11119297885	12	41	OXYCODONE HCL	1,440	170	$ 345.74
11119297885	12	51	OXYCODONE HCL	84	7	$ 35.22
Subtotal				**11,118**	**1,712**	**$ 17,850.65**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
22222309822	13	2	AZITHROMYCIN	3	3	$ 13.52
22222309822	13	2	PROVENTIL HFA	54	200	$ 635.76
22222309822	13	2	PREDNISONE	7	7	$ 6.55
22222309822	13	2	OXYCODONE HCL	90	15	$ 38.71
22222309822	13	2	OXYCODONE/ACETAMINOPHEN	180	30	$ 125.80
22222309822	13	2	HYDROCODONE/ACETAMINOPHEN	1,200	300	$ 325.62
22222309822	13	2	METHADONE HCL	3,960	330	$ 593.71
22222309822	13	2	ONDANSETRON ODT	10	3	$ 13.80
22222309822	13	2	CEFUROXIME AXETIL	14	7	$ 33.00
22222309822	13	2	GABAPENTIN	270	90	$ 47.01
22222309822	17	2	HYDROCODONE/ACETAMINOPHEN	120	30	$ 31.04
22222309822	17	2	PROVENTIL HFA	7	16	$ 82.54
22222309822	17	2	METHADONE HCL	360	30	$ 57.59
22222309822	23	2	GABAPENTIN	180	60	$ 43.65
22222309822	11	16	PROAIR HFA	17	33	$ 112.63
22222309822	11	16	ENOXAPARIN SODIUM	6	7	$ 104.15
22222309822	11	16	IPRATROPIUM BROMIDE/ALBUT	360	30	$ 32.82
22222309822	11	16	WARFARIN SODIUM	30	30	$ 16.51
22222309822	11	16	AMOXICILLIN	21	7	$ 11.73
22222309822	11	16	SULFAMETHOXAZOLE/TRIMETHO	14	7	$ 11.01
22222309822	11	16	PREDNISONE	20	8	$ 11.99
22222309822	13	27	DOXYCYCLINE HYCLATE	20	10	$ 29.55
22222309822	13	27	METHYLPREDNISOLONE DOSE P	21	6	$ 21.00
22222309822	13	36	PREDNISONE	5	5	$ 6.04
22222309822	13	36	CEFDINIR	20	10	$ 25.31
Subtotal				**6,988**	**1,274**	**$ 2,431.04**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
27483344445	1	4	SULFAMETHOXAZOLE/TRIMETHO	24	12	$ 12.10
27483344445	1	4	ACYCLOVIR	15	5	$ 11.67
27483344445	1	5	BRIMONIDINE TARTRATE	5	30	$ 93.15
27483344445	1	5	TRAVATAN Z	3	30	$ 155.06
27483344445	8	9	LEVOTHYROXINE SODIUM	30	30	$ 21.99
27483344445	8	9	PANTOPRAZOLE SODIUM	30	30	$ 12.17
27483344445	8	9	DOK	60	30	$ 7.33
27483344445	8	9	FERROUS SULFATE	60	30	$ 5.72
27483344445	8	9	LISINOPRIL	30	30	$ 10.70
27483344445	8	9	TEMAZEPAM	5	5	$ 9.18
27483344445	1	42	IBUPROFEN	90	22	$ 24.61
27483344445	1	52	ERYTHROMYCIN	4	15	$ 18.70
27483344445	1	52	AZITHROMYCIN	6	5	$ 12.84
27483344445	1	52	PREDNISOLONE ACETATE	20	30	$ 173.82
27483344445	1	52	POLYMYXIN B SULFATE/TRIME	20	30	$ 32.90
27483344445	1	52	NEVANAC	9	45	$ 682.32
27483344445	1	54	VALACYCLOVIR HCL	21	7	$ 24.01
27483344445	1	54	TRAMADOL HCL	2,700	360	$ 180.37
27483344445	1	54	AMITIZA	120	60	$ 666.22
27483344445	1	54	ALPRAZOLAM	65	43	$ 63.91
27483344445	1	54	VASCEPA	720	360	$ 1,520.90
27483344445	1	54	TORSEMIDE	180	150	$ 92.12
27483344445	1	54	PIOGLITAZONE HCL	180	180	$ 95.77
27483344445	1	54	PROCHLORPERAZINE MALEATE	60	15	$ 15.67
27483344445	1	54	POTASSIUM CHLORIDE ER	300	150	$ 169.99
27483344445	1	54	BENAZEPRIL HCL	300	300	$ 116.62
27483344445	1	54	LEVOFLOXACIN	10	10	$ 12.34
27483344445	1	54	GLIMEPIRIDE	390	390	$ 153.52
27483344445	1	54	MORPHINE SULFATE ER	990	330	$ 3,795.23
27483344445	1	54	ESTRADIOL	180	180	$ 57.64
27483344445	1	54	PROMETHAZINE HCL	240	4	$ 13.04
27483344445	1	54	ESCITALOPRAM OXALATE	120	120	$ 51.21
27483344445	1	54	MORPHINE SULFATE	2,639	278	$ 1,020.67
27483344445	1	54	METRONIDAZOLE	60	20	$ 35.74
27483344445	1	54	MEMANTINE HCL	240	120	$ 119.20
27483344445	1	54	SSKI	30	30	$ 21.66
27483344445	1	54	BUMETANIDE	330	330	$ 231.99
27483344445	1	54	TEMAZEPAM	570	300	$ 148.12
27483344445	1	54	OXYCODONE/ACETAMINOPHEN	1,980	272	$ 1,278.24
27483344445	1	54	NITROFURANTOIN MONOHYDRAT	200	100	$ 307.45
27483344445	1	54	AZITHROMYCIN	12	10	$ 25.70
27483344445	1	54	TANZEUM	8	58	$ 909.02
27483344445	1	54	METOCLOPRAMIDE HCL	270	90	$ 42.66
27483344445	1	54	KLOR-CON SPRINKLE	240	120	$ 125.87
27483344445	1	54	BACLOFEN	210	210	$ 131.16
27483344445	1	54	MELOXICAM	150	150	$ 54.59
27483344445	1	54	TRADJENTA	300	300	$ 3,577.79
27483344445	1	54	METFORMIN HCL	1,560	390	$ 137.45
27483344445	1	54	CARISOPRODOL	1,200	330	$ 183.27
27483344445	6	54	ONDANSETRON HCL	226	57	$ 152.45
27483344445	6	54	TORSEMIDE	60	30	$ 16.02
Subtotal				**17,271**	**6,233**	**$ 16,831.87**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
44448546720	16	39	LANTUS	300	354	$ 7,314.89
44448546720	16	39	MECLIZINE HCL	10	5	$ 8.77
44448546720	16	39	ONETOUCH VERIO TEST STRIP	550	175	$ 770.99
44448546720	16	39	VOLTAREN	300	21	$ 170.20
44448546720	16	39	GLIMEPIRIDE	540	270	$ 136.73
44448546720	16	39	RAMIPRIL	300	300	$ 95.97
44448546720	16	39	JARDIANCE	240	240	$ 3,231.59
44448546720	16	39	LISINOPRIL	180	180	$ 64.39
44448546720	16	39	CEPHALEXIN	42	14	$ 23.93
44448546720	16	39	AMITIZA	90	90	$ 525.70
44448546720	16	39	SYNJARDY	360	180	$ 2,382.72
44448546720	16	50	HYDROCODONE/ACETAMINOPHEN	1,950	345	$ 489.38
44448546720	16	50	GABAPENTIN	90	90	$ 42.02
44448546720	16	50	ALPRAZOLAM	780	270	$ 149.97
44448546720	16	50	GLIMEPIRIDE	420	210	$ 141.23
44448546720	16	50	AMITIZA	240	240	$ 1,364.34
44448546720	16	50	OXYCODONE HCL	4,680	390	$ 1,764.26
44448546720	16	50	ONETOUCH VERIO TEST STRIP	700	210	$ 976.99
44448546720	16	50	LANTUS	60	90	$ 1,468.48
Subtotal				**11,832**	**3,674**	**$ 21,122.55**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
56292500001	2	12	ACETAMINOPHEN/CODEINE	2,880	288	$ 814.20
56292500001	2	12	AZITHROMYCIN	18	15	$ 39.15
56292500001	2	12	PROVENTIL HFA	80	198	$ 955.10
56292500001	2	12	PHENYTOIN SODIUM EXTENDED	1,350	255	$ 389.90
56292500001	2	12	RANITIDINE HCL	720	240	$ 173.35
56292500001	2	12	AMITRIPTYLINE HCL	930	330	$ 882.43
56292500001	2	12	CYCLOBENZAPRINE HCL	2,160	360	$ 172.13
56292500001	2	12	PHENOBARBITAL	1,080	360	$ 578.02
56292500001	2	12	LORAZEPAM	1,530	378	$ 168.47
56292500001	2	12	BUTALBITAL/ASPIRIN/CAFFEI	810	270	$ 1,302.29
56292500001	2	12	LANTUS	90	294	$ 2,233.30
56292500001	2	12	TRUEPLUS INSULIN SYRINGE/	200	66	$ 44.74
56292500001	2	12	SODIUM BICARBONATE	90	30	$ 11.02
56292500001	2	12	FREESTYLE LITE TEST STRIP	700	231	$ 1,070.93
56292500001	2	12	LYRICA	990	330	$ 5,756.23
56292500001	2	12	ACETAMINOPHEN/CODEINE #4	720	72	$ 208.88
56292500001	2	12	PROMETHAZINE HCL	3,300	295	$ 412.35
56292500001	2	12	HYDROCODONE/IBUPROFEN	1,980	315	$ 777.93
56292500001	20	32	FREESTYLE LANCETS	100	30	$ 10.02
56292500001	20	32	LANTUS	10	28	$ 249.49
56292500001	20	32	SODIUM BICARBONATE	9	3	$ 4.00
56292500001	20	32	PANTOPRAZOLE SODIUM	15	15	$ 11.68
56292500001	20	32	RELION SHORT PEN NEEDLES	50	30	$ 9.00
56292500001	20	32	FREESTYLE LITE TEST STRIP	100	30	$ 152.99
56292500001	20	32	HUMALOG KWIKPEN	15	30	$ 486.31
56292500001	20	32	FREESTYLE LITE BLOOD GLUC	1	30	$ 17.63
56292500001	20	32	RELION INSULIN SYRINGE/U-	100	30	$ 12.58
56292500001	2	43	HYDROCODONE/IBUPROFEN	360	60	$ 125.20
56292500001	2	43	ACETAMINOPHEN/CODEINE	360	36	$ 101.97
Subtotal				**20,748**	**4,649**	**$ 17,171.29**

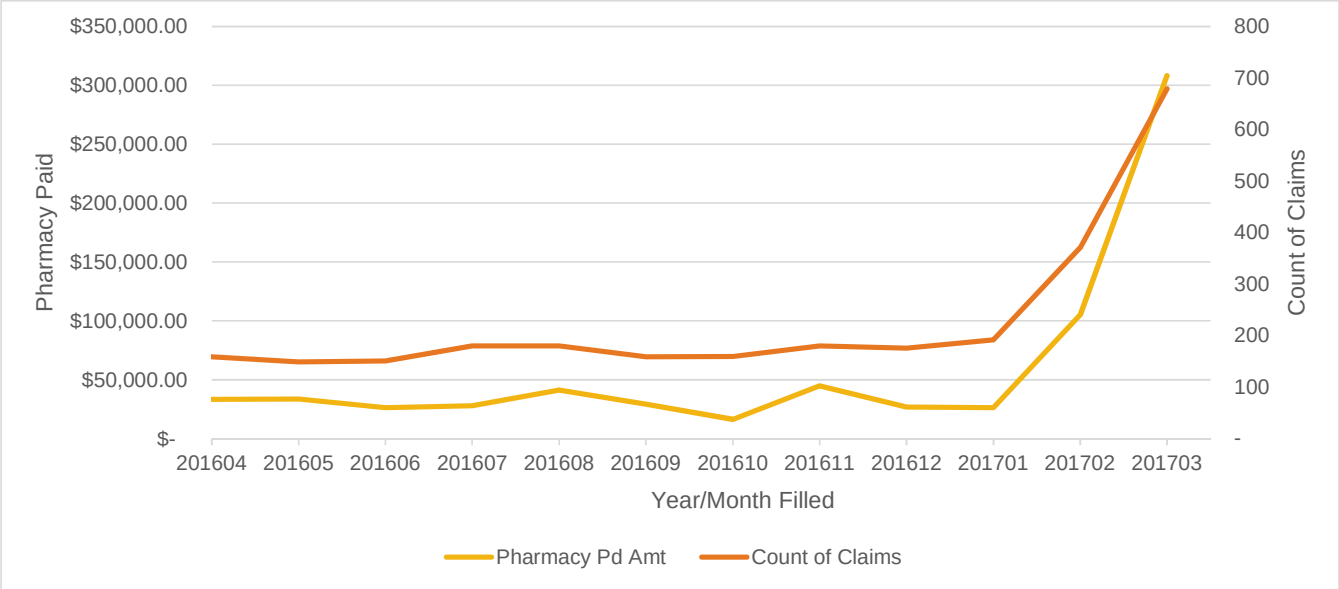
MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
66666846275	13	2	METHADONE HCL	270	30	$ 41.46
66666846275	19	2	ENALAPRIL MALEATE	300	150	$ 88.69
66666846275	19	2	METHADONE HCL	3,240	352	$ 544.27
66666846275	19	2	HYDROCODONE/ACETAMINOPHEN	3,540	394	$ 779.48
66666846275	19	2	ONDANSETRON ODT	36	12	$ 44.41
66666846275	19	2	CIPROFLOXACIN HCL	14	7	$ 12.19
66666846275	19	2	ALPRAZOLAM	1,080	360	$ 146.98
66666846275	19	12	FLUVIRIN 2016-2017	1	1	$ 23.47
66666846275	13	40	CYCLOBENZAPRINE HCL	15	5	$ 10.53
Subtotal				**8,496**	**1,311**	**$ 1,691.48**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
88889918278	15	1	CIPROFLOXACIN HCL	20	10	$ 12.80
88889918278	15	2	FLUCONAZOLE	7	7	$ 16.65
88889918278	15	2	NYSTATIN	30	7	$ 12.05
88889918278	15	2	DOXYCYCLINE HYCLATE	5	5	$ 13.66
88889918278	15	2	ALPRAZOLAM	1,020	330	$ 135.36
88889918278	15	2	TEMAZEPAM	330	330	$ 132.65
88889918278	15	2	DIAZEPAM	990	330	$ 132.00
88889918278	15	2	MORPHINE SULFATE	2,640	330	$ 1,001.52
88889918278	15	2	SULFAMETHOXAZOLE/TRIMETHO	14	7	$ 11.46
88889918278	15	2	MORPHINE SULFATE ER	990	330	$ 1,707.38
88889918278	15	2	SUMATRIPTAN SUCCINATE	18	39	$ 34.34
88889918278	15	3	POLYETHYLENE GLYCOL 3350	1,581	90	$ 68.95
88889918278	15	7	SULFAMETHOXAZOLE/TRIMETHO	40	20	$ 23.94
88889918278	4	10	CAPECITABINE	84	21	$ 1,428.68
88889918278	15	10	CEPHALEXIN	40	10	$ 13.80
88889918278	15	10	SULFAMETHOXAZOLE/TRIMETHO	20	10	$ 12.13
88889918278	15	10	METHADONE HCL	1,950	93	$ 976.32
88889918278	15	14	SULFAMETHOXAZOLE/TRIMETHO	14	7	$ 11.34
88889918278	15	20	METHADONE HCL	690	33	$ 500.53
88889918278	15	21	POLYETHYLENE GLYCOL 3350	527	30	$ 22.74
88889918278	15	25	CIPROFLOXACIN HCL	20	10	$ 13.20
88889918278	15	30	SULFAMETHOXAZOLE/TRIMETHO	28	14	$ 22.81
88889918278	15	30	FLUCONAZOLE	1	1	$ 11.50
88889918278	15	31	ONDANSETRON ODT	20	10	$ 28.15
88889918278	15	35	SULFAMETHOXAZOLE/TRIMETHO	28	14	$ 12.51
88889918278	15	38	SULFAMETHOXAZOLE/TRIMETHO	20	10	$ 11.99
88889918278	15	44	METHADONE HCL	2,010	96	$ 1,030.61
88889918278	15	46	METHADONE HCL	630	30	$ 42.31
88889918278	15	49	SULFAMETHOXAZOLE/TRIMETHO	10	5	$ 11.04
Subtotal				**13,777**	**2,229**	**$ 7,452.42**

MemberIDEncrypted	Phrm ID	Presc ID	ProductName	Qty	Days Supply	Pharmacy Pd
90209455556	22	24	METHADONE HCL	2,160	60	$ 287.19
90209455556	22	29	DIAZEPAM	120	30	$ 12.62
90209455556	22	53	PENICILLIN V POTASSIUM	120	60	$ 44.11
90209455556	22	53	METHADONE HCL	11,970	330	$ 1,522.06
90209455556	22	53	HYDROCODONE/ACETAMINOPHEN	60	10	$ 31.34
90209455556	22	53	PAROXETINE HCL	360	360	$ 154.55
90209455556	22	53	DIAZEPAM	1,320	330	$ 138.82
90209455556	22	53	GENERLAC	480	32	$ 16.03
Subtotal				**16,590**	**1,212**	**$ 2,206.72**

90 - Day Supply Utilization
Nevada Medicaid
4/1/2016 - 3/31/2017

YearMonthFilled	Member Count	Count of Claims	Days Supply	Total Qty	Disp Fee	Pharmacy Pd Amt
201604	159	159	16,315	13,059	$ 1,140.85	$ 33,566.57
201605	149	149	16,130	11,822	$ 1,186.34	$ 33,723.54
201606	151	151	16,684	12,084	$ 1,181.28	$ 26,314.79
201607	180	180	18,323	15,733	$ 1,307.74	$ 28,005.19
201608	180	180	18,779	15,042	$ 1,335.16	$ 41,493.70
201609	159	159	16,742	15,991	$ 1,209.14	$ 29,519.66
201610	160	160	16,137	13,323	$ 1,282.17	$ 16,464.21
201611	180	180	18,788	16,884	$ 1,297.74	$ 44,784.06
201612	176	176	17,477	15,664	$ 1,453.17	$ 26,994.17
201701	192	192	19,453	17,485	$ 1,281.01	$ 26,483.38
201702	371	371	38,454	33,761	$ 2,659.45	$ 105,183.24
201703	679	679	69,695	65,590	$ 5,151.70	$ 308,245.80



Top 10 Drug Group by Paid Amt

Q3 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	30,552	$ 8,866,116.41
85	HEMATOLOGICAL AGENTS - MISC.*	3,702	$ 8,454,118.82
12	ANTIVIRALS*	4,164	$ 7,812,360.33
27	ANTIDIABETICS*	28,313	$ 4,664,093.33
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4,271	$ 4,243,474.24
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	40,411	$ 4,218,066.23
72	ANTICONVULSANTS*	45,497	$ 3,680,634.15
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	3,996	$ 2,671,373.75
62	PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	4,990	$ 2,272,638.36
65	ANALGESICS - OPIOID*	62,601	$ 2,234,328.62

Q4 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	30,552	$ 8,866,116.41
85	HEMATOLOGICAL AGENTS - MISC.*	3,702	$ 8,454,118.82
12	ANTIVIRALS*	4,164	$ 7,812,360.33
27	ANTIDIABETICS*	28,313	$ 4,664,093.33
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4,271	$ 4,243,474.24
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	40,411	$ 4,218,066.23
72	ANTICONVULSANTS*	45,497	$ 3,680,634.15
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	3,996	$ 2,671,373.75
62	PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	4,990	$ 2,272,638.36
65	ANALGESICS - OPIOID*	62,601	$ 2,234,328.62

Q1 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
85	HEMATOLOGICAL AGENTS - MISC.*	3,662	$ 9,325,628.04
12	ANTIVIRALS*	5,203	$ 7,266,435.97
27	ANTIDIABETICS*	27,611	$ 6,425,317.42
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	32,411	$ 5,892,304.25
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	44,908	$ 4,796,359.79
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4,068	$ 3,991,362.58
72	ANTICONVULSANTS*	46,753	$ 3,945,512.52
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	4,017	$ 2,759,685.73
62	PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	5,400	$ 2,322,888.21
61	ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	10,959	$ 2,284,652.13

Top 10 Drug Group by Claim Count

Q3 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	62,601	$ 2,234,328.62
72	ANTICONVULSANTS*	45,497	$ 3,680,634.15
58	ANTIDEPRESSANTS*	45,076	$ 868,175.76
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	40,411	$ 4,218,066.23
36	ANTIHYPERTENSIVES*	36,018	$ 482,511.34
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	30,552	$ 8,866,116.41
27	ANTIDIABETICS*	28,313	$ 4,664,093.33
39	ANTIHYPERLIPIDEMICS*	27,580	$ 815,346.12
57	ANTIANXIETY AGENTS*	26,407	$ 295,554.55
49	ULCER DRUGS*	25,729	$ 1,248,026.99

Q4 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	56,599	$ 2,051,814.21
58	ANTIDEPRESSANTS*	43,569	$ 844,724.12
72	ANTICONVULSANTS*	43,293	$ 3,612,420.84
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	41,376	$ 4,323,625.98
36	ANTIHYPERTENSIVES*	33,634	$ 474,958.24
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	29,443	$ 8,542,669.89
27	ANTIDIABETICS*	25,956	$ 4,562,842.00
39	ANTIHYPERLIPIDEMICS*	25,544	$ 750,890.68
57	ANTIANXIETY AGENTS*	24,325	$ 283,154.70
66	ANALGESICS - ANTI-INFLAMMATORY*	24,105	$ 1,716,848.76

Q1 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	59,662	$ 2,086,447.21
72	ANTICONVULSANTS*	46,753	$ 3,945,512.52
58	ANTIDEPRESSANTS*	46,102	$ 901,813.95
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	44,908	$ 4,796,359.79
36	ANTIHYPERTENSIVES*	33,497	$ 535,039.24
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	32,411	$ 5,892,304.25
27	ANTIDIABETICS*	27,611	$ 6,425,317.42
39	ANTIHYPERLIPIDEMICS*	27,327	$ 773,511.80
57	ANTIANXIETY AGENTS*	26,161	$ 291,756.42
49	ULCER DRUGS*	25,806	$ 1,240,036.94

Top 10 Drug Classes by Paid Amt

Q3 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	88	$ 8,076,744.35
1235	HEPATITIS AGENTS**	308	$ 4,568,255.48
5925	QUINOLINONE DERIVATIVES**	4,406	$ 3,992,993.36
1210	ANTIRETROVIRALS**	2,328	$ 3,174,676.62
2710	INSULIN**	8,858	$ 3,144,114.67
4420	SYMPATHOMIMETICS**	26,952	$ 2,698,618.41
7260	ANTICONVULSANTS - MISC.**	33,362	$ 2,492,868.96
5907	BENZISOXAZOLES**	7,324	$ 2,134,646.60
6240	MULTIPLE SCLEROSIS AGENTS**	373	$ 1,799,241.23
5940	ANTIPSYCHOTICS - MISC.**	3,044	$ 1,419,696.63

Q4 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	94	$ 8,922,391.95
1235	HEPATITIS AGENTS**	297	$ 4,317,718.35
5925	QUINOLINONE DERIVATIVES**	4,496	$ 3,935,124.04
1210	ANTIRETROVIRALS**	2,219	$ 3,092,747.28
2710	INSULIN**	8,116	$ 3,045,841.66
4420	SYMPATHOMIMETICS**	28,338	$ 2,792,919.73
7260	ANTICONVULSANTS - MISC.**	31,667	$ 2,447,446.65
5907	BENZISOXAZOLES**	6,963	$ 2,020,701.71
6240	MULTIPLE SCLEROSIS AGENTS**	379	$ 1,591,092.89
5940	ANTIPSYCHOTICS - MISC.**	2,789	$ 1,383,181.37

Q1 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	118	$ 8,909,353.08
2710	INSULIN**	8,943	$ 4,283,103.71
1235	HEPATITIS AGENTS**	328	$ 3,929,771.33
4420	SYMPATHOMIMETICS**	30,551	$ 3,170,155.87
1210	ANTIRETROVIRALS**	2,535	$ 3,157,821.11
7260	ANTICONVULSANTS - MISC.**	34,315	$ 2,705,834.35
5907	BENZISOXAZOLES**	7,659	$ 2,163,906.94
6240	MULTIPLE SCLEROSIS AGENTS**	324	$ 1,751,131.75
5940	ANTIPSYCHOTICS - MISC.**	3,090	$ 1,472,868.59
2153	ANTINEOPLASTIC ENZYME INHIBITORS**	174	$ 1,366,624.72

Top 10 Drug Classes by Claim Count

Q3 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
6599	OPIOID COMBINATIONS**	35,062	$ 941,484.91
7260	ANTICONVULSANTS - MISC.**	33,362	$ 2,492,868.96
4420	SYMPATHOMIMETICS**	26,952	$ 2,698,618.41
6510	OPIOID AGONISTS**	26,555	$ 1,132,091.18
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSA	24,658	$ 267,791.59
3940	HMG COA REDUCTASE INHIBITORS**	22,704	$ 436,188.00
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSF	22,223	$ 275,751.75
5710	BENZODIAZEPINES**	19,312	$ 193,330.77
7510	CENTRAL MUSCLE RELAXANTS**	16,436	$ 311,663.31
3610	ACE INHIBITORS**	15,687	$ 148,005.42

Q4 2016

Class	Drug Class Name	Count of Claims	Pharmacy Paid
6599	OPIOID COMBINATIONS**	31,931	$ 863,099.94
7260	ANTICONVULSANTS - MISC.**	31,667	$ 2,447,446.65
4420	SYMPATHOMIMETICS**	28,338	$ 2,792,919.73
6510	OPIOID AGONISTS**	23,801	$ 1,016,722.41
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSA	23,636	$ 310,226.82
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSF	21,287	$ 270,181.48
3940	HMG COA REDUCTASE INHIBITORS**	21,156	$ 395,673.72
5710	BENZODIAZEPINES**	17,507	$ 182,854.92
7510	CENTRAL MUSCLE RELAXANTS**	15,661	$ 287,458.13
3610	ACE INHIBITORS**	14,335	$ 140,103.07

Q1 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
7260	ANTICONVULSANTS - MISC.**	34,315	$ 2,705,834.35
6599	OPIOID COMBINATIONS**	33,578	$ 810,834.57
4420	SYMPATHOMIMETICS**	30,551	$ 3,170,155.87
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSA	25,202	$ 321,555.13
6510	OPIOID AGONISTS**	25,168	$ 1,063,262.89
3940	HMG COA REDUCTASE INHIBITORS**	22,722	$ 428,842.94
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSF	22,212	$ 270,607.46
5710	BENZODIAZEPINES**	18,734	$ 189,624.66
7510	CENTRAL MUSCLE RELAXANTS**	16,795	$ 290,601.35
2210	GLUCOCORTICOSTEROIDS**	14,370	$ 180,288.84

Top 50 Drugs by Amount - Q3 2016

Drug Code	Drug Name	Claim Count		Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
5925001500	ARIPIPRAZOLE	4,240	$	3,829,892.30	16	15
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	13	$	3,138,689.01	137,656	20
1235990240	LEDIPASVIR-SOFOSBUVIR	158	$	2,799,494.79	12	12
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	6	$	2,520,061.02	210,000	30
5907005010	PALIPERIDONE PALMITATE	665	$	1,479,314.85	1	19
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	13	$	1,446,033.00	75,789	25
5940002310	LURASIDONE HCL	1,296	$	1,199,171.74	17	15
2710400300	INSULIN GLARGINE	3,451	$	1,143,189.92	11	24
9410003000	GLUCOSE BLOOD	7,102	$	939,242.88	73	22
1235308000	SOFOSBUVIR	39	$	915,208.32	12	12
4420101010	ALBUTEROL SULFATE	17,945	$	910,766.86	38	16
4420990270	FLUTICASONE-SALMETEROL	3,002	$	879,853.11	42	22
5915307010	QUETIAPINE FUMARATE	8,153	$	873,329.19	29	20
7260005700	PREGABALIN	2,789	$	868,815.25	48	20
4927002510	ESOMEPRAZOLE MAGNESIUM	3,942	$	861,984.55	21	21
3010002000	SOMATROPIN	217	$	754,623.04	2	11
6627001500	ADALIMUMAB	160	$	674,087.40	1	11
2710400500	INSULIN LISPRO	1,577	$	664,388.76	11	20
1210990429	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE	253	$	582,218.92	19	19
3030001000	CORTICOTROPIN	11	$	544,655.87	3	5
6240552500	DIMETHYL FUMARATE	87	$	540,600.22	15	7
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2,181	$	534,592.70	23	24
2710400200	INSULIN ASPART	1,321	$	529,981.68	11	21
8240157000	PEGFILGRASTIM	105	$	527,518.52	1	2
6629003000	ETANERCEPT	136	$	515,580.21	2	13
4530402000	DORNASE ALFA	158	$	510,810.10	53	18
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	390	$	503,832.40	20	20
6135303010	GUANFACINE HCL (ADHD)	1,796	$	490,174.46	20	18
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2,424	$	477,340.83	8	24
6599000220	OXYCODONE W/ ACETAMINOPHEN	10,855	$	474,787.07	57	15
2153253000	EVEROLIMUS	26	$	448,196.63	13	9
6510007510	OXYCODONE HCL	8,706	$	443,106.22	75	18
7260003600	LACOSAMIDE	882	$	428,883.48	52	14
6110002510	LISDEXAMFETAMINE DIMESYLATE	1,732	$	409,027.49	23	22
6140002010	METHYLPHENIDATE HCL	2,345	$	406,508.57	36	19
6599170210	HYDROCODONE-ACETAMINOPHEN	22,071	$	404,677.94	59	15
7210000700	CLOBAZAM	336	$	399,786.53	62	14
2710400600	INSULIN DETEMIR	1,297	$	397,732.41	11	22
3890004000	EPINEPHRINE	636	$	387,638.38	1	5
9085006000	LIDOCAINE	1,537	$	387,257.59	59	16
9310002500	DEFERASIROX	70	$	386,255.32	20	11
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	29	$	381,564.45	5,657	9
3090404500	NITISINONE	6	$	375,016.98	77	13
700007000	TOBRAMYCIN	116	$	364,743.49	107	11
6110990210	AMPHETAMINE-DEXTROAMPHETAMINE	2,801	$	361,665.71	29	20
6240306045	INTERFERON BETA-1A	71	$	356,733.76	1	10
1235302510	DACLATASVIR DIHYDROCHLORIDE	20	$	320,151.51	12	12
1910002010	IMMUNE GLOBULIN (HUMAN) IV	88	$	318,451.39	444	3
2135307000	TRASTUZUMAB	88	$	303,659.65	1	2
2133502000	BEVACIZUMAB	302	$	301,701.60	5	1

Top 50 Drugs by Amount - Q4 2016

Drug Code	Drug Name	Claim Count		Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	16.00	$	3,830,078.78	114,532	16
5925001500	ARIPIPRAZOLE	4,288.00	$	3,736,132.19	17	15
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	6.00	$	2,520,061.02	210,000	30
1235990240	LEDIPASVIR-SOFOSBUVIR	143.00	$	2,330,403.27	12	12
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	15.00	$	1,646,384.77	56,593	20
5907005010	PALIPERIDONE PALMITATE	657.00	$	1,432,521.34	1	21
5940002310	LURASIDONE HCL	1,092.00	$	1,160,264.16	17	15
2710400300	INSULIN GLARGINE	3,240.00	$	1,105,835.88	12	25
1950206000	PALIVIZUMAB	409.00	$	1,086,912.38	1	20
9410003000	GLUCOSE BLOOD	7,091.00	$	950,744.77	73	22
4420101010	ALBUTEROL SULFATE	19,301.00	$	950,467.96	39	15
4420990270	FLUTICASONE-SALMETEROL	2,950.00	$	882,791.36	42	22
7260005700	PREGABALIN	2,594.00	$	833,824.70	48	20
4927002510	ESOMEPRAZOLE MAGNESIUM	3,734.00	$	829,043.22	21	20
3010002000	SOMATROPIN	219.00	$	813,914.39	2	10
5915307010	QUETIAPINE FUMARATE	7,895.00	$	747,871.32	28	19
6627001500	ADALIMUMAB	175.00	$	737,241.66	1	11
1235308000	SOFOSBUVIR	29.00	$	710,313.33	9	9
1235990265	SOFOSBUVIR-VELPATASVIR	46.00	$	691,074.97	10	10
2710400500	INSULIN LISPRO	1,450.00	$	632,595.93	10	20
1210990429	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE	256.00	$	593,770.89	20	20
4530402000	DORNASE ALFA	169.00	$	552,055.44	53	17
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	1,994.00	$	525,987.92	22	24
6629003000	ETANERCEPT	127.00	$	510,570.23	2	14
2710400200	INSULIN ASPART	1,200.00	$	505,962.40	11	20
2153253000	EVEROLIMUS	29.00	$	502,226.40	17	12
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2,358.00	$	494,814.93	8	24
6135303010	GUANFACINE HCL (ADHD)	1,796.00	$	486,986.45	19	18
6240552500	DIMETHYL FUMARATE	73.00	$	461,737.41	16	8
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	347.00	$	458,269.72	20	20
1235302510	DACLATASVIR DIHYDROCHLORIDE	27.00	$	448,243.09	9	9
7210000700	CLOBAZAM	347.00	$	441,138.25	62	14
6599000220	OXYCODONE W/ ACETAMINOPHEN	9,986.00	$	438,852.33	58	15
6110002510	LISDEXAMFETAMINE DIMESYLATE	1,866.00	$	438,045.68	22	21
7260003600	LACOSAMIDE	800.00	$	430,259.25	61	15
6140002010	METHYLPHENIDATE HCL	2,347.00	$	405,406.70	35	19
8240157000	PEGFILGRASTIM	84.00	$	405,347.56	1	3
9310002500	DEFERASIROX	65.00	$	403,717.03	23	11
6510007510	OXYCODONE HCL	8,249.00	$	401,081.87	73	18
3090685000	IDURSULFASE	18.00	$	395,054.84	20	9
9340002010	NALOXONE HCL	169.00	$	379,844.11	0	7
7460003500	ETEPLIRSEN	4.00	$	377,640.68	14	3
0700007000	TOBRAMYCIN	118.00	$	377,466.68	111	11
2710400600	INSULIN DETEMIR	1,141.00	$	373,242.54	11	22
8580005000	ECULIZUMAB	18.00	$	372,012.00	97	1
6599170210	HYDROCODONE-ACETAMINOPHEN	20,021.00	$	367,433.47	61	16
9085006000	LIDOCAINE	1,582.00	$	353,261.05	53	13
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	21.00	$	344,384.57	6,092	11
6110990210	AMPHETAMINE-DEXTROAMPHETAMINE	2,806.00	$	340,917.45	28	20
1910002010	IMMUNE GLOBULIN (HUMAN) IV	78.00	$	331,920.18	506	3

Top 50 Drugs by Amount - Q1 2017

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	18	$ 3,839,329.14	84,192	12
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	26	$ 2,342,506.36	54,693	23
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	4	$ 1,747,240.68	70,000	10
1235990240	LEDIPASVIR-SOFOSBUVIR	110	$ 1,667,082.78	14	14
5907005010	PALIPERIDONE PALMITATE	870	$ 1,540,505.35	1	21
2710400300	INSULIN GLARGINE	3562	$ 1,500,640.34	14	30
1235990265	SOFOSBUVIR-VELPATASVIR	110	$ 1,369,292.39	10	10
7460003500	ETEPLIRSEN	15	$ 1,304,152.55	24	5
1950206000	PALIVIZUMAB	476	$ 1,279,326.33	1	23
5940002310	LURASIDONE HCL	1297	$ 1,254,908.36	19	16
4420101010	ALBUTEROL SULFATE	20177	$ 1,134,441.48	36	14
9410003000	GLUCOSE BLOOD	7239	$ 984,523.11	75	23
7260005700	PREGABALIN	2943	$ 940,770.95	49	21
4420990270	FLUTICASONE-SALMETEROL	3098	$ 940,038.25	42	23
6627001500	ADALIMUMAB	216	$ 901,309.53	1	10
2710400500	INSULIN LISPRO	1515	$ 885,555.96	13	25
4927002510	ESOMEPRAZOLE MAGNESIUM	3726	$ 855,958.62	22	21
5925001500	ARIPIPRAZOLE	4802	$ 807,374.79	16	15
3010002000	SOMATROPIN	196	$ 759,977.48	2	11
2710400200	INSULIN ASPART	1351	$ 724,327.84	14	26
5915307010	QUETIAPINE FUMARATE	8615	$ 721,499.51	30	20
1910002010	IMMUNE GLOBULIN (HUMAN) IV	114	$ 629,454.96	530	4
1210990429	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE	276	$ 590,289.02	20	20
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2313	$ 581,000.18	23	25
2710400600	INSULIN DETEMIR	1285	$ 549,479.14	13	25
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2721	$ 540,719.19	8	24
4530402000	DORNASE ALFA	160	$ 527,980.89	49	17
7260003600	LACOSAMIDE	992	$ 522,831.76	55	14
2153253000	EVEROLIMUS	28	$ 508,688.67	14	9
6135303010	GUANFACINE HCL (ADHD)	1861	$ 507,517.53	20	19
7470005000	NUSINERSEN	3	$ 500,030.51	1	3
9310002500	DEFERASIROX	68	$ 494,704.90	21	10
6110002510	LISDEXAMFETAMINE DIMESYLATE	1953	$ 491,320.59	22	22
6240552500	DIMETHYL FUMARATE	73	$ 483,939.47	14	7
7210000700	CLOBAZAM	390	$ 467,317.24	67	15
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	364	$ 450,240.89	21	20
8240157000	PEGFILGRASTIM	83	$ 447,135.96	0	4
6629003000	ETANERCEPT	113	$ 446,375.49	2	12
3090685000	IDURSULFASE	24	$ 432,964.43	14	6
6140002010	METHYLPHENIDATE HCL	2404	$ 427,317.93	34	19
6599000220	OXYCODONE W/ ACETAMINOPHEN	10650	$ 405,381.61	58	15
3090404500	NITISINONE	6	$ 397,514.34	51	13
6510007510	OXYCODONE HCL	8937	$ 393,651.50	72	18
9085006000	LIDOCAINE	1887	$ 386,563.39	65	15
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	23	$ 382,498.53	5,552	11
2755007010	SITAGLIPTIN PHOSPHATE	1190	$ 379,463.48	29	29
1235308000	SOFOSBUVIR	17	$ 368,836.29	8	8
3030001000	CORTICOTROPIN	6	$ 363,881.02	2	2
6599170210	HYDROCODONE-ACETAMINOPHEN	21026	$ 352,175.15	60	15
0700007000	TOBRAMYCIN	102	$ 347,845.19	119	13

Top 50 Drugs by Claim Count - Q3 2016

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	22071	$ 404,677.94	59	15
4420101010	ALBUTEROL SULFATE	17945	$ 910,766.86	38	16
3610003000	LISINOPRIL	14035	$ 109,463.82	29	26
7260003000	GABAPENTIN	13628	$ 200,210.61	69	22
6610002000	IBUPROFEN	11458	$ 106,920.49	44	13
3940001010	ATORVASTATIN CALCIUM	11136	$ 116,059.67	25	25
3400000310	AMLODIPINE BESYLATE	10870	$ 83,105.53	27	26
6599000220	OXYCODONE W/ ACETAMINOPHEN	10855	$ 474,787.07	57	15
5710001000	ALPRAZOLAM	10812	$ 111,011.95	50	21
2725005000	METFORMIN HCL	10388	$ 167,045.72	55	27
2810001010	LEVOTHYROXINE SODIUM	10388	$ 155,233.35	28	28
6510007510	OXYCODONE HCL	8706	$ 443,106.22	75	18
5812008010	TRAZODONE HCL	8182	$ 85,754.47	28	21
5915307010	QUETIAPINE FUMARATE	8153	$ 873,329.19	29	20
6510005510	MORPHINE SULFATE	7214	$ 200,630.22	24	10
9410003000	GLUCOSE BLOOD	7102	$ 939,242.88	73	22
4450505010	MONTELUKAST SODIUM	7060	$ 118,862.53	21	21
5025006505	ONDANSETRON HCL	7049	$ 35,408.12	4	2
5816007010	SERTRALINE HCL	6972	$ 75,363.93	28	23
3320003010	METOPROLOL TARTRATE	6913	$ 51,970.35	43	23
4220003230	FLUTICASONE PROPIONATE (NASAL)	6673	$ 78,794.42	12	23
6410001000	ASPIRIN	6360	$ 33,676.08	23	22
3940007500	SIMVASTATIN	6143	$ 48,302.55	28	28
4927007010	PANTOPRAZOLE SODIUM	5979	$ 60,757.81	19	18
5907007000	RISPERIDONE	5962	$ 100,813.82	35	20
6510009510	TRAMADOL HCL	5814	$ 56,996.48	57	16
7720203200	CHOLECALCIFEROL	5801	$ 41,555.10	24	22
4920002010	RANITIDINE HCL	5700	$ 71,645.03	45	22
3720003000	FUROSEMIDE	5638	$ 38,320.15	29	23
120001010	AMOXICILLIN	5531	$ 57,202.63	52	6
5816004000	FLUOXETINE HCL	5419	$ 93,989.71	29	22
7510005010	CYCLOBENZAPRINE HCL	5357	$ 59,732.07	43	19
4155003000	LORATADINE	5275	$ 55,475.89	31	21
7210001000	CLONAZEPAM	5190	$ 55,058.03	44	21
7975001000	SODIUM CHLORIDE	5020	$ 13,745.22	460	1
3615004020	LOSARTAN POTASSIUM	4970	$ 41,428.88	25	23
3620101010	CLONIDINE HCL	4904	$ 64,594.37	37	21
5816002010	CITALOPRAM HYDROBROMIDE	4875	$ 43,344.16	24	23
2210004500	PREDNISONE	4609	$ 40,034.49	18	9
5025006500	ONDANSETRON	4606	$ 52,421.36	6	3
7250001010	DIVALPROEX SODIUM	4560	$ 232,343.82	55	19
5710006000	LORAZEPAM	4497	$ 43,287.66	22	10
7720203000	ERGOCALCIFEROL	4487	$ 47,766.96	4	22
3330000700	CARVEDILOL	4403	$ 33,303.87	47	24
5925001500	ARIPIPRAZOLE	4240	$ 3,829,892.30	16	15
7510009010	TIZANIDINE HCL	4231	$ 115,116.00	53	21
6610005200	MELOXICAM	4220	$ 36,965.32	27	24
7260004000	LAMOTRIGINE	4200	$ 247,172.82	43	21
3760004000	HYDROCHLOROTHIAZIDE	4181	$ 29,687.05	29	28
4155002010	CETIRIZINE HCL	4170	$ 45,142.77	40	20

Top 50 Drugs by Claim Count - Q4 2016

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	20021	$ 367,433.47	61	16
4420101010	ALBUTEROL SULFATE	19301	$ 950,467.96	39	15
3610003000	LISINOPRIL	12793	$ 102,955.51	32	29
7260003000	GABAPENTIN	12769	$ 186,635.62	70	22
6610002000	IBUPROFEN	11339	$ 107,259.48	47	13
3940001010	ATORVASTATIN CALCIUM	10703	$ 112,201.25	26	26
3400000310	AMLODIPINE BESYLATE	10082	$ 78,325.14	27	26
6599000220	OXYCODONE W/ ACETAMINOPHEN	9986	$ 438,852.33	58	15
5710001000	ALPRAZOLAM	9796	$ 105,865.78	50	22
2810001010	LEVOTHYROXINE SODIUM	9724	$ 148,347.60	30	29
2725005000	METFORMIN HCL	9702	$ 231,185.78	56	28
6510007510	OXYCODONE HCL	8249	$ 401,081.87	73	18
5812008010	TRAZODONE HCL	8101	$ 88,664.55	29	21
5915307010	QUETIAPINE FUMARATE	7895	$ 747,871.32	28	19
9410003000	GLUCOSE BLOOD	7091	$ 950,744.77	73	22
4450505010	MONTELUKAST SODIUM	6778	$ 113,460.24	21	21
5816007010	SERTRALINE HCL	6740	$ 73,828.41	27	22
0120001010	AMOXICILLIN	6670	$ 70,952.42	58	6
4220003230	FLUTICASONE PROPIONATE (NASAL)	6539	$ 78,146.84	13	24
3320003010	METOPROLOL TARTRATE	6424	$ 50,657.51	45	24
6410001000	ASPIRIN	6240	$ 34,429.09	24	23
6510005510	MORPHINE SULFATE	6184	$ 178,619.54	29	12
5025006505	ONDANSETRON HCL	6083	$ 35,887.99	5	2
7720203200	CHOLECALCIFEROL	5842	$ 43,455.74	24	22
5907007000	RISPERIDONE	5660	$ 91,465.09	35	20
3940007500	SIMVASTATIN	5575	$ 43,960.27	29	29
4927007010	PANTOPRAZOLE SODIUM	5573	$ 55,318.11	21	20
4920002010	RANITIDINE HCL	5479	$ 69,692.48	44	22
0340001000	AZITHROMYCIN	5450	$ 75,873.83	7	4
6510009510	TRAMADOL HCL	5227	$ 49,991.91	58	16
5816004000	FLUOXETINE HCL	5222	$ 94,505.77	26	20
2210004500	PREDNISONE	5099	$ 44,127.46	16	9
7510005010	CYCLOBENZAPRINE HCL	5058	$ 53,623.28	37	16
4155003000	LORATADINE	4965	$ 53,111.15	32	21
7210001000	CLONAZEPAM	4943	$ 52,514.14	45	22
3620101010	CLONIDINE HCL	4883	$ 68,442.96	38	22
3720003000	FUROSEMIDE	4873	$ 36,222.10	30	24
5025006500	ONDANSETRON	4844	$ 57,500.27	6	3
3615004020	LOSARTAN POTASSIUM	4631	$ 39,176.46	28	26
5816002010	CITALOPRAM HYDROBROMIDE	4431	$ 40,609.31	25	24
7250001010	DIVALPROEX SODIUM	4427	$ 217,346.48	58	20
7720203000	ERGOCALCIFEROL	4317	$ 46,102.27	4	23
5925001500	ARIPIPRAZOLE	4288	$ 3,736,132.19	17	15
6610005200	MELOXICAM	4252	$ 36,331.68	26	23
7975001000	SODIUM CHLORIDE	4211	$ 10,448.88	484	1
7510009010	TIZANIDINE HCL	4204	$ 109,194.06	51	21
4155002010	CETIRIZINE HCL	4127	$ 45,664.10	42	20
7260004000	LAMOTRIGINE	4120	$ 246,319.29	43	21
3330000700	CARVEDILOL	4103	$ 33,323.89	49	25
5710006000	LORAZEPAM	3962	$ 39,018.92	23	10

Top 50 Drugs by Claim Count - Q1 2017

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	21026	$ 352,175.15	60	15
4420101010	ALBUTEROL SULFATE	20177	$ 1,134,441.48	36	14
7260003000	GABAPENTIN	13926	$ 194,129.29	71	23
3610003000	LISINOPRIL	12603	$ 100,453.99	40	36
6610002000	IBUPROFEN	12049	$ 110,434.50	47	13
3940001010	ATORVASTATIN CALCIUM	11798	$ 122,816.93	27	27
6599000220	OXYCODONE W/ ACETAMINOPHEN	10650	$ 405,381.61	58	15
5710001000	ALPRAZOLAM	10585	$ 109,483.61	50	22
2810001010	LEVOTHYROXINE SODIUM	10274	$ 151,489.65	29	30
3400000310	AMLODIPINE BESYLATE	10098	$ 73,020.04	36	35
2725005000	METFORMIN HCL	9709	$ 290,240.42	68	33
6510007510	OXYCODONE HCL	8937	$ 393,651.50	72	18
5915307010	QUETIAPINE FUMARATE	8615	$ 721,499.51	30	20
5812008010	TRAZODONE HCL	8561	$ 93,315.60	30	22
0120001010	AMOXICILLIN	7821	$ 83,475.39	63	6
4220003230	FLUTICASONE PROPIONATE (NASAL)	7490	$ 86,066.49	12	23
4450505010	MONTELUKAST SODIUM	7416	$ 119,008.11	22	22
9410003000	GLUCOSE BLOOD	7239	$ 984,523.11	75	23
5816007010	SERTRALINE HCL	7109	$ 76,036.66	27	22
6510005510	MORPHINE SULFATE	6640	$ 160,160.00	26	11
0340001000	AZITHROMYCIN	6555	$ 86,352.66	7	4
5025006505	ONDANSETRON HCL	6455	$ 37,693.16	5	2
6410001000	ASPIRIN	6434	$ 34,570.31	23	22
3320003010	METOPROLOL TARTRATE	6414	$ 52,266.28	59	32
7720203200	CHOLECALCIFEROL	6181	$ 46,380.73	24	22
4927007010	PANTOPRAZOLE SODIUM	6149	$ 57,699.94	21	21
5907007000	RISPERIDONE	5968	$ 101,042.46	37	21
2210004500	PREDNISONE	5749	$ 48,602.15	16	9
3940007500	SIMVASTATIN	5730	$ 42,726.75	31	31
4920002010	RANITIDINE HCL	5625	$ 70,155.71	46	23
5816004000	FLUOXETINE HCL	5563	$ 93,185.41	30	23
4155003000	LORATADINE	5408	$ 58,871.07	34	21
7510005010	CYCLOBENZAPRINE HCL	5388	$ 54,584.87	39	17
6510009510	TRAMADOL HCL	5315	$ 48,457.17	58	16
7210001000	CLONAZEPAM	5280	$ 52,585.02	44	21
5025006500	ONDANSETRON	5073	$ 55,526.12	7	3
7250001010	DIVALPROEX SODIUM	4875	$ 211,227.34	56	20
3720003000	FUROSEMIDE	4852	$ 35,588.32	38	30
3615004020	LOSARTAN POTASSIUM	4826	$ 39,490.01	37	35
5925001500	ARIPIPRAZOLE	4802	$ 807,374.79	16	15
6610005200	MELOXICAM	4669	$ 39,791.60	27	24
3620101010	CLONIDINE HCL	4634	$ 67,221.11	50	29
7510009010	TIZANIDINE HCL	4537	$ 103,551.25	51	21
7720203000	ERGOCALCIFEROL	4535	$ 47,908.25	4	25
7975001000	SODIUM CHLORIDE	4469	$ 11,103.14	454	1
5816002010	CITALOPRAM HYDROBROMIDE	4469	$ 39,656.51	26	25
4155002010	CETIRIZINE HCL	4459	$ 49,592.44	42	20
7260004000	LAMOTRIGINE	4356	$ 226,335.99	42	21
5710006000	LORAZEPAM	4213	$ 39,458.32	22	10
6020408010	ZOLPIDEM TARTRATE	4186	$ 38,016.79	24	24

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

Apr 18, 2017 12:57:43 PM

Client Totals:

Total Rxs	Plan Paid	Member Paid
767,409	$75,054,137	$0

DUR Information as a percent of total:

DUR Type	Total Rxs	Percent of Total Rxs - Paid	Cases	Rejected Rxs	Percent of Total Rxs - Rejects
Total Claims Paid	767,409	0.0%	0	0	0.0%
Cases / Rxs	375,004	48.9%	331,371	247,266	32.2%
TD - Therapeutic Duplication	106,746	13.9%	89,520	106,443	13.9%
LR - Underuse Precaution	69,228	9.0%	69,613	7,989	1.0%
ID - Ingredient Duplication	54,394	7.1%	19,998	54,689	7.1%
DD - Drug-Drug Interaction	51,423	6.7%	60,232	65,091	8.5%
LD - Low Dose Alert	37,037	4.8%	36,656	4,991	0.7%
MN - Insufficnt Duration Alert	25,259	3.3%	24,645	1,470	0.2%
HD - High Dose Alert	21,473	2.8%	21,224	4,158	0.5%
MX - Excessive Duration Alert	9,406	1.2%	9,442	2,434	0.3%
PA - Drug-Age Precaution	32	0.0%	35	1	0.0%
SX - Drug Gender Alert	6	0.0%	6	0	0.0%

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

DD

Curr Rank	Top Drug Drug Interaction	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	TRAZODONE HCL - QUETIAPINE	Message Only	1,059	268	$12,465.81	$11.77	$0.00	25.31	35.16
2	TRAZODONE - QUETIAPINE FUMARATE	Message Only	1,024	223	$15,542.86	$15.18	$0.00	25.64	40.86
3	TRAZODONE HCL - CITALOPRAM	Message Only	800	188	$6,206.86	$7.76	$0.00	22.81	29.66
4	TRAZODONE - CITALOPRAM HYDROBROMIDE	Message Only	789	152	$5,020.35	$6.36	$0.00	23.48	24.26
5	TRAZODONE - ONDANSETRON HCL	Message Only	709	36	$388.83	$0.55	$0.00	1.00	2.03
6	SPIRONOLACTONE - LISINOPRIL	Message Only	701	198	$7,269.75	$10.37	$0.00	34.60	37.20
7	SPIRONOLACT - LISINOPRIL	Message Only	693	179	$5,807.25	$8.38	$0.00	34.43	41.10
8	SIMVASTATIN - FENOFIBRATE	Message Only	550	161	$8,159.65	$14.84	$0.00	32.91	33.12
9	QUETIAPINE - CITALOPRAM HYDROBROMIDE	Message Only	543	163	$4,649.66	$8.56	$0.00	26.46	29.17
10	DIVALPROEX - CLONAZEPAM	Message Only	542	199	$4,404.76	$8.13	$0.00	22.37	45.65
All Others			52,822	63,324	$5,746,928.83	$108.80	$0.00	22.05	44.37
Summary			60,232	65,091	$5,816,844.61	$96.57	$0.00	22.38	42.85

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

HD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	628	32	$7,754.91	$12.35	$0.00	1.00	6.03
2	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	437	69	$13,135.80	$30.06	$0.00	15.03	116.17
3	DEXAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 2.60UN	Message Only	360	58	$5,778.93	$16.05	$0.00	1.00	17.79
4	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	316	20	$1,053.51	$3.33	$0.00	29.44	29.44
5	GRANISETRON HCL	GERIATRIC MAX DLY = .85UN	Message Only	291	4	$6,528.24	$22.43	$0.00	1.00	1.59
6	MIDAZOLAM HCL	GERIATRIC MAX DLY = 3.50UN	Message Only	278	18	$673.66	$2.42	$0.00	1.00	6.75
7	KENALOG-40	GERIATRIC MAX DLY = 2.00UN	Message Only	239	8	$7,403.83	$30.98	$0.00	1.00	5.55
8	CEFTRIAXONE SODIUM	GERIATRIC MAX DLY = 2.00UN	Message Only	230	9	$53,273.40	$231.62	$0.00	1.00	223.63
9	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	192	0	$817,922.72	$4,260.01	$0.00	20.93	3.11
10	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	182	119	$372,977.22	$2,049.33	$0.00	27.37	1.50
All Others				18,071	3,821	$5,645,659.56	$312.42	$0.00	16.43	121.03
HD				21,224	4,158	$6,932,161.78	$326.62	$0.00	15.26	108.99

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

ID

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	GABAPENTIN	GABAPENTIN CAP 300MG	Message Only	310	18	$4,259.96	$13.74	$0.00	34.02	101.55
2	PROAIR HFA	PROAIR HFA AER	Message Only	271	19	$17,935.46	$66.18	$0.00	24.25	9.69
3	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 5-325MG	Message Only	204	0	$42.89	$0.21	$0.00	1.00	1.60
4	TRAZODONE HCL	TRAZODONE TAB 100MG	Message Only	196	10	$2,304.23	$11.76	$0.00	29.27	41.39
5	METFORMIN HCL	METFORMIN TAB 500MG	Message Only	171	10	$1,587.37	$9.28	$0.00	40.42	79.79
6	CLONIDINE HCL	CLONIDINE TAB 0.1MG	Message Only	166	10	$1,733.09	$10.44	$0.00	31.13	51.93
7	AMLODIPINE BESYLATE	AMLODIPINE TAB 10MG	Message Only	159	9	$1,586.27	$9.98	$0.00	30.53	30.53
8	TRAZODONE HCL	TRAZODONE TAB 50MG	Message Only	157	7	$1,645.12	$10.48	$0.00	29.22	36.39
9	LISINOPRIL	LISINOPRIL TAB 20MG	Message Only	153	4	$1,453.50	$9.50	$0.00	45.33	51.21
10	METFORMIN HCL	METFORMIN TAB 1000MG	Message Only	152	10	$1,580.97	$10.40	$0.00	43.53	85.49
All Others				18,059	54,592	$2,764,729.07	$153.09	$0.00	27.24	83.72
ID				19,998	54,689	$2,798,857.93	$139.96	$0.00	27.50	80.41

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

LD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	2,956	65	$803.74	$0.27	$0.00	1.10	1.08
2	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	1,230	26	$603.05	$0.49	$0.00	1.33	1.24
3	HEPARIN SODIUM	GERIATRIC MIN DLY = 4.00UN	Message Only	781	12	$1,622.40	$2.08	$0.00	1.18	1.99
4	IPRATROPIUM BROMIDE/ ALBUT	GERIATRIC MIN DLY = 9.00UN	Message Only	624	13	$373.81	$0.60	$0.00	1.64	7.06
5	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	558	108	$4,885.02	$8.75	$0.00	36.15	35.85
6	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	533	70	$5,137.33	$9.64	$0.00	30.76	3.08
7	ALBUTEROL SULFATE	GERIATRIC MIN DLY = 9.00UN	Message Only	501	38	$474.45	$0.95	$0.00	2.78	13.26
8	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	479	81	$4,974.40	$10.38	$0.00	31.84	52.84
9	METFORMIN HCL	GERIATRIC MIN DLY = 1.70UN	Message Only	427	55	$1,138.96	$2.67	$0.00	33.33	33.23
10	GABAPENTIN	GERIATRIC MIN DLY = 3.00UN	Message Only	401	40	$699.49	$1.74	$0.00	20.21	30.92
All Others				28,166	4,483	$2,817,883.57	$100.05	$0.00	22.49	49.85
LD				36,656	4,991	$2,838,596.22	$77.44	$0.00	19.53	40.78

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

LR

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	100	8	$755.69	$7.56	$0.00	28.86	31.13
2	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	88	10	$773.37	$8.79	$0.00	29.41	31.92
3	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	80	5	$668.64	$8.36	$0.00	28.14	28.98
4	LEVOTHYROXINE SODIUM	7 DAYS LATE REFILLING	Message Only	79	4	$850.20	$10.76	$0.00	27.90	27.52
5	ATORVASTATIN CALCIUM	7 DAYS LATE REFILLING	Message Only	73	7	$830.16	$11.37	$0.00	29.05	29.47
5	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	73	8	$659.75	$9.04	$0.00	29.11	30.03
7	ATORVASTATIN CALCIUM	8 DAYS LATE REFILLING	Message Only	70	8	$787.87	$11.26	$0.00	29.67	29.46
8	MONTELUKAST SODIUM	7 DAYS LATE REFILLING	Message Only	68	1	$1,249.43	$18.37	$0.00	29.71	29.71
9	GABAPENTIN	8 DAYS LATE REFILLING	Message Only	66	6	$904.28	$13.70	$0.00	28.98	98.24
9	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	66	2	$1,015.62	$15.39	$0.00	29.26	93.30
All Others				68,850	7,930	$7,333,540.23	$106.51	$0.00	28.64	51.78
LR				69,613	7,989	$7,342,035.24	$105.47	$0.00	28.65	51.66

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

MN

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	1,640	189	$12,181.07	$7.43	$0.00	4.82	62.22
2	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	1,114	35	$252.24	$0.23	$0.00	1.09	3.27
3	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	912	25	$176.96	$0.19	$0.00	1.07	1.13
4	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	Message Only	737	24	$247.61	$0.34	$0.00	1.07	1.22
5	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	734	24	$226.53	$0.31	$0.00	1.10	1.84
6	AMLODIPINE BESYLATE	MIN. DAYS THERAPY = 7	Message Only	732	14	$151.35	$0.21	$0.00	1.06	1.25
7	CARVEDILOL	MIN. DAYS THERAPY = 7	Message Only	655	16	$113.52	$0.17	$0.00	1.13	1.88
8	LEVETIRACETAM	MIN. DAYS THERAPY = 14	Message Only	559	33	$3,490.65	$6.24	$0.00	3.11	30.29
9	FUROSEMIDE	MIN. DAYS THERAPY = 7	Message Only	526	17	$519.55	$0.99	$0.00	1.42	2.57
10	CLONIDINE HCL	MIN. DAYS THERAPY = 7	Message Only	507	20	$719.90	$1.42	$0.00	1.25	3.24
All Others				16,529	1,073	$1,354,989.62	$81.98	$0.00	2.04	14.95
MN				24,645	1,470	$1,373,069.00	$55.71	$0.00	2.03	15.34

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

MX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	2,737	1,760	$29,564.83	$10.80	$0.00	30.11	66.37
2	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	1,480	0	$15,638.93	$10.57	$0.00	30.05	68.23
3	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	544	127	$7,440.63	$13.68	$0.00	6.51	2.97
4	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	466	17	$312,167.84	$669.89	$0.00	11.60	2.45
5	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	237	54	$5,101.39	$21.52	$0.00	13.14	18.85
6	MAPAP	MAX DAYS THERAPY = 10	Message Only	219	13	$2,057.28	$9.39	$0.00	26.53	118.48
7	EPIPEN-JR 2-PAK	MAX DAYS THERAPY = 1	Message Only	212	9	$163,174.46	$769.69	$0.00	10.88	2.73
8	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	201	13	$7,098.86	$35.32	$0.00	27.49	106.66
9	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	157	15	$5,543.03	$35.31	$0.00	28.25	32.08
10	SENEXON-S	MAX DAYS THERAPY = 14	Message Only	145	11	$1,337.25	$9.22	$0.00	30.32	58.20
All Others				3,044	415	$909,314.66	$298.72	$0.00	24.61	70.06
MX				9,442	2,434	$1,458,439.16	$154.46	$0.00	25.03	59.79

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

PA

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	11	0	$120.67	$10.97	$0.00	6.00	68.55
2	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	9	1	$69.28	$7.70	$0.00	7.00	63.11
3	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	7	0	$52.63	$7.52	$0.00	6.71	137.14
4	PROMETHEGAN	AGE LESS THAN 4	Message Only	5	0	$216.11	$43.22	$0.00	1.40	4.00
5	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	2	0	$25.01	$12.50	$0.00	5.00	150.00
6	PROMETHAZINE/ PHENYLEPHRIN	AGE LESS THAN 4	Message Only	1	0	$33.33	$33.33	$0.00	34.00	85.00
PA				35	1	$517.03	$14.77	$0.00	6.49	76.77

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

SX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	BICALUTAMIDE	GENERAL CONTRAINDICATION	Message Only	6	0	$72.54	$12.09	$0.00	7.00	7.00
SX				6	0	$72.54	$12.09	$0.00	7.00	7.00

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

TD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx
1	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	2,282	0	$37,192.82	$16.30	$0.00	28.34
2	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,712	168	$4,503.99	$2.63	$0.00	1.00
3	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	1,630	0	$20,798.87	$12.76	$0.00	27.88
4	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,400	139	$5,923.32	$4.23	$0.00	1.00
5	GABAPENTIN	GABAPENTIN AND RELATED	Message Only	1,297	0	$21,970.48	$16.94	$0.00	32.53
6	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	1,039	0	$9,206.09	$8.86	$0.00	42.31
7	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,033	124	$19,908.97	$19.27	$0.00	18.98
8	LEVOTHYROXINE SODIUM	THYROID HORMONES	Message Only	956	0	$14,545.20	$15.21	$0.00	40.25
9	OXYCODONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	890	70	$27,787.44	$31.22	$0.00	23.02
10	KETOROLAC TROMETHAMINE	NON-STEROIDAL ANTI-INFLAMMATOR	Message Only	850	234	$3,785.83	$4.45	$0.00	1.00
All Others				76,431	105,708	$11,532,239.53	$150.88	$0.00	22.56
TD				89,520	106,443	$11,697,862.54	$130.67	$0.00	22.37

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RXT6050D - Summarized DUR Activity Report

Between 2016-07-01 and 2016-09-30

TD

Quantity Per Rx
41.48
1.62
47.28
2.45
100.46
46.15
71.35
39.35
102.68
2.21
63.39
60.38

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Start Date:	2016-07-01
End Date:	2016-09-30
Relative Description:	Select Date Range
Display Report Description:	No
Top Values to Display:	10

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

Apr 18, 2017 1:00:13 PM

Client Totals:

Total Rxs	Plan Paid	Member Paid
735,135	$75,586,654	$0

DUR Information as a percent of total:

DUR Type	Total Rxs	Percent of Total Rxs - Paid	Cases	Rejected Rxs	Percent of Total Rxs - Rejects
Total Claims Paid	735,135	0.0%	0	0	0.0%
Cases / Rxs	355,263	48.3%	307,190	240,497	32.7%
TD - Therapeutic Duplication	102,700	14.0%	83,887	104,733	14.2%
LR - Underuse Precaution	66,289	9.0%	66,544	7,852	1.1%
ID - Ingredient Duplication	54,619	7.4%	19,621	54,524	7.4%
DD - Drug-Drug Interaction	47,058	6.4%	53,213	61,192	8.3%
LD - Low Dose Alert	34,959	4.8%	34,780	4,775	0.6%
MN - Insufficnt Duration Alert	21,182	2.9%	20,731	1,280	0.2%
HD - High Dose Alert	19,468	2.6%	19,192	3,743	0.5%
MX - Excessive Duration Alert	8,930	1.2%	9,158	2,396	0.3%
PA - Drug-Age Precaution	50	0.0%	56	2	0.0%
SX - Drug Gender Alert	8	0.0%	8	0	0.0%

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

DD

Curr Rank	Top Drug Drug Interaction	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	TRAZODONE HCL - QUETIAPINE	Message Only	997	248	$11,369.75	$11.40	$0.00	26.67	36.37
2	TRAZODONE - QUETIAPINE FUMARATE	Message Only	944	233	$14,315.81	$15.17	$0.00	25.93	40.53
3	SPIRONOLACTONE - LISINOPRIL	Message Only	619	168	$6,701.43	$10.83	$0.00	35.01	38.75
4	SPIRONOLACT - LISINOPRIL	Message Only	568	140	$4,633.55	$8.16	$0.00	33.55	39.35
5	TRAZODONE HCL - CITALOPRAM	Message Only	534	180	$5,428.43	$10.17	$0.00	29.50	37.98
6	TRAZODONE - CITALOPRAM HYDROBROMIDE	Message Only	526	148	$4,588.39	$8.72	$0.00	28.93	29.49
7	DIVALPROEX - CLONAZEPAM	Message Only	462	186	$4,359.02	$9.44	$0.00	26.29	55.54
8	SIMVASTATIN - FENOFIBRATE	Message Only	452	129	$7,386.65	$16.34	$0.00	35.00	34.92
9	FENOFIBRATE - ATORVASTATIN CALCIUM	Message Only	439	120	$4,876.97	$11.11	$0.00	31.28	31.35
10	QUETIAPINE - ONDANSETRON HCL	Message Only	432	3	$180.49	$0.42	$0.00	1.00	1.69
10	TRAZODONE - ONDANSETRON HCL	Message Only	432	24	$182.52	$0.42	$0.00	1.00	2.05
All Others			46,808	59,613	$4,932,892.68	$105.39	$0.00	23.41	44.65
Summary			53,213	61,192	$4,996,915.69	$93.90	$0.00	23.70	43.29

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

HD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	521	41	$7,640.63	$14.67	$0.00	1.00	6.11
2	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	433	54	$12,277.73	$28.36	$0.00	14.57	111.47
3	GRANISETRON HCL	GERIATRIC MAX DLY = .85UN	Message Only	278	20	$3,368.99	$12.12	$0.00	1.00	1.00
4	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	276	20	$847.06	$3.07	$0.00	30.34	30.34
5	MIDAZOLAM HCL	GERIATRIC MAX DLY = 3.50UN	Message Only	259	7	$746.48	$2.88	$0.00	1.00	8.43
6	MIDAZOLAM HCL	GERIATRIC MAX DLY = .70UN	Message Only	244	6	$287.63	$1.18	$0.00	1.00	1.39
7	IBUPROFEN	ADULT MAX DLY = 4.00 UN	Message Only	190	30	$2,055.12	$10.82	$0.00	7.89	37.52
8	BETAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 1.50UN	Message Only	186	13	$4,901.49	$26.35	$0.00	1.00	5.26
9	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	182	115	$368,399.64	$2,024.17	$0.00	27.31	1.50
10	CEFTRIAXONE SODIUM	GERIATRIC MAX DLY = 4.00UN	Message Only	179	2	$6,574.05	$36.73	$0.00	1.00	51.31
All Others				16,444	3,435	$6,992,866.61	$425.25	$0.00	15.47	258.08
HD				19,192	3,743	$7,399,965.43	$385.58	$0.00	14.44	225.31

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

ID

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROAIR HFA	PROAIR HFA AER	Message Only	270	17	$18,440.80	$68.30	$0.00	24.14	9.76
2	GABAPENTIN	GABAPENTIN CAP 300MG	Message Only	254	7	$3,357.39	$13.22	$0.00	34.17	100.24
3	ONDANSETRON ODT	ONDANSETRON TAB 4MG ODT	Message Only	203	0	$85.17	$0.42	$0.00	1.00	1.07
4	CLONIDINE HCL	CLONIDINE TAB 0.1MG	Message Only	189	12	$2,007.15	$10.62	$0.00	30.28	52.55
5	TRAZODONE HCL	TRAZODONE TAB 100MG	Message Only	168	16	$2,037.58	$12.13	$0.00	29.47	43.48
6	TRAZODONE HCL	TRAZODONE TAB 50MG	Message Only	154	6	$1,612.18	$10.47	$0.00	28.79	37.11
7	AMLODIPINE BESYLATE	AMLODIPINE TAB 10MG	Message Only	150	7	$1,476.02	$9.84	$0.00	31.37	31.57
8	PANTOPRAZOLE SODIUM	PANTOPRAZOLE TAB 40MG	Message Only	147	9	$1,650.99	$11.23	$0.00	29.65	30.54
8	ONETOUCH ULTRA BLUE	ONETOUCH TES ULTRA BL	Message Only	147	0	$17,121.24	$116.47	$0.00	28.08	86.43
10	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 5-325MG	Message Only	146	0	$34.58	$0.24	$0.00	1.00	1.78
All Others				17,793	54,450	$2,833,999.47	$159.28	$0.00	27.44	93.95
ID				19,621	54,524	$2,881,822.57	$146.87	$0.00	27.12	88.94

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

LD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	2,445	57	$595.43	$0.24	$0.00	1.13	1.13
2	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	1,306	16	$596.42	$0.46	$0.00	1.22	1.12
3	IPRATROPIUM BROMIDE/ ALBUT	GERIATRIC MIN DLY = 9.00UN	Message Only	1,006	23	$480.42	$0.48	$0.00	1.59	6.74
4	ALBUTEROL SULFATE	GERIATRIC MIN DLY = 9.00UN	Message Only	637	22	$749.12	$1.18	$0.00	2.96	14.86
5	HEPARIN SODIUM	GERIATRIC MIN DLY = 4.00UN	Message Only	569	13	$1,358.21	$2.39	$0.00	1.16	1.87
6	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	534	63	$5,142.83	$9.63	$0.00	31.21	3.23
7	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	487	107	$4,334.04	$8.90	$0.00	36.00	35.17
8	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	442	87	$4,665.93	$10.56	$0.00	32.82	52.86
9	PROPRANOLOL HCL	ADULT MIN DLY = 3.00 UN	Message Only	371	68	$6,114.94	$16.48	$0.00	29.75	52.53
10	ZOFRAN ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	334	3	$6,896.20	$20.65	$0.00	1.00	1.00
All Others				26,649	4,316	$3,744,584.18	$140.51	$0.00	24.37	45.54
LD				34,780	4,775	$3,775,517.72	$108.55	$0.00	20.64	37.30

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

LR

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	91	13	$779.36	$8.56	$0.00	29.00	32.30
2	ATORVASTATIN CALCIUM	7 DAYS LATE REFILLING	Message Only	86	18	$978.15	$11.37	$0.00	30.00	30.00
3	METFORMIN HCL	7 DAYS LATE REFILLING	Message Only	82	5	$676.40	$8.25	$0.00	30.73	62.01
4	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	74	3	$1,254.11	$16.95	$0.00	29.58	99.53
5	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	73	9	$592.56	$8.12	$0.00	29.66	31.51
6	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	70	2	$590.80	$8.44	$0.00	30.20	30.73
6	ATORVASTATIN CALCIUM	8 DAYS LATE REFILLING	Message Only	70	7	$789.15	$11.27	$0.00	29.70	29.49
8	LEVOTHYROXINE SODIUM	8 DAYS LATE REFILLING	Message Only	66	5	$803.32	$12.17	$0.00	29.98	29.53
9	LISINOPRIL	9 DAYS LATE REFILLING	Message Only	65	5	$515.19	$7.93	$0.00	30.02	30.94
10	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	64	5	$501.37	$7.83	$0.00	28.73	29.44
All Others				65,803	7,780	$7,414,496.61	$112.68	$0.00	28.72	52.09
LR				66,544	7,852	$7,421,977.02	$111.53	$0.00	28.73	51.96

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

MN

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	1,880	201	$13,187.60	$7.01	$0.00	4.88	62.10
2	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	754	14	$161.86	$0.21	$0.00	1.05	1.12
3	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	730	19	$153.22	$0.21	$0.00	1.07	1.44
4	AMLODIPINE BESYLATE	MIN. DAYS THERAPY = 7	Message Only	563	8	$89.86	$0.16	$0.00	1.04	1.15
5	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	518	27	$149.56	$0.29	$0.00	1.09	1.62
6	CLONIDINE HCL	MIN. DAYS THERAPY = 7	Message Only	469	27	$656.49	$1.40	$0.00	1.31	3.41
7	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	Message Only	462	1	$261.84	$0.57	$0.00	1.13	1.29
8	QUETIAPINE FUMARATE	MIN. DAYS THERAPY = 7	Message Only	440	50	$339.15	$0.77	$0.00	1.12	2.43
9	LEVETIRACETAM	MIN. DAYS THERAPY = 14	Message Only	392	27	$2,898.08	$7.39	$0.00	3.41	33.39
10	CARVEDILOL	MIN. DAYS THERAPY = 7	Message Only	386	12	$44.28	$0.11	$0.00	1.02	1.93
All Others				14,137	894	$1,243,665.75	$87.97	$0.00	2.38	21.67
MN				20,731	1,280	$1,261,607.69	$60.86	$0.00	2.36	21.40

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

MX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	2,692	1,746	$28,601.84	$10.62	$0.00	30.19	66.31
2	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	1,585	1	$17,235.39	$10.87	$0.00	30.16	68.62
3	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	505	123	$6,561.90	$12.99	$0.00	6.41	3.00
4	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	297	54	$6,688.89	$22.52	$0.00	11.64	19.84
5	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	241	11	$156,702.17	$650.22	$0.00	11.26	2.42
6	MAPAP	MAX DAYS THERAPY = 10	Message Only	235	6	$2,170.12	$9.23	$0.00	25.26	120.57
7	SENEXON-S	MAX DAYS THERAPY = 14	Message Only	172	13	$1,622.71	$9.43	$0.00	31.40	59.16
8	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	163	9	$5,393.33	$33.09	$0.00	27.83	99.12
9	PHENAZOPYRIDINE HCL	MAX DAYS THERAPY = 2	Message Only	151	1	$6,202.94	$41.08	$0.00	5.61	15.01
10	EVZIO	MAX DAYS THERAPY = 1	Message Only	147	2	$470,871.75	$3,203.21	$0.00	22.31	0.78
All Others				2,970	430	$709,868.39	$239.01	$0.00	24.74	70.02
MX				9,158	2,396	$1,411,919.43	$154.17	$0.00	25.33	61.18

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

PA

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	16	0	$106.22	$6.64	$0.00	10.06	84.12
2	NITROFURANTOIN	AGE LESS THAN 4	Message Only	12	2	$2,637.69	$219.81	$0.00	16.50	162.50
3	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	10	0	$186.74	$18.67	$0.00	9.20	91.80
4	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	8	0	$88.65	$11.08	$0.00	9.75	97.00
5	NITROFURANTOIN MACROCRYST	AGE LESS THAN 4	Message Only	3	0	$68.05	$22.68	$0.00	30.00	20.00
5	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	3	0	$15.98	$5.33	$0.00	4.33	73.33
7	PROMETHAZINE/ CODEINE	AGE LESS THAN 4	Message Only	2	0	$20.80	$10.40	$0.00	9.50	180.00
8	INFANRIX	AGE GREATER THAN 64	Message Only	1	0	$22.40	$22.40	$0.00	1.00	0.50
8	NITROFURANTOIN MONOHYDRAT	AGE LESS THAN 4	Message Only	1	0	$20.56	$20.56	$0.00	5.00	10.00
PA				56	2	$3,167.09	$56.56	$0.00	11.73	100.72

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

SX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	BICALUTAMIDE	GENERAL CONTRAINDICATION	Message Only	8	0	$102.45	$12.81	$0.00	9.62	9.62
SX				8	0	$102.45	$12.81	$0.00	9.62	9.62

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

TD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx
1	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	2,268	0	$40,462.54	$17.84	$0.00	28.53
2	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	1,537	0	$19,976.33	$13.00	$0.00	28.43
3	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,420	140	$3,968.55	$2.79	$0.00	1.00
4	GABAPENTIN	GABAPENTIN AND RELATED	Message Only	1,147	0	$19,514.19	$17.01	$0.00	32.60
5	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	995	73	$4,299.59	$4.32	$0.00	1.00
6	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	965	0	$8,713.92	$9.03	$0.00	41.02
7	LEVOTHYROXINE SODIUM	THYROID HORMONES	Message Only	853	0	$13,846.55	$16.23	$0.00	41.31
8	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	829	114	$16,086.68	$19.40	$0.00	19.38
9	OXYCODONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	801	68	$24,681.28	$30.81	$0.00	25.04
10	ABILIFY	ORAL ANTIPSYCHOTICS	Message Only	786	0	$833,973.02	$1,061.03	$0.00	28.40
All Others				72,286	104,338	$10,925,863.58	$151.15	$0.00	22.94
TD				83,887	104,733	$11,911,386.23	$141.99	$0.00	23.12

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RXT6050D - Summarized DUR Activity Report

Between 2016-10-01 and 2016-12-31

TD

Quantity Per Rx
41.63
48.68
1.71
102.75
2.84
44.96
40.83
77.69
107.91
32.93
64.68
62.26

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Start Date:	2016-10-01
End Date:	2016-12-31
Relative Description:	Select Date Range
Display Report Description:	No
Top Values to Display:	10

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

Apr 18, 2017 12:47:21 PM

Client Totals:

Total Rxs	Plan Paid	Member Paid
769,702	$78,090,741	$0

DUR Information as a percent of total:

DUR Type	Total Rxs	Percent of Total Rxs - Paid	Cases	Rejected Rxs	Percent of Total Rxs - Rejects
Total Claims Paid	769,702	0.0%	0	0	0.0%
Cases / Rxs	367,423	47.7%	323,381	254,287	33.0%
TD - Therapeutic Duplication	107,656	14.0%	90,863	109,640	14.2%
LR - Underuse Precaution	64,369	8.4%	64,769	8,063	1.0%
ID - Ingredient Duplication	55,795	7.2%	21,111	55,727	7.2%
DD - Drug-Drug Interaction	51,923	6.7%	59,733	67,948	8.8%
LD - Low Dose Alert	35,131	4.6%	34,893	4,874	0.6%
MN - Insufficnt Duration Alert	22,759	3.0%	22,388	1,316	0.2%
HD - High Dose Alert	20,176	2.6%	19,883	4,041	0.5%
MX - Excessive Duration Alert	9,550	1.2%	9,669	2,674	0.3%
PA - Drug-Age Precaution	58	0.0%	66	3	0.0%
SX - Drug Gender Alert	6	0.0%	6	1	0.0%

* More than one DUR message per paid, rejected or reversed claim(Cases > Rxs)
* Same claims could have multiple DUR messages. And there could multiple of the same DUR message on a claim
* This report does not include reversals.

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

DD

Curr Rank	Top Drug Drug Interaction	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	TRAZODONE HCL - QUETIAPINE	Message Only	1,092	301	$13,009.86	$11.91	$0.00	28.15	38.76
2	TRAZODONE - QUETIAPINE FUMARATE	Message Only	1,044	267	$16,036.62	$15.36	$0.00	28.35	44.80
3	SPIRONOLACTONE - LISINOPRIL	Message Only	648	155	$6,959.49	$10.74	$0.00	43.02	46.98
4	TRAZODONE - CITALOPRAM HYDROBROMIDE	Message Only	622	181	$5,341.86	$8.59	$0.00	30.57	31.72
5	TRAZODONE HCL - CITALOPRAM	Message Only	612	203	$6,682.12	$10.92	$0.00	31.08	41.68
6	SPIRONOLACT - LISINOPRIL	Message Only	611	146	$4,516.55	$7.39	$0.00	40.91	47.89
7	DIVALPROEX - CLONAZEPAM	Message Only	605	260	$4,979.97	$8.23	$0.00	24.24	49.45
8	TRAZODONE - ONDANSETRON HCL	Message Only	548	20	$303.07	$0.55	$0.00	1.11	2.29
9	QUETIAPINE - CITALOPRAM HYDROBROMIDE	Message Only	516	156	$4,892.47	$9.48	$0.00	30.09	32.38
10	SIMVASTATIN - FENOFIBRATE	Message Only	515	152	$6,870.56	$13.34	$0.00	35.81	36.00
All Others			52,920	66,107	$6,030,125.51	$113.95	$0.00	25.13	45.69
Summary			59,733	67,948	$6,099,718.08	$102.12	$0.00	25.62	44.84

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

HD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	478	40	$1,086.50	$2.27	$0.00	29.63	29.63
2	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	451	14	$6,505.72	$14.43	$0.00	1.00	7.60
3	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	400	64	$10,833.97	$27.08	$0.00	14.90	115.22
4	GRANISETRON HCL	GERIATRIC MAX DLY = .85UN	Message Only	288	8	$4,416.62	$15.34	$0.00	1.00	1.16
5	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	226	0	$561,235.30	$2,483.34	$0.00	23.92	1.85
5	MIDAZOLAM HCL	GERIATRIC MAX DLY = 3.50UN	Message Only	226	5	$692.64	$3.06	$0.00	1.00	9.15
7	MIDAZOLAM HCL	GERIATRIC MAX DLY = .70UN	Message Only	219	3	$268.94	$1.23	$0.00	1.00	1.42
8	IBUPROFEN	ADULT MAX DLY = 4.00 UN	Message Only	216	13	$2,273.41	$10.53	$0.00	7.67	34.57
9	BETAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 1.50UN	Message Only	202	2	$5,033.42	$24.92	$0.00	1.00	5.03
10	DEXAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 4.00UN	Message Only	199	8	$3,558.34	$17.88	$0.00	1.00	36.81
All Others				16,978	3,884	$9,186,884.10	$541.11	$0.00	16.63	145.47
HD				19,883	4,041	$9,782,788.96	$492.02	$0.00	15.65	128.38

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

ID

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROVENTIL HFA	PROVENTIL AER HFA	Message Only	346	20	$31,780.04	$91.85	$0.00	25.68	7.82
2	GABAPENTIN	GABAPENTIN CAP 300MG	Message Only	291	17	$4,081.99	$14.03	$0.00	37.98	118.51
3	TRAZODONE HCL	TRAZODONE TAB 100MG	Message Only	195	7	$2,197.53	$11.27	$0.00	31.67	43.48
4	HYDROCODONE/ ACETAMINOPHEN	HYDROCO/APAP TAB 5-325MG	Message Only	180	0	$46.65	$0.26	$0.00	1.00	2.00
5	AMLODIPINE BESYLATE	AMLODIPINE TAB 10MG	Message Only	176	12	$1,803.88	$10.25	$0.00	50.64	51.59
6	ONDANSETRON ODT	ONDANSETRON TAB 4MG ODT	Message Only	168	0	$61.57	$0.37	$0.00	1.00	1.01
7	SERTRALINE HCL	SERTRALINE TAB 100MG	Message Only	163	4	$2,048.41	$12.57	$0.00	33.42	47.62
8	FLUTICASONE PROPIONATE	FLUTICASONE SPR 50MCG	Message Only	157	12	$2,043.45	$13.02	$0.00	33.50	16.61
9	TRAZODONE HCL	TRAZODONE TAB 50MG	Message Only	156	9	$1,683.18	$10.79	$0.00	33.15	42.60
10	CLONIDINE HCL	CLONIDINE TAB 0.1MG	Message Only	152	13	$1,784.89	$11.74	$0.00	46.82	84.66
10	PREDNISONE	PREDNISONE TAB 20MG	Message Only	152	0	$52.73	$0.35	$0.00	1.00	2.49
All Others				18,975	55,633	$2,983,942.04	$157.26	$0.00	33.23	91.23
ID				21,111	55,727	$3,031,526.36	$143.60	$0.00	32.64	86.05

CONFIDENTIAL

RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

LD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	1,343	26	$602.77	$0.45	$0.00	1.39	1.32
2	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	1,222	73	$322.07	$0.26	$0.00	1.82	1.89
3	IPRATROPIUM BROMIDE/ ALBUT	GERIATRIC MIN DLY = 9.00UN	Message Only	1,042	17	$624.67	$0.60	$0.00	1.68	7.34
4	HEPARIN SODIUM	GERIATRIC MIN DLY = 4.00UN	Message Only	728	4	$2,206.55	$3.03	$0.00	1.36	2.47
5	ALBUTEROL SULFATE	GERIATRIC MIN DLY = 9.00UN	Message Only	705	27	$908.89	$1.29	$0.00	3.07	14.89
6	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	547	99	$4,811.65	$8.80	$0.00	50.44	49.70
7	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	527	54	$5,296.75	$10.05	$0.00	35.10	3.72
8	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	467	76	$4,616.89	$9.89	$0.00	33.30	54.74
9	PROPRANOLOL HCL	ADULT MIN DLY = 3.00 UN	Message Only	372	63	$6,567.33	$17.65	$0.00	38.73	64.34
10	ALBUTEROL SULFATE	PEDIATRIC MIN DLY = 9.00UN	Message Only	369	16	$5,857.51	$15.87	$0.00	24.66	121.50
All Others				27,571	4,419	$4,046,737.32	$146.78	$0.00	26.45	45.32
LD				34,893	4,874	$4,078,552.40	$116.89	$0.00	23.60	40.03

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

LR

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ATORVASTATIN CALCIUM	8 DAYS LATE REFILLING	Message Only	85	9	$935.42	$11.00	$0.00	30.42	30.60
2	LISINOPRIL	7 DAYS LATE REFILLING	Message Only	83	7	$709.45	$8.55	$0.00	41.59	44.69
3	ATORVASTATIN CALCIUM	7 DAYS LATE REFILLING	Message Only	82	10	$842.71	$10.28	$0.00	29.50	29.50
4	LEVOTHYROXINE SODIUM	7 DAYS LATE REFILLING	Message Only	73	4	$859.20	$11.77	$0.00	30.40	30.05
4	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	73	5	$886.59	$12.15	$0.00	28.97	99.97
6	AMLODIPINE BESYLATE	7 DAYS LATE REFILLING	Message Only	68	7	$507.25	$7.46	$0.00	41.13	44.66
7	PROVENTIL HFA	11 DAYS LATE REFILLING	Message Only	61	3	$5,167.66	$84.72	$0.00	19.21	6.92
7	GABAPENTIN	8 DAYS LATE REFILLING	Message Only	61	7	$822.04	$13.48	$0.00	29.16	92.10
9	LISINOPRIL	8 DAYS LATE REFILLING	Message Only	60	7	$509.28	$8.49	$0.00	44.00	49.50
10	PROVENTIL HFA	12 DAYS LATE REFILLING	Message Only	57	6	$4,775.29	$83.78	$0.00	19.63	6.94
10	AMLODIPINE BESYLATE	9 DAYS LATE REFILLING	Message Only	57	0	$440.86	$7.73	$0.00	41.30	44.70
10	AMLODIPINE BESYLATE	8 DAYS LATE REFILLING	Message Only	57	5	$485.92	$8.52	$0.00	40.25	40.25
10	LEVOTHYROXINE SODIUM	8 DAYS LATE REFILLING	Message Only	57	4	$811.47	$14.24	$0.00	31.00	30.12
All Others				63,895	7,989	$7,595,022.23	$118.87	$0.00	32.18	58.81
LR				64,769	8,063	$7,612,775.37	$117.54	$0.00	32.19	58.59

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

MN

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	2,065	204	$15,062.53	$7.29	$0.00	4.71	61.94
2	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	844	11	$70.61	$0.08	$0.00	1.03	1.24
3	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	768	8	$111.15	$0.14	$0.00	1.02	1.07
4	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	622	20	$132.34	$0.21	$0.00	1.06	1.40
5	AMLODIPINE BESYLATE	MIN. DAYS THERAPY = 7	Message Only	500	2	$79.50	$0.16	$0.00	1.05	1.19
6	LEVETIRACETAM	MIN. DAYS THERAPY = 14	Message Only	486	30	$2,955.71	$6.08	$0.00	2.61	31.60
7	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	Message Only	442	11	$172.71	$0.39	$0.00	1.08	1.19
8	QUETIAPINE FUMARATE	MIN. DAYS THERAPY = 7	Message Only	414	34	$422.46	$1.02	$0.00	1.24	3.28
9	CARVEDILOL	MIN. DAYS THERAPY = 7	Message Only	403	7	$99.24	$0.25	$0.00	1.04	1.53
10	KLOR-CON M20	MIN. DAYS THERAPY = 7	Message Only	394	3	$181.43	$0.46	$0.00	1.00	1.90
All Others				15,450	986	$1,256,149.08	$81.30	$0.00	2.27	20.00
MN				22,388	1,316	$1,275,436.76	$56.97	$0.00	2.26	20.50

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

MX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	2,796	1,889	$28,144.65	$10.07	$0.00	30.81	66.08
2	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	1,634	0	$17,086.26	$10.46	$0.00	30.98	71.12
3	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	527	178	$6,516.00	$12.36	$0.00	6.69	2.84
4	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	313	68	$6,471.38	$20.68	$0.00	12.22	19.33
5	MAPAP	MAX DAYS THERAPY = 10	Message Only	274	17	$2,504.74	$9.14	$0.00	26.06	114.49
6	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	233	20	$7,227.86	$31.02	$0.00	28.63	110.45
7	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	231	13	$145,369.87	$629.31	$0.00	11.22	2.43
8	CEFDINIR	MAX DAYS THERAPY = 10	Message Only	178	15	$6,857.96	$38.53	$0.00	16.66	87.08
9	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	177	7	$6,292.04	$35.55	$0.00	31.08	33.60
10	SENEXON-S	MAX DAYS THERAPY = 14	Message Only	175	25	$1,679.81	$9.60	$0.00	31.58	57.60
All Others				3,131	442	$992,229.98	$316.91	$0.00	25.34	60.91
MX				9,669	2,674	$1,220,380.55	$126.22	$0.00	26.25	60.86

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

PA

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	19	2	$150.40	$7.92	$0.00	9.00	70.53
2	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	11	0	$53.63	$4.88	$0.00	6.91	99.36
3	NITROFURANTOIN	AGE LESS THAN 4	Message Only	10	0	$867.13	$86.71	$0.00	27.10	155.00
4	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	8	0	$67.13	$8.39	$0.00	10.50	111.62
5	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	7	1	$77.93	$11.13	$0.00	9.29	86.43
6	NITROFURANTOIN MACROCRYST	AGE LESS THAN 4	Message Only	4	0	$381.55	$95.39	$0.00	25.00	21.25
7	PHENYLEPHRINE HCL	AGE LESS THAN 4	Message Only	3	0	$241.63	$80.54	$0.00	49.67	11.67
8	INFANRIX	AGE GREATER THAN 64	Message Only	2	0	$44.80	$22.40	$0.00	1.00	0.50
9	PROMETHAZINE/ CODEINE	AGE LESS THAN 4	Message Only	1	0	$8.95	$8.95	$0.00	8.00	120.00
9	PROMETHAZINE VC PLAIN	AGE LESS THAN 4	Message Only	1	0	$15.70	$15.70	$0.00	3.00	50.00
PA				66	3	$1,908.85	$28.92	$0.00	14.08	87.45

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

SX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	BICALUTAMIDE	GENERAL CONTRAINDICATION	Message Only	6	1	$115.74	$19.29	$0.00	12.67	33.33
SX				6	1	$115.74	$19.29	$0.00	12.67	33.33

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

TD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx
1	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	2,551	0	$39,253.86	$15.39	$0.00	29.34
2	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	1,605	0	$20,786.34	$12.95	$0.00	28.86
3	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,524	92	$4,107.74	$2.70	$0.00	1.00
4	GABAPENTIN	GABAPENTIN AND RELATED	Message Only	1,237	0	$20,174.02	$16.31	$0.00	34.38
5	ARIPIPRAZOLE	ORAL ANTIPSYCHOTICS	Message Only	1,086	0	$85,522.23	$78.75	$0.00	29.42
6	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	967	0	$9,076.75	$9.39	$0.00	53.66
7	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	930	132	$4,696.61	$5.05	$0.00	1.00
8	OLANZAPINE	ORAL ANTIPSYCHOTICS	Message Only	905	0	$14,995.26	$16.57	$0.00	29.00
9	LEVOTHYROXINE SODIUM	THYROID HORMONES	Message Only	901	0	$14,245.09	$15.81	$0.00	42.83
10	HYDROCODONE/ ACETAMINOPHEN	SHORT ACTING NARCOTIC ANALGESI	Message Only	845	107	$15,220.05	$18.01	$0.00	19.24
All Others				78,312	109,309	$12,753,581.20	$162.86	$0.00	25.59
TD				90,863	109,640	$12,981,659.15	$142.87	$0.00	25.70

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RXT6050D - Summarized DUR Activity Report

Between 2017-01-01 and 2017-03-31

TD

Quantity Per Rx
42.81
48.80
1.58
110.92
35.26
58.59
2.81
36.46
41.28
76.65
70.23
66.69

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Start Date:	2017-01-01
End Date:	2017-03-31
Relative Description:	Previous Quarter
Display Report Description:	No
Top Values to Display:	10