BRIAN SANDOVAL
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NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

AGENDA

Date of Posting:	**October 5, 2017**
Date of Meeting:	**Thursday, October 19, 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:	**Hyatt Place Reno-Tahoe Airport** **1790 E. Plumb Lane** **Reno, Nevada 89502** **Phone: (775) 826-2500**
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e9c44e8a68230d7778589b7e53dcd11d3 **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:	**315 214 493** **Click "Join Now."**

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For Audio Only:
Phone: (763) 957-6300
Event: 315 214 493

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 August 24, 2017.

b. Status Update by the DHCFP.

4. Clinical Presentations

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

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

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

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 Valbenazine (Ingrezza®).

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

iv. Proposed adoption of updated prior authorization criteria.

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

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

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

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

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

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

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

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

5. Public Comment on any DUR Board Requested Report

6. DUR Board Requested Reports

a. Anticonvulsant 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. 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.

c. Opioid Utilization – Top prescriber and member.

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

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.

7. Public Comment on any Standard DUR Report

8. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q4 2016, Q1 2017 and Q2 2017 (by Payment and by Claims).
ii. Top 50 Drugs of Q4 2016, Q1 2017 and Q2 2017 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q4 2016, Q1 2017 and Q2 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.

10. Adjournment

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

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

Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

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

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

Note: We are pleased to make accommodations for members of the public who have disabilities and wish to attend the meeting. If special arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at cmclach@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Colleen McLachlan at (775) 684-3722.

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MARTA JENSEN
Acting Administrator

DRUG USE REVIEW BOARD

Meeting Minutes

Date of Meeting: **Thursday, August 24, 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: **Holiday Inn Reno-Sparks**
55 East Nugget Ave
Sparks, NV 89431
Phone: (775) 358-6900

Event Number: **311 118 149**

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Attendees

Board Members (Present)
James Marx, MD
Chris Shea, Pharm.D.
David England, Pharm.D.
Michael Owens, MD
Jennifer Wheeler, Pharm.D.
Marta Bunuel, MD

Board Members (Absent)
Paul Oesterman, Pharm.D.

Reno

DHCFP:
Shannon Sprout, Deputy Administrator
Darrell Faircloth, Deputy Attorney General
Holly Long, Social Services Program Sp
Duane Young, Chief, DHCFP

HPES:
Beth Slamowitz, Pharm.D.

OptumRx:
Carl Jeffery, Pharm.D.

Public:
Tom Beranell, Silver Summit
Paul Benham, Avexis
Lisa Wilson, Biogen
Kaysen Bacit, Biogen
Cheryl Donahue, Sarepta
Lisa Borland, Sarepta
Coleen Lawrence, Moxy Health
Keri Smith, ViiV
Lovel Robinson, Abbvie
Nindhana Paranthaman, BMS
Gary Okano, BMS
Jane Stephen, Allergan
Slater Sparks, Insys
Ann Nelson, Vertex

Teleconference
Laura Hill, Abbvie
Ryan Bitton, UHC
Chris Anstead
Elaine DeFelice, UCB
Jonathan McKinnon, MD

1. Call to Order and Roll Call

Chairman Dave England, Pharm.D., called the meeting to order at 5:30 PM and asked for a roll call. A quorum was established. Ground rules for the public speaking were established.

2. Public Comment on Any Matter on the Agenda

Dr. England called for public comment.

No comments.

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from April 27, 2017.

There was a motion to accept the minutes as submitted and a motion seconding the approval. The minutes from April 27, 2017 were approved.

b. **For Possible Action:** Review and Approve Meeting Minutes from July 13, 2017.

There was a motion to accept the minutes as submitted and a motion seconding the approval. The minutes from July 13, 2017 were approved.

c. Status Update by DHCFP

Mr. Duane Young, Chief of Behavioral Health and Pharmacy Services for the Division of Health Care Financing and Policy (DHCFP), provided an update of activities for the Division. Mr. Young spoke about CCHB going live on July 1 of this year in Reno, Las Vegas, Fallon and Elko. Mental health parody bill is under way, requires mental health parody among managed care plans and fee for service. An analysis of Children's Health Insurance in the MCO's has been conducted. The MCO expansion was effective July 1, 2017, Aetna is no longer participating and will be out of the MCO program effective August 31, 2017, leaving three MCO's. Dental benefits will begin August 25, 2017, but fee for service will continue handling the benefits until January 1, 2018. Mr. Young welcomed two new members to the board nominated by the MCO's, Dr. Marta Bunuel and Dr. Jennifer Wheeler, a third will be appointed and now this DUR Board represents all Medicaid for the State of Nevada.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for eteplirsen (Exondys 51®)

Dr. England reminded the Board this is being reviewed to update the reauthorization criteria.

Dr. England called for public comment.

Ms. Lisa Borland, Medical Affairs representative from Serepta Pharmaceuticals, offered availability for questions.

Dr. Carl Jeffery, OptumRx, offered proposed criteria for Exondys 51 that removed the criteria for the ambulatory requirement in the re-authorization criteria.

Dr. England asked if there is a requirement to establish a baseline.

Dr. Jeffery suggests it would be based on the opinion of the prescriber. If the member was not maintaining or improving, the call center would not reauthorize the request.

Dr. Chris Shea, Pharm.D., asked if the intention was to remove the ambulatory requirement from the criteria.

Dr. Jeffery answered the initial evaluation and the renewal criteria was not consistent. The goal is to make the renewal criteria match with the initial criteria.

Dr. Michael Owens, MD, asked if there is some standard language that could be used, like maintaining clinically significant status.

Dr. James Marx, MD, pointed out that ambulatory status does not have to mean the patient is ambulating. Suggesting nothing in the language needs to be updated.

Mr. Darryl Faircloth, DAG, stated as long as the call center that evaluates and reviews the prior authorizations is consistent with the Board's intent, the language is fine, but clarification would be helpful.

Dr. Beth Slamowitz, Pharm.D., DXC, asked if there is anything listed in the package insert.

Ms. Borland replied there is no restriction based on the indication. The intent of the treatment is to slow the disease, not necessarily maintain the same baseline status.

Dr. Jeffery suggested language could be borrowed from the Spinraza criteria, the patient has experienced a benefit from therapy compared to untreated patients.

Dr. Owens suggested leaving the language as clinically significant status would leave the judgement to the prescriber.

Dr. Slamowitz asked if the call center will know how to evaluate a clinical benefit.

Dr. Jeffery responded that the call center would rely on the word of the prescriber.

A motion was made that line 1.1.2 in the proposed criteria be amended to read the patient is showing satisfactory benefit from the treatment. The motion was seconded and approved.

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

Dr. Jeffery reminded the Board for purpose for this topic is to clarify the renewal criteria for Spinraza.

Dr. England called for public comment.

No public comment.

A motion was made the criteria for Spinraza be accepted as presented. The motion was seconded and accepted.

Dr. Marx asked for more information about SMA.

Dr. Jeffery provided information on utilization trends and the usual dosage patterns.

Dr. Bunuel asked if the numbers were just for Nevada.

Dr. Jeffery responded that this information is just for the fee for service data, not MCO utilization data.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria for COX-2 Inhibitors.

Dr. Jeffery stated this item was brought to the board to remove the clinical criteria. The medication is non-preferred through the preferred drug list and the utilization is not high.

Dr. Marx asked what the exception criteria is to get the medication.

Dr. Jeffery responded that two preferred agents would be tried unless there is some compelling reason the prescriber needs to have the non-preferred medication for a specific indication.

Dr. England called for public comment.

No public comment.

The Board reviewed the utilization data and the current prior authorization criteria. The request made to the board was to remove the criteria to allow easier access for members.

A motion was made to remove the celecoxib, COX-2 clinical criteria. The motion was seconded and accepted.

d. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Antiemetics – Delta-9-Tetrahydrocnnabinol (THC) Derivatives.

Dr. Jeffery provided a brief description of the new drug, Syndros, available in this class. A red-lined version of the criteria was presented to remove the brand names and instead make reference to the class or generic name.

Dr. England called for public comment.

No public comment.

A motion was made to accept the changes to the criteria as presented. The motion was seconded and accepted.

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

Dr. Jeffery provided an overview of the proposed criteria to include Siliq in the product list. The current rules for plaque psoriasis listed in MSM Chapter 1200 contains the necessary information for approval of Siliq.

Dr. England reminded the Board off label use is allowed if there is sufficient evidence showing it is safe and effective.

Dr. Marx asked if we are limiting to FDA approved indications or is the call center's responsibility to assess the quality of peer-reviewed literature.

Dr. Jeffery responded that indications must be FDA approved, listed in a common compendia or accepted use in peer-reviewed literature.

Dr. England called for public comment.

Dr. Nindhana Paranthaman, Medical Doctor from Bristol Myers Squib, provided information on Orencia including new indications, dosing procedures, study designs and results. Agreed current criteria provides coverage sufficiently.

Dr. England asked if this new indication is included in the criteria already.

Dr. Jeffery responded psoriatic arthritis is included in the criteria. Asked Dr. Paranthaman if the criteria is suitable to the updated indications.

Dr. Paranthaman responded that the criteria does allow appropriate access.

A motion was made to include the new product, Siliq, in the list of products. The motion was seconded and accepted.

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

Dr. Jeffery provided an overview of the FDA and American Academy of Pediatrics warning of tramadol and codeine use in children. Utilization reports were included with the binder. Requested age limits of 12 or under be restricted.

Dr. England asked the Board if limitations were added for codeine and tramadol, what would be recommended instead.

Dr. Marx responded most children should not be using opioids. Anti-inflammatories work very well for most children in emergency situations or oncology.

Dr. Slamowitz offered that a lot of opioids in children are used for sleep.

Dr. Marx offered alternative opioids more appropriate for children including oxycodone elixir.

Dr. Jeffery clarified the call center is not doing anything with these because there are not any system limitations currently.

Dr. England suggested having the topic at the next meeting with some specific criteria recommendations and information from other State Medicaid programs.

Dr. Jeffery asked the Board for opinions on what appropriate options should be included in the proposed criteria.

Dr. Marx suggested looking at children's hospitals for what is used.

Dr. Slamowitz suggested taking the question to Dr. Dimuro for input.

5. Public Comment on any DUR Board Requested Report

Dr. England called for public comment.

No comments.

6. DUR Board Requested Reports

a. Psychotropic medications used for children and adolescents.

Dr. Jeffery presented the reference page of the general population of total enrollees and children enrolled in Fee for Service Medicaid. Data presented for four or more psychotropics. Two years of data is included in the reports and only for children under age 18. The medications being used and presented and discussed. The number of children on two or more agents in the same class was presented. Anticonvulsants are the most common agents used when two or more agents within the same class.

Dr. Bunuel asked what diagnosis these medications are being used for.

Dr. Jeffery responded that diagnosis for use of these medications is difficult to tease out because they are submitted on the medical claim.

Dr. Marx asked if the Board of Pharmacy requires the diagnosis be listed on the prescription.

Dr. Wheeler stated it is only at the patient request.

Dr. Jeffery reiterated how difficult and unreliable matching the diagnosis to the prescription claims is. Multiple anticonvulsant use vs. multiple antipsychotics is a different conversation.

Dr. England posed the question to the Board, would adding a diagnosis requirement add an undue burden.

Ms. Sprout updated the Board on the modernization of the MMIS and getting to the point of having better data set available.

Dr. Owens stated he has a lot of patients who don't know what their medication is treating. It does take a little extra time to include the diagnosis, but it makes sense for safety and precautionary measures.

Dr. Slamowitz stated requiring labeling with a diagnosis is not something this Board can enforce, it is the responsibility of the Board of Pharmacy.

Dr. England posed to the Board if a requirement for a diagnosis would be a benefit.

Dr. Bunuel stated it would help to know why these medications are being used.

Dr. Slamowitz stated use for the children in foster children is being monitored.

Dr. England clarified the intent is to not restrict utilization, but to make sure it is appropriate. Requested the board look at specific diagnosis before any changes can take place.

Ms. Sprout suggests we look at the percentage of the population that is using psychotropics.

Dr. Marx stated a good database is important for utilization and retro-DUR.

Ms. Sprout responded that the Directors office is focused on meaningful data and is a focus.

Dr. England requested this topic be brought back with some of the information discussed.

b. Opioid Utilization – Top prescriber and member

Dr. Jeffery provided an overview of reports including specific strengths and opioid names broken down by member.

Dr. England asked for input regarding using different opioids for short-acting vs. long-acting.

Dr. Marx responded that pain management is a balance of using long-acting agents and a short-acting for breakthrough. Uses more frequent low doses rather than higher dose long-acting which may promote liking. Sometimes a different molecule hits different receptors that can provide a benefit. Patients getting opioids from illicit places is really the problem.

Dr. England stated the usage seems to be logical. Suggests we continue to monitor for opiate use.

Dr. Shea stated the majority of patients appear to be on appropriate therapy.

Dr. Jeffery called out some members using high amounts of methadone. The reports break down the utilization and give a better picture.

Dr. England asked that the Board continue to monitor opioids.

Dr. Jeffery presented the utilization for the top opioid prescribers were discussed. Data goes back two years, changing the names from the last report.

Dr. England asked if there is any red flags for follow up.

Dr. Jeffery responded that much of the opioid use is for dental procedures.

Dr. Marx stated that much of the opioids prescribed by dentals is probably not necessary.

Dr. Jeffery presented the trending utilization of opioids since implementing the new quantity limit on May 15, 2017. Members were grandfathered in who were stable on an opioid. Maybe looking at dose reductions may be the next option.

Dr. Marx responded that doing dose reductions with opioids is misguided and not appropriate.

Dr. England agreed that dose reductions are not a good idea.

Dr. Marx added that blood pressure or diabetes medications are not tapered off.

Dr. Owen stated that there are opportunities to reduce hypertension or diabetes medications if the patient lost weight. The same could be true for pain treatment if they are doing physical therapy or some other treatments.

Dr. Marx stated 95% of opioid deaths are obtained through illicit means.

Dr. Jeffery pointed out another graph showing some downward trends of opioids members and claims since May 2017.

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

Dr. Jeffery presented the information including medical claims data who have had an endoscopy who are also receiving proton pump inhibitors. The majority of recipients on PPI's have never been scoped.

Dr. England stated it appears the utilization seems to be appropriate.

d. Impact of 90 day maintenance medication requirement.

Dr. Jeffery presented data since the end of April 2017 when a 90 day requirement to fill maintenance medications was implemented. A few requests have been received to override the 90 day requirement.

Dr. England suggests continued follow up on the information would be helpful.

7. Public Comment on any Standard DUR Report

Dr. England asked for public comment.

No comment.

8. Standard DUR Reports

a. Review of Prescribing/Program Trends.

Dr. Jeffery presented trend reports, nothing out of the ordinary is showing on the reports. A request for ideas to manage hemophilia is made. Two new hepatitis C medications are now available and included in the antiviral classes.

Dr. England states he doesn't see a lot of fluctuation in the reports.

b. Concurrent Drug Utilization Review (ProDUR)

Dr. Jeffery presented the trending DUR edits.

Dr. England added that not much has changed.

c. Retrospective Drug Utilization Review (RetroDUR)

Dr. Jeffery presented the RetroDUR letters and results. The response rate is very low. A stamped postcard was included for physician response.

Dr. Marx suggested receiving responses via text message.

Dr. Jeffery presented a draft letter for codeine and tramadol retroDUR.

9. Closing Discussion

a. Public comments on any subject.

Dr. England asks for public comment.

No comments.

b. Date and location of the next meeting.

The date of the next meeting will be October 19th and will be at the Hyatt Place.

c. Adjournment.

The meeting adjourned at 7:35 PM.

Nevada Medicaid
Austedo (deutetrabenazine)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Austedo	deutetrabenazine

CRITERIA FOR COVERAGE/NONCOVERAGE

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

1. Diagnosis of chorea associated with Huntington's disease **AND**
2. Prescribed by or in consultation with a neurologist

Initial Authorization: 3 months

Reauthorization Duration:

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

1. Documentation of positive clinical response to therapy

Austedo (deutetrabenazine)

Override(s)	Approval Duration
Prior Authorization	1 year

Medications	Quantity Limit
Austedo (deutetrabenazine)	May be subject to quantity limit

APPROVAL CRITERIA

Requests for Austedo (deutetrabenazine) may be approved for individuals who meet the following criteria:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of chorea associated with Huntington's disease;

Requests for Austedo (deutetrabenazine) may not be approved for individuals who meet the following criteria:

I. Individual is suicidal or has untreated/inadequately treated depression; **OR**
II. Individual has hepatic impairment; **OR**
III. Individual is currently utilizing monoamine oxidase inhibitors (MAOIs), reserpine, or tetrabenazine.

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

Key References:

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2017. URL: http://www.clinicalpharmacology.com. Updated periodically.

DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed January 30, 2017.

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

Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2017; Updated periodically.

Amerigroup Utilization Summary

Specific Therapeutic Class Description	GCN Description	Drug Label	Net Rxs	Total Rx Users	Total Plan Cost
Monoclonal Antibodies To Immunoglobulin E (Ig	OMALIZUMAB	XOLAIR 150 MG VIAL	374	75	$1,096,720.97
Monoclonal Antibody - Interleukin-5 Antagonis	MEPOLIZUMAB	NUCALA 100 MG VIAL	13	3	$33,532.17
Glucocorticoids	DEFLAZACORT	EMFLAZA 30 MG TABLET	3	1	$19,784.82
Monoclonal Antibody - Interleukin-5 Antagonis	RESLIZUMAB	CINQAIR 100 MG/10 ML VIAL	7	1	$17,681.55
			397		**$1,167,719.51**

INTRODUCTION

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

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

INDICATIONS

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

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

CLINICAL EFFICACY SUMMARY

Huntington Disease (HD)

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

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

Table 1. First-HD Study Efficacy Results

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

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

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

Tardive Dyskinesia (TD)

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

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

CLINICAL GUIDELINES

Huntington Disease (HD)

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

Tardive Dyskinesia (TD)

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

Table 2. Guideline Recommendations for Tardive Syndromes

Level of evidence	Recommendation
Level A (Recommendation must be done; high confidence in the evidence with high benefit and low risk)	None

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

SAFETY SUMMARY

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

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

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

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

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

See the current prescribing information for full details

CONCLUSION

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

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

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Publication Date: September 13, 2017

Nevada Medicaid

Brineura (cerliponase alfa)

Pharmacy Coverage Guideline

Brand Name	Generic Name
Brineura	cerliponase alfa

Indication

Late Infantile Neuronal Ceroid Lipofuscinosis Type 2	Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

CRITERIA FOR COVERAGE/NONCOVERAGE

Brineura (cerliponase alfa) will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Diagnosis of symptomatic late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) (also known as tripeptidyl peptidase 1 (TPP1) deficiency)
   AND
2. Diagnosis is confirmed by tripeptidyl peptidase 1 (TPP1) enzyme detected by a dried blood spot test and CLN2 genotype analysis
   AND
3. Patient is 3 years of age or older
   AND
4. Patient does not have acute intraventricular access-related complications (e.g., leakage, device failure, or device-related infections)
   AND
5. Patient does not have ventriculoperitoneal shunts
   AND
6. Prescribed by or in consultation with a neurologist with expertise in the diagnosis of CLN2
   AND
7. Administered by, or under the direction of, a physician knowledgeable in intraventricular administration

Initial Authorization: 4 months

Nevada Medicaid
Brineura (cerliponase alfa)
Pharmacy Coverage Guideline

Reauthorization Duration: 12 Months

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

1. Patient does not have acute intraventricular access-related complications (e.g., leakage, device failure, or device-related infections)
   AND
2. Patient does not have ventriculoperitoneal shunts
   AND
3. Patient has experienced a benefit from therapy (e.g., improvement in walking or crawling, or no evidence of disease progression)

Brineura (cerliponase alfa)

DRUG.00099

Override(s)	Approval Duration
Prior Authorization	1 year

Medications
Brineura (cerliponase alfa)

APPROVAL CRITERIA

Requests for Brineura (cerliponase alfa) may be approved when the following criteria are met:

I. Individual has late infantile neuronal ceroid lipofuscinosis type 2; **AND**
II. Individual is symptomatic; **AND**
III. Treatment is being given to slow the loss of ambulation.

Requests for Brineura (cerliponase alfa) may not be approved for all other indications.

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

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INTRODUCTION

- Neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of inherited, childhood lysosomal storage disorders (LSDs) characterized by the intracellular accumulation of storage material (lipopigment) leading to severe neurodegeneration *(FDA Summary Review 2017)*. NCLs are collectively referred to as Batten disease *(Brineura Formulary Submission Dossier 2017, Batten Disease Fact Sheet)*.
- Neuronal ceroid lipofuscinosis Type 2 (CLN2) is the second most common form of NCL and is due to a deficiency of the lysosomal enzyme tripeptidyl peptidase-1 (TPP1) *(FDA Summary Review 2017)*. The disease follows a relatively predictable phenotype, with onset between 2 and 4 years of age followed by a progressive, steady deterioration resulting in profound neurological deficits by 6 years of age and death in adolescence *(FDA Summary Review 2017)*.
  - CLN2 classically manifests with the onset of seizures, typically in combination with a history of early language delay *(Brineura Formulary Submission Dossier 2017)*. Disease progression includes a loss of language and walking ability; movement disorders (eg, myoclonus, dystonia, chorea, pain, progressive dementia); and the eventual loss of vision *(Brineura Formulary Submission Dossier 2017)*. Most children with CLN2 disease die between the ages of 8 years and early adolescence *(Brineura Formulary Submission Dossier 2017)*.
  - Despite rapid disease progression, a definitive diagnosis of CLN2 disease (made by measurement of TPP1 enzymatic activity or CLN2 genotyping), is often delayed due to the lack of symptom specificity early in the disease and a general, low clinical awareness of CLN2 disease *(Brineura Formulary Submission Dossier 2017)*.
  - CLN2 is very rare, with an estimated incidence between 0.56 and 4 patients per 100,000 live births in the United States and Europe *(FDA Summary Review 2017)*.
- As there is no cure for CLN2, the current standard of care relies on a multidisciplinary approach including seizure management; physical, occupational, and speech therapy to optimize residual motor function; nutritional management; the general treatment of complications related to the loss of mobility and swallowing; management of sleep disturbances and behavior symptoms; and social and educational interventions *(FDA Summary Review 2017)*.
- On April 27, 2017, the Food and Drug Administration (FDA) announced the approval of BioMarin's Brineura (cerliponase alfa), to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile CLN2, also known as TPP1 deficiency *(FDA Web site)*. Cerliponase alfa underwent a priority review and was granted breakthrough therapy and orphan drug designations by the FDA; it is the first approved pharmacological treatment (ie, enzyme replacement therapy [ERT]) for CLN2 *(FDA News Release 2017)*.
  - Under the same trade name, cerliponase alfa was also approved by the European Commission, but with an expanded age indication for the treatment of CLN2 in patients of all ages from birth *(European Medicines Agency [EMA] 2017, Markham 2017)*.
- Cerliponase alfa is a recombinant form of human TPP1 (rhTPP1), the enzyme deficient in patients with CLN2.
  - After infusion, the cerliponase alfa proenzyme enters target cells in the central nervous system (CNS) where it is then transported into lysosomes via the cation-independent, mannose-6-phosphate receptor *(Markham 2017)*. The drug is then activated in the lysosome to a proteolytic form of rhTPP1, which functions to cleave tripeptides from the N-terminus of proteins *(Markham 2017)*.
  - Because cerliponase alfa cannot cross the blood-brain barrier, the drug is administered directly into the intracerebroventricular space via a specific surgically implanted reservoir and catheter in the head (intraventricular access device) *(FDA Summary Review 2017)*.
- Medispan Class: Endocrine and Metabolic Agents – Misc; Metabolic Modifiers; Tripeptidyl Peptidase 1 Deficiency Treatment - Agents

INDICATIONS

- Cerliponase alfa is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile CLN2, also known as TPP1 deficiency *(Brineura prescribing information 2017)*.

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

CLINICAL EFFICACY SUMMARY

- The cerliponase alfa clinical program included an interventional clinical study (Study 190-201) with an extension (Study 190-202) and comparison to an historical, untreated cohort (Study 190-901) *(Brineura Formulary Submission Dossier 2017, ClinicalTrials.gov Web site, FDA Statistical and Summary Reviews 2017)*. The results of Studies 190-201/202 and 190-901 are currently unpublished.
  - Study 190-201 was a 48-week, Phase 1/2, single-arm, open-label (OL), clinical trial that enrolled 24 patients ≥ 3 years of age with symptomatic CLN2 disease. Twenty-three patients entered the currently ongoing, 5-year extension phase (Study 190-202). Cerliponase alfa-treated patients were compared with an independent historical control group with similar, but not identical baseline characteristics (N = 42 untreated patients; Study 190-901).
  - Efficacy assessments were based on a clinician-reported outcome (ClinRo) known as the CLN2 Clinical Rating Scale that typically consists of 4 domains: Motor, Language, Visual, and Seizures. In studies of cerliponase alfa, only the Motor and Language domains were assessed; efficacy conclusions were based on multiple analyses of the best matched patients in the 2 cohorts and accounted for several confounding factors (age, genotype, screening motor score).
    - Motor function (walking or crawling ability) was assessed using the Motor domain of the CLN2 Clinical Rating Scale, which could range from a score of 3 (normal) to a score of zero (profoundly impaired).
      - Treatment with cerliponase alfa was associated with a slowing in progression of motor deterioration relative to a reasonably matched control cohort. There was a progressively larger difference with time between the treated and historical groups: 18%, 29%, and 59% at 48, 72, and 96 weeks, respectively. Of note, at Week 96, the 95% confidence interval (CI) for the odds ratio (OR) excluded 1 (ie, OR = 11; 95% CI: 1.6 to 500), which was not observed with shorter exposure to treatment.
      - In its analysis, the FDA noted that a longer duration of treatment was necessary to identify a treatment difference. The initial efficacy comparisons at 48 weeks were inconclusive, as were comparisons after 72 weeks of treatment (although an efficacy trend was observed at both time points, and more clearly at 72 weeks compared to 48 weeks). The 96-week time point ultimately provided adequate evidence of effectiveness.
    - Due to the inability to establish comparability for the CLN2 Language domain ratings between the clinical study with extension and the natural history cohort, the efficacy of cerliponase alfa for the Language domain could not be established.

CLINICAL GUIDELINES

Note: No CLN2 management guidelines exist and there is a paucity of published disease-specific evidence to inform clinical practice, which currently draws upon experience from the field of childhood neuro-disability *(Williams et al 2017)*. A group of 24 disease experts were surveyed on CLN2 disease management and a subset met to discuss current practice; their recommendations (see below) were generally consistent and guided by the principles of pediatric palliative care *(Williams et al 2017)*.

- **Management strategies for CLN2 disease** *(Williams et al 2017)*
  - Early diagnosis of CLN2 disease is critical to ensure optimal care for patients and families, but is challenging primarily due to a lack of disease awareness and the non-specificity of initial presenting symptoms. Most patients are diagnosed around 5 years of age when substantial loss of function has already occurred.
  - Once clinical suspicion of CLN2 disease or an NCL disorder has been established, the patient should undergo biochemical testing. The recommended gold standard for definitive diagnosis of CLN2 disease is the demonstration of deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots), together with the detection of pathogenic mutations in each allele of the TPP1 gene (also known as the CLN2 gene).
  - Management of CLN2 disease should be guided by the principles of pediatric palliative care, a holistic approach to caring for children with complex medical needs. Optimizing the quality of life for patients and their families requires a multidisciplinary team of health care professionals, including physicians, nurses, therapists (ie, physical, occupational, and speech), dietitians, psychologists, social workers, and counselors, working collaboratively to manage symptoms, minimize pain and suffering, and provide psychosocial and spiritual support. A supervising clinician (neurologist, palliative care specialist, or general pediatric specialist) typically oversees the coordination of care.

- As the disease evolves beyond the initial presentation and the symptom burden increases, maintenance of function (particularly ambulation and communication) for as long as possible is the main goal of management. In the late stage, maintenance of the quality of life and the prevention of complications secondary to immobility and functional loss (eg, decubitus ulcers, muscle atrophy, aspiration pneumonia) are the priorities of care.
- Optimal management of patients requires ongoing assessments and modification of treatment plans as needed. The frequency of clinic visits/assessments should be tailored to meet the individual needs of each child/family.

SAFETY SUMMARY

- Contraindications
  - Patients with acute intraventricular access device-related complications (eg, leakage, device failure, or device-related infection).
  - Patients with ventriculoperitoneal shunts.

- Warnings/precautions
  - Intraventricular access device-related complications
    - The scalp should be inspected for skin integrity and for signs of intraventricular access device leakage; cerliponase alfa should not be administered if there are signs of device leakage or infection. Cerebrospinal fluid (CSF) samples should routinely be sent for testing to detect subclinical device-related infections.
  - Cardiovascular adverse reactions
    - Vital signs should be monitored before, during, and post-infusion. Electrocardiograms (ECGs) should be monitored in patients with a history of bradycardia, conduction disorder, or with structural heart disease, during the infusion. In patients without cardiac abnormalities, regular 12-lead ECG evaluations should be performed every 6 months.
  - Hypersensitivity reactions
    - Patients should be observed during and after the infusion. If a severe hypersensitivity reaction occurs, the infusion should be stopped immediately and appropriate treatment initiated.

- Adverse effects
  - The most common adverse reactions (≥ 8%) reported in Studies 190-201/202 at Week 96 were: pyrexia (17/24 [71%]), ECG abnormalities (17 [71%]), decreased CSF protein (17 [71%]), vomiting (15 [63%]), seizures (12 [50%]), hypersensitivity (11 [46%]), increased CSF protein (5 [21%]), hematoma (5 [21%]), headache (4 [17%]), irritability (4 [17%]), pleocytosis (4 [17%]), device-related infection (2 [8%]), bradycardia (2 [8%]), feeling jittery (2 [8%]), and hypotension (2 [8%]).
    - Pyrexia includes: pyrexia and increased body temperature
    - ECG abnormalities include: non-specific repolarization abnormality, notched QRS, ST segment elevation, biphasic T wave abnormality, supraventricular extrasystoles, bradycardia, sinus tachycardia, and intraventricular conduction delay
    - Seizure types reported included atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anti-convulsive therapies and did not result in discontinuation of cerliponase alfa treatment.
    - Hypersensitivity includes: immune reactions and signs and symptoms observed concomitantly with hypersensitivity reactions including pyrexia, vomiting, pleocytosis or irritability
    - Device-related infections include: *Propionibacterium acnes* and *Staphylococcus epidermidis*
  - As with all therapeutic proteins, there is a potential for immunogenicity.
    - The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cerliponase alfa in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
    - Anti-drug antibodies (ADAs) to cerliponase alfa were detected in both serum and CSF in 79% and 33%, respectively, of patients treated with cerliponase alfa for up to 161 weeks. Patients who experienced hypersensitivity adverse reactions were tested for drug-specific IgE and found to be negative, including 3 patients for whom grade 3 (severe) hypersensitivity adverse reactions were reported.

- No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity. Drug-specific neutralizing antibodies have not been evaluated.

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brineura (cerliponase alfa)	Injection	Intraventricular infusion	Every other week Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.	Must be administered under sterile conditions by, or under the direction of a physician knowledgeable in intraventricular administration. Following administration of cerliponase alfa, an infusion of intraventricular electrolytes must follow. The entire procedure takes approximately 4.5 hours. Cerliponase alfa is a drug-device combination product; it is co-packaged with the intraventricular electrolytes injection and with an administration kit containing syringes, needles, infusion set with filter, extension and a port needle. Cerliponase alfa is intended to be administered via the Codman® HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman® Ventricular Catheter (Part Number: 82-1650). The pump to be used is the B Braun Perfusor® Space Infusion Pump System.

See the current prescribing information for full details

CONCLUSION

- Brineura (cerliponase alfa) is indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency.
- Cerliponase alfa is the first approved pharmacological treatment (ie, enzyme replacement therapy) for CLN2, a pediatric-onset, autosomal recessive, neurodegenerative, lysosomal storage disorder caused by the deficient activity of the enzyme TPP1. The data supporting the approval of cerliponase alfa are currently unpublished.
- Treatment with cerliponase alfa was associated with a slowing in progression of motor deterioration relative to a reasonably matched untreated cohort. There was a progressively larger difference with time between the treated and historical groups (N = 17 pairs): 18%, 29%, and 59% at 48, 72, and 96 weeks, respectively. Of note, at Week 96, the

95% confidence interval (CI) for the odds ratio (OR) excluded 1 (ie, OR = 11; 95% CI: 1.6 to 500), which was not observed with shorter exposure to treatment.

- Because cerliponase alfa cannot cross the blood-brain barrier, the drug is administered directly into the intracerebroventricular space via a specific surgically implanted reservoir and catheter in the head (intraventricular access device).
- Although the intraventricular infusions required to administer cerliponase alfa carry several inherent risks and must be performed under the supervision of knowledgeable healthcare providers, the approval of cerliponase alfa marked an important treatment milestone for patients with rare CLN2 disease. While the effects of cerliponase alfa on the language, visual, and seizure complications associated with CLN2 remain unknown, a significant slowing in the progression of motor deterioration in cerliponase alfa-treated patients relative to a reasonably matched, untreated cohort was demonstrated by 96 weeks.

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Nevada Medicaid
Ingrezza (valbenazine)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Ingrezza	valbenazine

Indication

Tardive Dyskinesia	Indicated for the treatment of adults with tardive dyskinesia.

CRITERIA FOR COVERAGE/NONCOVERAGE

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

1. Diagnosis of moderate to severe tardive dyskinesia
AND
2. The patient is 18 years old or older
AND
3. One of the following
3.1. Patient has persistent symptoms of tardive dyskinesia despite a trial of dose reduction, tapering, or discontinuation of the offending medication
OR
3.2. Patient is not a candidate for a trial of dose reduction, tapering, or discontinuation of the offending medication
AND
4. Prescribed by or in consultation with a Neurologist or Psychiatrist

Initial Authorization: 3 months

Reauthorization Duration: 12 Months

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

1. Documentation of positive clinical response to Ingrezza therapy

Ingrezza (valbenazine)

Override(s)	Approval Duration
Prior Authorization Quantity Limit	1 year

Medications	Quantity Limit
Ingrezza (valbenazine)	May be subject to quantity limit

APPROVAL CRITERIA

Requests for Ingrezza (valbenazine) may be approved for individuals who meet the following criteria:

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of tardive dyskinesia (TD) confirmed by the following (DSM-5):
    A. At least 60 days of stable (drug, dose) neuroleptic medication exposure (either typical or first generation antipsychotic agents [such as, chlorpromazine, haloperidol, fluphenazine], atypical or second-generation antipsychotic agents [such as, clozapine, risperidone, olanzapine, quetiapine, aripiprazole], or certain dopamine receptor-blocking drugs used in treatment of nausea and gastroparesis [such as, prochlorperazine, promethazine, metoclopramide]); AND
    B. Presence of involuntary athetoid or choreiform movements lasting at least 30 days.

Requests for Ingrezza (valbenazine) **may not** be approved for individuals who meet the following criteria:

I. Individual has congenital long QT syndrome or arrhythmia associated with a prolonged QT interval; **OR**
II. Individual is currently using a strong CYP 3A4 Inducer (examples: rifampin, carbamazepine, phenytoin, St. John's wort); **OR**
III. Individual is currently using a monoamine oxidase inhibitor (MAOI) (examples: isocarboxazid, phenelzine, selegiline).

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

Key References:

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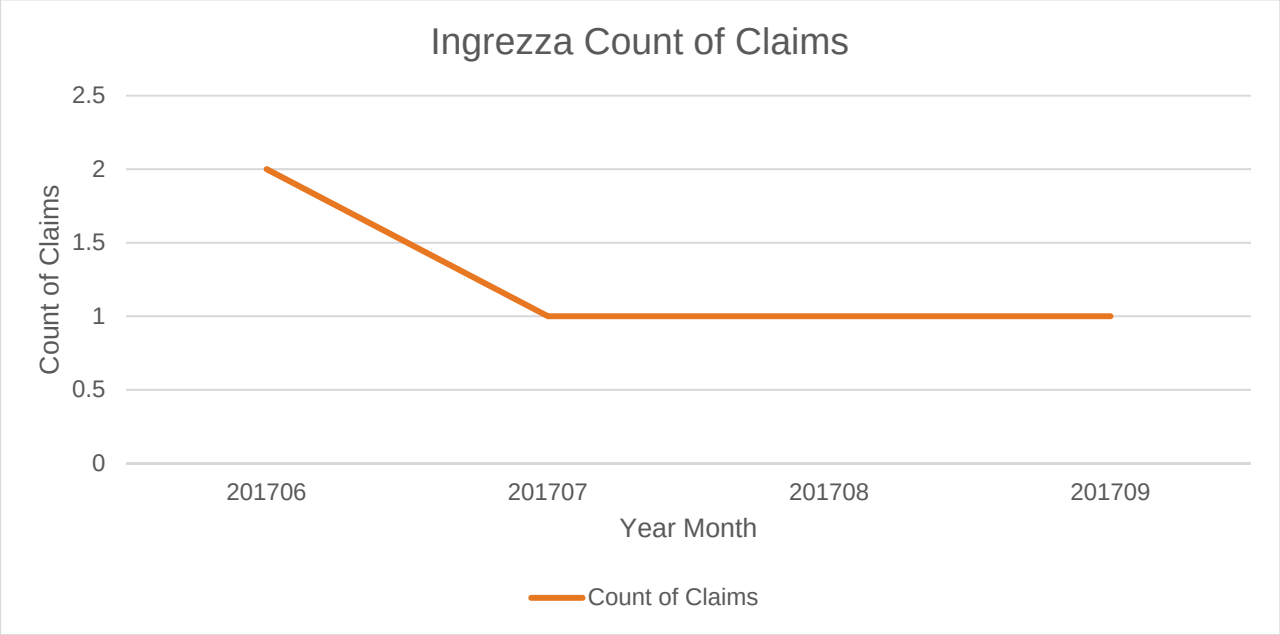
Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2017; Updated periodically.

Ingrezza Utilization

September 1, 2016 - August 31, 2017

YearMonth Filled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201706	INGREZZA	CAP 40MG	2	2	60	106	$ 18,658.68
201707	INGREZZA	CAP 40MG	1	1	30	53	$ 9,329.34
201708	INGREZZA	CAP 40MG	1	1	30	60	$ 10,560.17
201709	INGREZZA	CAP 40MG	1	1	30	60	$ 10,560.17



New Drug Overview
Ingrezza (valbenazine)

INTRODUCTION

- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents (DRBAs), predominantly antipsychotics/neuroleptics (first generation antipsychotics [FGAs], also known as typical antipsychotics, as well as second-generation antipsychotics [SGAs], which are also known as atypical antipsychotics) and metoclopramide *(Rana et al 2013).*
- While the pathophysiology of TD is not well-understood, the most prominent theory suggests chronic exposure to neuroleptics results in dopamine-2 (D2) receptor up-regulation with postsynaptic dopamine receptor supersensitivity *(Waln and Jankovic 2013).*
- Prospective studies of patients treated with FGAs suggest that the annual incidence of TD is between 3 to 8%. With SGAs, the mean annual incidence is estimated at 2.1 to 4.2%. Although TD prevalence has been less studied with metoclopramide, the published data indicate a prevalence ranging from 1 to 10% (*Waln and Jankovic 2013).*
- The lower incidence of TD with SGAs compared to FGAs is hypothesized to be a result of pharmacologic differences in dopamine and serotonin receptor affinity. SGAs tend to have lower D2 receptor occupancy and higher serotonin receptor activity than FGAs *(Howland et al 2011, Vijayakumar and Jankovic 2016).*
- TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area (Muller et al 2015). Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Rana et al 2013*).
- TD can affect the ability of patients to perform activities of daily living as well as make it more difficult for them to engage in the community or workplace, given the visibility of involuntary movements and societal stigma related to mental illness *(FDA Ingrezza Medical Review*).
- According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for ≥ 3 months (or one month in patients ≥ 60 years of age) or within four weeks of withdrawal from an oral medication (or within eight weeks of withdrawal from a depot medication). The disorder should persist for at least one month after discontinuation of an offending drug to qualify as TD (*Waln and Jankovic 2013*).
- The first step in the treatment of TD is to discontinue the offending agent via slow taper. Sudden withdrawal of the offending drug should be avoided, as symptoms of TD could worsen. In patients with psychiatric conditions which require continued use of a neuroleptic, switching from an FGA to an SGA could be considered. Quetiapine and clozapine are the preferred SGAs due to their low receptor occupancy and fast dissociation from D2 receptors (*Vijayakumar and Jankovic 2016*).
- Ingrezza (valbenazine), a vesicular monoamine transporter 2 (VMAT2) inhibitor approved by the Food and Drug Administration (FDA) on April 11, 2017, was granted fast track status, priority review, and breakthrough therapy designation *(FDA Web site).*
  - Valbenazine is the first and only drug approved by the FDA for TD.
  - The mechanism of action of valbenazine is thought to be mediated through the reversible inhibition of VMAT2, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. In other words, by modulating the pre-synaptic packaging and release of dopamine into the synapse, striatal dopamine depletion can be achieved (*Hauser et al 2017, Jankovic 2016*).
  - Valbenazine is the third VMAT2 inhibitor approved by the FDA; Xenazine (tetrabenazine) and Austedo (deutetrabenazine) were the first VMAT2 inhibitors approved in August 2008 and April 3, 2017, respectively. Both are indicated in the treatment of Huntington's chorea (*Austedo product information 2017, Xenazine product information 2015*).
  - Unlike tetrabenazine and deutetrabenazine, valbenazine does not carry a boxed warning for increased risk of depression and suicidal thoughts or behavior (*Austedo product information 2017, Xenazine product information 2015).*
  - Valbenazine is currently being studied as a potential treatment for Tourette's syndrome (phase 2) *(Ingrezza Web site).*
- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder.

INDICATION

- Valbenazine is indicated for the treatment of adults with TD *(Ingrezza prescribing information 2017*).

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

CLINICAL EFFICACY SUMMARY

- The FDA approval of valbenazine was based on the results from the KINECT 3 trial, a 6-week, phase 3, double-blind, placebo-controlled, multicenter, randomized clinical trial with 224 patients with moderate to severe TD *(Hauser et al 2017, FDA Ingrezza Medical Review).*
  - In this trial, 66.1% of patients had schizophrenia or schizoaffective disorder, while 33.9% had a mood disorder. Additionally, 85.5% received concomitant antipsychotics (16.7% on FGAs and 76.7% on SGAs).
  - The mean baseline Abnormal Involuntary Movement Scale (AIMS) dyskinesia score was 10.0 (range 0 to 20) between the treatment groups.
  - Patients were randomized 1:1:1 to receive valbenazine 40 mg once daily, valbenazine 80 mg once daily, or placebo.
  - The primary endpoint was the AIMS dyskinesia score, which was a modified version of the AIMS score. The AIMS dyskinesia score included 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia). The original AIMS consists of a 12-item rating scale that includes the 7 aforementioned items as well as three items rating global severity, patients awareness, and distress associated with movements, and 2 items concerning problems with teeth and dentures. AIMS has been validated and widely used to assess the presence and severity of TD.
    - The AIMS dyskinesia score was evaluated by remote central video raters (movement specialists) via recordings for each patient visit. These raters were blinded to the patient's identity, visit number, and treatment arm.
    - The AIMS dyskinesia score was reduced from baseline to six weeks by 3.2 in the valbenazine 80 mg group compared to 0.1 in the placebo group ($p < 0.001$). In the valbenazine 40 mg group, the AIMS dyskinesia score decreased by 1.9 compared to 0.1 in the placebo group ($p = 0.002$).
  - The percentage of patients who achieved an AIMS response (defined in the trial as a reduction of ≥ 50% from baseline score) was 40.0% in the 80 mg group ($p < 0.001$) and 23.8% in the 40 mg group ($p = 0.02$), compared to 8.7% in the placebo group.
  - The key secondary endpoint of mean Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) score was used by site investigators to rate the overall change in TD from baseline at Week 6. CGI-TD scores ranged from 1 (very much improved) to 7 (very much worse). The mean CGI-TD score did not reach statistical significance for either valbenazine dosage group when compared to placebo ($p = 0.056$ and $p = 0.074$ for valbenazine 80 mg and 40 mg, respectively).
  - Another secondary endpoint was Patient Global Impression of Change (PGIC), which characterized the patient's perception of improvement in their TD symptoms. The mean PGIC score at Week 6 was slightly worse in both valbenazine treatment groups compared to placebo, but the differences did not reach nominal statistical significance.
  - With the exploratory endpoint of improvement in tardive dyskinesia impact scale (TDIS) score, both doses of valbenazine were numerically superior to placebo at Weeks 4 and 6, however, the differences did not reach statistical significance.
  - The most common adverse effects (AE) observed with valbenazine (both dosage groups combined) vs. placebo were somnolence (5.3% vs. 3.9%), akathisia (3.3% vs. 1.3%), and dry mouth (3.3% vs. 1.3%). Suicidal ideation was the most common AE in the placebo group (5.3% vs. 2.6% in both valbenazine groups combined).
  - The results from the long-term extension study (KINECT 3 Extension) were presented in the form of a poster at the 55th Annual Meeting of the American College of Neuropsychopharmacology in December 2016 *(Grigoriadis et al 2016)*.
    - Subjects who completed the 6-week trial were eligible to participate in the 42-week extension period (with a 4-week washout period at the end of the 48-week period). Those initially randomized to placebo were re-randomized 1:1 to valbenazine 80 or 40 mg/day; those initially randomized to valbenazine 80 or 40 mg/day continued at the same dose.
    - The primary and secondary endpoints (ie, AIMS dyskinesia score change from baseline to Week 48 and CGI-TD score at Week 48, respectively) remained the same in the extension period.

- At Week 48, mean changes from baseline (of the six week trial) were -4.8 and -3.0for valbenazine 80 and 40 mg/day, respectively (p-value not provided).
- At Week 48, 52.4% and 28.3% of patients on valbenazine 80 mg/day and 40 mg/day, respectively, were AIMS 50% responders (p-value not provided).
- CGI-TD scores demonstrated clinically meaningful global improvement for both treatment groups (p-value not provided).
- The PGIC and TDIS scores showed improvement in patient perception from Week 8 to Week 48 in both valbenazine groups, however, the FDA stated that the patient's awareness of their treatment with active drug and attrition bias could have confounded these results.
- After the 4-week treatment washout period (at week 52), TD severity began reverting towards baseline levels, and responder rates were lower than those observed at week 8.

CLINICAL GUIDELINE

- **American Academy of Neurology (AAN)** Evidence-based guideline: Treatment of tardive syndromes (TS) *(Bhidayasiri et al 2013)*
  - Level A recommendations (recommendation must be done; high confidence in the evidence with high benefit and low risk)
    - None
  - Level B recommendations (recommendation should be done based on benefit/risk profile)
    - Ginkgo biloba extract (EGb-761) for schizophrenia only
    - Clonazepam, for short-term use
  - Level C recommendations (recommendation may or might be done; lowest recommendation level considered useful within the scope of practice)
    - Amantadine for short-term use
    - Tetrabenazine
  - Level U (available evidence is insufficient to support or refute efficacy of an intervention)
    - Withdrawal of DRBAs
    - Switching from typical to atypical antipsychotics
    - Acetazolamide plus thiamine
    - Typical antipsychotics
    - Atypical antipsychotics
    - Electroconvulsive therapy
    - Reserpine or α-methyldopa
    - Bromocriptine
    - Anticholinergic agents (other than galantamine)
    - Biperiden discontinuation
    - Antioxidants (vitamin E, vitamin B6, melatonin, selegiline, yi-gan san)
    - Baclofen
    - Levetiracetam
    - Nifedipine
    - Buspirone
    - Botulinum toxin
    - Pallidal deep-brain stimulation

SAFETY SUMMARY

- **Contraindications**
  - None

- **Warnings/precautions**
  - Somnolence
  - QT prolongation
    - Valbenazine should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval.

- **Adverse effects**

Table 1. AEs reported in ≥ 2% of patients

AE	Valbenazine (n = 262)	Placebo (n = 183)
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Anticholinergic effects (dry mouth, constipation, disturbance in attention blurred vision, urinary retention)	5.4%	4.9%
Balance disorders/falls (fall gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Arthralgia	2.3%	0.5%

- **Drug Interactions**
  - Concomitant use of monamine oxidase inhibitors (MAOI) is not recommended, as this could result in increased synaptic levels of monoamine oxidase, which can lead to serotonin syndrome.
  - Concomitant use with strong Cytochrome P450 (CYP) 3A4 inducers is also not recommended, as this could lead to decreased levels of valbenazine.
  - Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ingrezza (valbenazine)	Capsules	Oral	Daily	A lower dose should be administered in patients with moderate to severe hepatic failure

See the current prescribing information for full details

CONCLUSION

- The approval of valbenazine has provided the first FDA-approved treatment option for TD.
  - Valbenazine was granted priority review, accelerated approval, breakthrough therapy designation by the FDA.
- Prior to the approval of valbenazine, tetrabenazine, a VMAT2 inhibitor FDA-approved for Huntington's chorea, was used off-label to treat TD.
- The first step in the treatment of TD is to discontinue the offending agent by slow taper. The patient can switch to quetiapine and clozapine (SGAs of choice) if needed.
- The KINECT 3 trial demonstrated a significant reduction in AIMS dyskinesia score at -3.2 in the valbenazine 80 mg/day group and -1.9 in the valbenazine 40 mg/day group, however, there were no significant improvements in the CGI-TD score or patient-perceived improvement in function or QOL.
- The extension trial continued to demonstrate reductions in AIMS dyskinesia score at week 48, from baseline in both dosage groups.
- The 2013 American Academy of Neurology (AAN) evidence-based guidelines for the treatment of tardive syndromes (TS) did not make any level A (highest level of evidence for efficacy) treatment recommendations. Gingko biloba and clonazepam were recommended in the level B category, amantadine and tetrabenazine were recommended in the level

C category, and a large number of other agents/therapies were recommended in the level U (insufficient evidence) category.

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Publication Date: September 8, 2017

Nevada Medicaid
Xadago (safinamide)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Xadago	safinamide

Indication

Parkinson's disease	Indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes. Limitations of use: Xadago has not been shown to be effective as monotherapy for the treatment of Parkinson's disease.

CRITERIA FOR COVERAGE/NONCOVERAGE

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

1. Diagnosis of Parkinson's Disease
   AND
2. Levodopa and/or other dopaminergic treatments will be continued
   AND
3. Patient reports greater than 1.5 hours per day of "Off" periods

Initial Authorization: 12 months

Reauthorization Duration: 12 Months

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

1. Documentation of positive clinical response to Xadago therapy
   AND
2. Levodopa and/or other dopaminergic treatments will be continued

Non-Preferred Anti-Parkinson Agents

Override(s)	Approval Duration
Prior Authorization	1 year

Medications	Comments	Quantity Limit
amantadine tablets, capsule, oral solution benztropine tablets bromocriptine 2.5mg, 5mg tablets carbidopa/levodopa tablets all strengths carbidopa/levodopa/entacapone tablets all strengths pramipexole tablets all strengths ropinirole tablets all strengths selegiline tablets all strengths trihexyphenidyl elixir, tablets all strengths	Preferred	May be subject to quantity limit
pramipexole ER tablets all strengths ropinirole ER tablets all strengths Apokyn (apomorphine) cartridges all strengths Azilect (rasagiline mesylate) tablets all strengths Rytary (carbidopa/levodopa extended release) capsules all strengths Xadago (safinamide) tablets all strengths Zelapar (selegiline) ODT all strengths all MSB antiparksion agents	Non-Preferred	

APPROVAL CRITERIA

Requests for non-preferred anti-Parkinson agents may be approved if the following criteria are met:

I. Individual has had a previous trial (medication samples/coupons/discount cards are excluded from consideration as a trial) and inadequate response or intolerance to one preferred generic agent.

Preferred generic agents: amantadine, benztropine, bromocriptine, carbidopa/levodopa, carbidopa/levodopa/entacapone, pramipexole, ropinirole, selegiline, trihexyphenidyl.

Non-Preferred agents: pramipexole ER, ropinirole ER, Apokyn (apomorphine), Azilect (rasagiline mesylate), Rytary (carbidopa/levodopa extended release), Xadago (safinamide) Zelapar (selegiline) ODT, all MSB antiparksion agents.

II. Requests for Apokyn (apomorphine) may be approved if the following criteria are met, in addition to I. above:

A. Individual has a diagnosis of advanced Parkinson's disease; **AND**

B. The individual is using Apokyn (apomorphine) for the acute, intermittent treatment of hypomobility "off" episodes**.

Apokyn (apomorphine) **may not** be approved for:

I. Requests for Erectile Dysfunction (ED).

****Note**: Off episodes refer to the "end-of-dose wearing off" and unpredictable "on/off" episodes.

Note: At least one agent from each of the following categories must be included as a preferred agent:

- Carbidopa/dopa combination: carbidopa/levodopa agents
- Dopamine agonist: bromocriptine, pramipexole, ropinirole
- Anticholinergic: benztropine, trihexphenidyl
- MAOB: selegiline

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

Key References:

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

New Drug Overview
Xadago (safinamide)

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other nonmotor manifestations. The disease is diagnosed in an estimated 50,000 people each year in the United States, with about half a million people living with the disease *(Chou 2017, Jankovic 2017, National Institute of Health [NIH] 2010).*
- The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and the preferred choice as symptoms, especially bradykinesia, become troublesome; however, levodopa-induced complications (eg, motor fluctuations ["wearing off" phenomenon], dyskinesia, dystonia) develop within several years of starting levodopa in a substantial number of patients *(Tarsy 2017b).*
  - Levodopa complications may be managed through levodopa dose adjustments or the addition of a dopamine agonist (DA), a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO)-B inhibitor *(Tarsy 2017a)*.
- There are currently 3 unique MAO-B inhibitors that are Food and Drug Administration (FDA)-approved for use in PD. Selegiline was FDA-approved in 1989 and is indicated as an adjunct in the management of patients with PD being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. It carries the limitation that there is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy. An additional selegiline orally-disintegrating tablet (ODT) shares the same indication. Rasagiline was FDA-approved in 2006 and is indicated for the treatment of PD as monotherapy, as an adjunct without levodopa, or as an adjunct to levodopa. The newest molecular entity, safinamide, was FDA-approved in March 2017 as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes with the limitation that it has not been shown to be effective as monotherapy for the treatment of PD *(FDA Web site).*
- Safinamide is an α-aminoamide with both dopaminergic and nondopaminergic actions, including inhibition of MAO-B, sodium channel blockage, and modulation of stimulated release of glutamate. The clinical implications of its actions beyond MAO-B inhibition are currently unclear *(Borgohain et al 2014a).*
- Medispan class: Antiparkinson Agents; Antiparkinson Monoamine Oxidase Inhibitors

INDICATIONS

- Safinamide is indicated as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes *(Xadago prescribing information 2017).*
  Limitations of Use: Safinamide has not been shown to be effective as monotherapy for the treatment of PD.

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

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of safinamide as levodopa add-on therapy was demonstrated in two 24-week, double-blind (DB), placebo-controlled (PC), randomized controlled trials (RCTs) and an 18-month extension study. Patients with mid-to-late stage PD experiencing motor fluctuations while receiving levodopa and other dopaminergic treatments were randomized to receive safinamide or placebo in combination with their baseline treatment regimen. Study 016 examined both safinamide 50 mg and safinamide 100 mg once daily, while the SETTLE study initiated patients at safinamide 50 mg and titrated to a target dose of 100 mg. The primary efficacy endpoint in both Study 016 and SETTLE was change in mean daily total "on" time with no or nontroublesome dyskinesia from baseline as recorded in patient diaries. Patients treated with safinamide had a statistically significant increase in "on" time in both studies (see Table 1). Treatment-emergent adverse event (TEAE) rates were similar between safinamide and placebo groups, although dyskinesia was reported more frequently in safinamide-treated patients *(Borgohain et al 2014a, Schapira et al 2017)*.
  - The 18-month extension study (Study 018) enrolled patients from Study 016 and maintained blinding. The primary endpoint was mean change from baseline (at Study 016 start) to study completion of the total score of the Dyskinesia

Rating Scale (DRS) during "on" time. There were no statistically significant changes in DRS score in the safinamide groups vs. placebo, but the authors attributed this to the low average DRS scores at baseline. The secondary endpoint of mean "on" time without troublesome dyskinesia showed a continued trend as demonstrated in the original 24-week Study 016 (see Table 1) *(Borgohain et al 2014b)*.

Table 1. Mean daily total "on" time with no or nontroublesome dyskinesia

	Baseline* (hr)	Δ from baseline* (hr)	LS difference vs. placebo (95% CI)	p-value vs. placebo
Study 016				
Placebo (n = 222)	9.3	0.8	--	--
Safinamide 50 mg (n = 223)	9.4	1.23	0.51 (0.07 to 0.94)	0.0223
Safinamide 100 mg (n = 224)	9.6	1.28	0.55 (0.12 to 0.99)	0.0130
SETTLE				
Placebo (n = 275)	9.06	0.57	--	--
Safinamide 100 mg (n = 274)	9.30	1.42	0.96 (0.56 to 1.37)	< 0.001
Study 018 18-month extension**				
Placebo (n = 222)	9.301	0.34	--	--
Safinamide 50 mg (n = 223)	9.373	1.01	0.67 (0.23 to 1.11)	0.0031
Safinamide 100 mg (n = 224)	9.520	1.18	0.83 (0.39 to 1.27)	0.0002

Abbreviations: CI = confidence interval, LS = least squares, Δ = change
* Least squares mean
** Mean daily total "on" time with no or nontroublesome dyskinesia was evaluated as a secondary endpoint; intention-to-treat (ITT) population from Study 016 used

- Safinamide has been studied in patients with early PD on DA therapy without motor fluctuations; however, the studies failed to show statistical superiority of safinamide over placebo in the primary efficacy endpoint of improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores from baseline to end of study. Therefore, safinamide was not given an indication for use in early PD *(FDA Medical Review 2017, Stocchi et al 2012).*

CLINICAL GUIDELINES

- Current PD guidelines from the American Academy of Neurology (AAN), the European Federation of Neurological Societies (EFNS) and the Movement Disorders Society (MDS) recommend the addition of either a COMT inhibitor or MAO-B inhibitor to therapy in patients experiencing levodopa-induced motor fluctuations; no recommendations can be made as to which treatment should be chosen first. On average, both classes of medication reduce daily "off" time by 1 to 1.5 hours. The guidelines have not yet been updated to address safinamide *(Fox et al 2011, Oertel 2011, Pahwa et al 2006).*

SAFETY SUMMARY

- Contraindications:
  - Concomitant use of the following drugs:
    - Other MAO inhibitors or other drugs that are potent inhibitors of MAO (eg, linezolid)
    - Opioid drugs (eg, tramadol, meperidine and related derivatives)
    - Selective norepinephrine reuptake inhibitors (SNRIs)
    - Tri-or tetra-cyclic or triazolopyridine antidepressants (TCAs)
    - Cyclobenzaprine
    - Methylphenidate, amphetamine, and their derivatives
    - St. John's wort
    - Dextromethorphan
  - Severe hepatic impairment (Child-Pugh C)
- Warnings and Precautions:
  - May cause or exacerbate hypertension
  - May cause serotonin syndrome when used with MAO inhibitors, antidepressants, or opioid drugs
  - May cause falling asleep during activities of daily living
  - May cause or exacerbate dyskinesia; levodopa dose reduction should be considered

- May cause hallucinations and psychotic behavior
- May cause problems with impulse control/compulsive behaviors
- May cause withdrawal-emergent hyperpyrexia and confusion

- Adverse Events (AEs):
  - The most common AEs (incidence on safinamide 100 mg/day at least 2% greater than placebo) were dyskinesia, fall, nausea, and insomnia.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xadago (safinamide)	50 mg,100 mg tablets	Oral	50 mg daily for 2 weeks, then increased to 100 mg daily based on individual need and tolerability	Dose adjustment is necessary in moderate hepatic impairment (Child-Pugh B). Safinamide is contraindicated in severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Safinamide, a novel α-aminoamide with similar action to the MAO-B inhibitors rasagiline and selegiline, has demonstrated safety and efficacy as adjunct treatment to levodopa in patients with mid-to-late stage PD experiencing motor fluctuations.
  - Safinamide, unlike rasagiline, is not indicated for use as monotherapy and has not demonstrated clinical efficacy in patients with early PD.
- Contraindications of safinamide include concomitant use of opioids, SNRIs, TCAs, amphetamines, and dextromethorphan, as well as severe hepatic impairment; safinamide may cause or exacerbate hypertension, somnolence, hallucinations, compulsive behavior, and dyskinesias. The most common AEs experienced by safinamide-treated patients were dyskinesia, fall, nausea, and insomnia.
- Current guidelines recommend a COMT inhibitor or MAO-B inhibitor as adjunct therapy in patients experiencing levodopa-induced motor fluctuations; no recommendations can be made as to which treatment should be chosen first. The guidelines have not been updated to include safinamide *(Fox et al 2011, Oertel 2011, Pahwa et al 2006).*

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Publication Date: September 13, 2017

Nevada Medicaid
Emflaza (deflazacort)
Pharmacy Coverage Guideline

Brand Name	Generic Name
Emflaza	deflazacort

Indication

Duchenne muscular dystrophy (DMD)	Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.

CRITERIA FOR COVERAGE/NONCOVERAGE

Emflaza (deflazacort) 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. Patient has received genetic testing for a mutation of the dystrophin gene
   AND
3. One of the following:
   3.1. Documentation of a confirmed mutation of the dystrophin gene
   OR
   3.2. Muscle biopsy confirmed an absence of dystrophin protein
   AND
4. Patient is 5 years of age or older
   AND
5. Prescribed by or in consultation with a neurologist who has experience treating children
   AND
6. Patient has had a trial and failure or intolerance to prednisone given at a dose of 0.75 mg/kg/day or 10 mg/kg/weekend
   AND
7. Dose will not exceed 0.9 milligrams per kilogram of body weight once daily

Initial Authorization: 12 months

Reauthorization Duration: 12 Months

Nevada Medicaid
Emflaza (deflazacort)
Pharmacy Coverage Guideline

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

1. Patient has experienced a benefit from therapy (e.g., improvement or preservation of muscle strength
   AND
2. Dose will not exceed 0.9 milligrams per kilogram of body weight once daily

Emflaza (deflazacort)

Override(s)	Approval Duration
Prior Authorization	Initial Approval Duration: 6 months Subsequent Approval Duration: 12 months

Medications
Emflaza (deflazacort)

APPROVAL CRITERIA

Requests for initial therapy with Emflaza (deflazacort) may be approved when the following criteria are met:

I. Individual is 5 years of age or older; **AND**
II. Individual has a diagnosis of Duchenne Muscular Dystrophy (DMD); **AND**
III. Individual has had a 6 month trial of oral prednisone (AAN 2016, DrugPoints B, IIa); **AND**
IV. One of the following:
    A. Documentation has been provided regarding the presence of clinically significant neuropsychiatric side effects while on prednisone (such as but not limited to aggression); **AND**
    B. Neuropsychiatric side effects are likely to be the direct result of prednisone use;

    OR
    C. Documentation has been provided for excessive weight-gain with prednisone (increase of >0.5 Z score from prior growth curve expectations [American Academy of Pediatrics/CDC Weight for Age Growth Chart*; Z-score data files, CDC, Weight-for-age charts, 2 to 20 years, selected weight z-scores in kilograms, by sex and age**]); **AND**
    D. Weight gain is likely to be a direct result of prednisone use.

Requests for continuation of therapy with Emflaza (deflazacort) may be approved when one of the following criteria are met:

I. When approved due to excessive weight gain with prednisone, individual has experienced a return to baseline growth curve expectations or remained on the same growth curve that was in effect when Emflaza (deflazacort) was initiated (American Academy of Pediatrics/CDC Weight for Age Growth Chart*; Z-score data files, CDC, Weight-for-age charts, 2 to 20 years, selected weight z-scores in kilograms, by sex and age**); **OR**
II. When approved due to neuropsychiatric side effects while on prednisone, individual has shown improvement in neuropsychiatric symptoms.

* American Academy of Pediatrics/CDC Weight for Age Growth Chart: https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf

** Z-score data files, CDC, Weight-for-age charts, 2 to 20 years, selected weight z-scores in kilograms, by sex and age: https://www.cdc.gov/growthcharts/data/zscore/zwtage.xls; this file contains the z-score values for the z-scores of -2, -1.5, -1, -0.5, 0, 0.5, 1, 1.5 and 2 by sex (1 = male; 2 = female) and half month of age. For example, 1.5 months represents 1.25-1.75 months. Information needed: age in months, weight in kilograms, and gender.

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

Key References:

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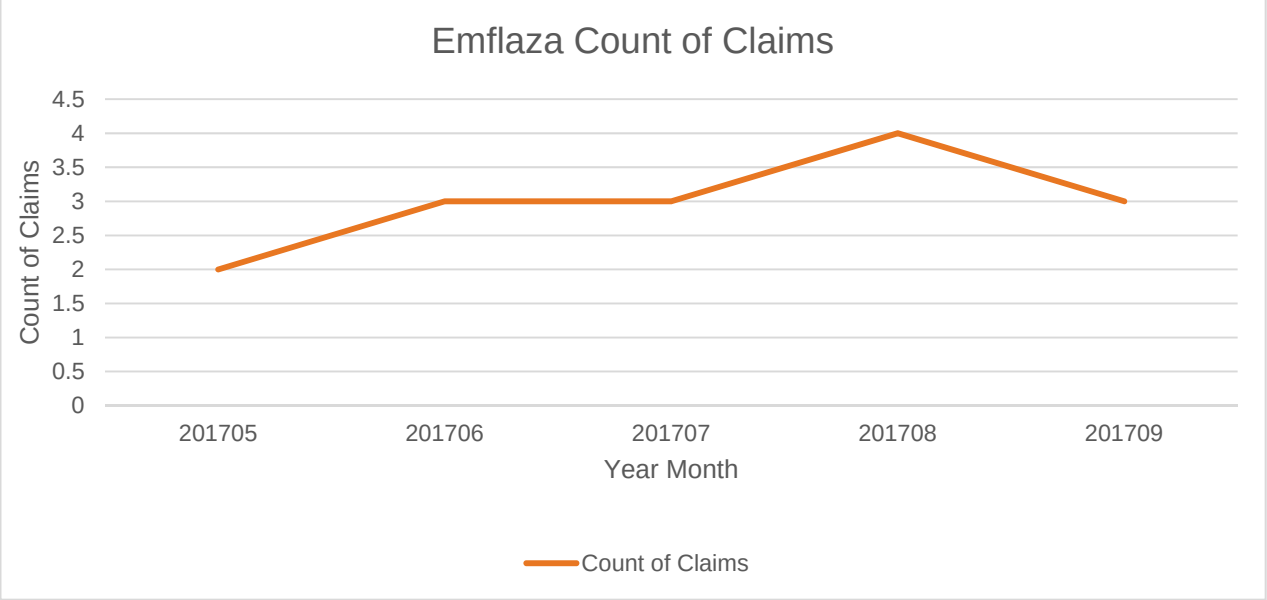
Emflaza Utilization

September 1, 2016 - August 31, 2017

YearMonthFilled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201705	EMFLAZA	SUS 22.75/ML	2	2	51	78	$ 17,258.34
201706	EMFLAZA	SUS 22.75/ML	3	3	81	117	$ 25,887.51
201707	EMFLAZA	SUS 22.75/ML	3	3	81	117	$ 25,887.51
201708	EMFLAZA	SUS 22.75/ML	3	4	108	169	$ 37,389.68
201709	EMFLAZA	SUS 22.75/ML	3	3	81	117	$ 25,887.51



New Drug Overview
Emflaza (deflazacort)

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 2017)*. 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 2017)*.
  - 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 2017)*. Absence of dystrophin leads to muscle damage, with replacement by fibrotic and adipose tissue *(FDA Summary Review 2017)*.
  - 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 *(Emflaza Formulary Submission Dossier 2017, FDA Summary Review 2017, 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 2017, MDA Web site)*.
- DMD occurs in approximately 1 out of every 3600 to 6000 male births worldwide; female-manifesting carriers are rarer, but can present with a range of symptoms that vary in their severities *(FDA Medical Review 2017)*.
- Treatment for DMD has been largely supportive and utilizes corticosteroids such as prednisone, which are widely believed to delay the loss of ambulation (LoA) and respiratory decline by several years *(FDA Summary Review 2017, Gloss et al 2016, UpToDate 2017)*. Outside of the United States, the glucocorticoid, deflazacort, has been approved for various auto-immune disorders and hypersensitivity reactions for over 30 years; while both prednisone and deflazacort are considered standards of care for DMD, deflazacort has not previously been approved in any country for the treatment of DMD *(FDA Summary Review 2017)*.
- Following a priority review by the FDA, Emflaza (deflazacort) tablets and oral suspension were approved on February 9, 2017 for the treatment of DMD in patients ≥ 5 years of age *(FDA Web site)*. Deflazacort was additionally granted orphan drug and fast track designations.
- Deflazacort is a corticosteroid prodrug whose active metabolite (21-desDFZ) binds glucocorticoid receptors to exert immunosuppressive and anti-inflammatory effects. The precise mechanism by which deflazacort exerts its therapeutic effects in patients with DMD is unknown.
- Medispan Class: Corticosteroids; Glucocorticosteroids; Deflazacort

INDICATIONS

- Deflazacort is indicated for the treatment of DMD in patients 5 years of age and older *(Emflaza prescribing information 2017)*.

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

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of deflazacort were demonstrated in 2 pivotal, double-blind (DB), placebo-controlled (PC), multi-center, randomized controlled trials (RCTs) that were conducted in the 1980s and 1990s *(Angelini et al 1994, Emflaza Formulary Submission Dossier 2017, Griggs et al 2016)*.
- In Study 1 (MP-104-NM-001), 196 males diagnosed with DMD and between the ages of 5 and 15 years were randomized to receive treatment with deflazacort 0.9 mg/kg/day (n = 51), deflazacort 1.2 mg/kg/day (n = 49), prednisone 0.75 mg/kg/day (n = 46), or placebo (n = 50) for 12 weeks (Phase 1) *(Griggs et al 2016)*. Randomization was stratified according to ambulatory vs. non-ambulatory status. At the conclusion of Phase 1, patients treated with placebo were re-randomized to 1 of the 3 active treatment groups for the remaining duration of the 52-week study (ie, Phase 2). Since

the PC phase was limited to 12 weeks, interpretation of the results reported overall from BL to Week 52 and from Weeks 12 to 52 were limited.

Muscle strength scores (intention-to-treat [ITT] population)

- For the primary efficacy endpoint, all treatment groups demonstrated statistically significant improvements in muscle strength scores vs. placebo from baseline (BL) to Week 12. The least squares (LS) mean change from BL (95% confidence interval [CI]) for each treatment group and the p-values for the between-treatment difference in change from BL were as follows:
  - Deflazacort 0.9 mg/kg/day (n = 48): 0.15 (0.01, 0.28); p = 0.0173
  - Deflazacort 1.2 mg/kg/day (n = 46): 0.26 (0.12, 0.40); p = 0.0003
  - Prednisone 0.75 mg/kg/day (n = 45): 0.27 (0.13, 0.41); p = 0.0002
  - Placebo (n = 50): -0.10 (-0.23, 0.03)
- During Phase 2, only the deflazacort 0.9 mg/kg/day group maintained a statistically significant improvement in muscle strength, while the prednisone group trended in the opposite direction.
  - Deflazacort 0.9 mg/kg/day (n = 41): 0.17 (0.03, 0.31); p = 0.0044
  - Deflazacort 1.2 mg/kg/day (n = 34): 0.04 (-0.11, 0.19); p = 0.1788
  - Prednisone 0.75 mg/kg/day (n = 37): -0.12 (-0.26, 0.03)
- Overall, both deflazacort groups demonstrated greater improvements from BL to Week 52 in muscle strength scores vs. the prednisone group.
  - Deflazacort 0.9 mg/kg/day (n = 41): 0.39 (0.25, 0.54)
  - Deflazacort 1.2 mg/kg/day (n = 34): 0.38 (0.23, 0.54)
  - Prednisone 0.75 mg/kg/day (n = 37): 0.23 (0.07, 0.38)

Weight gain comparisons (ITT population)

- During the first 12 weeks of treatment, a statistically significant weight gain was demonstrated only in the prednisone group vs. placebo. The LS mean change from BL (95% CI) for each treatment group (kg) and the p-values for the between-treatment difference in change from BL to Week 12 were as follows:
  - Deflazacort 0.9 mg/kg/day (n = 48): 1.72 (0.51, 2.93); p = 0.8848
  - Deflazacort 1.2 mg/kg/day (n = 47): 1.71 (0.47, 2.94); p = 0.8921
  - Prednisone 0.75 mg/kg/day (n = 45): 3.23 (1.94, 4.52); p = 0.0459
  - Placebo (n = 50): 1.23 (0.00, 2.46)
- From Weeks 12 to 52, the deflazacort groups showed significantly smaller increases in weight vs. prednisone.
  - Deflazacort 0.9 mg/kg/day (n = 40): 3.64 (2.90, 4.38); p = 0.0003
  - Deflazacort 1.2 mg/kg/day (n = 35): 4.16 (3.37, 4.94); p = 0.0130
  - Prednisone 0.75 mg/kg/day (n = 37): 5.57 (4.76, 6.37)

- In Study 2 (MP-104-NM-002), 29 ambulatory males diagnosed with DMD and between the ages of 5 and 11 years were randomized 2:1 to receive treatment with deflazacort 2 mg/kg every 2 days (n = 18) or placebo (n = 11) for 2 years *(Angelini et al 1994)*. The primary endpoint was the change in muscle strength score from BL to Year 2 or the LoA, whichever occurred first.
  - The study failed to yield statistically significant results for the primary endpoint at the pre-determined 2-year assessment time, with a between-treatment difference in change from BL between the placebo and deflazacort groups of 5.2 (95% CI: -3.16 to 13.56; p = 0.2107).
- A 2016 Cochrane review of corticosteroids for the treatment of DMD concluded the following: *(Matthews et al 2016)*
  - RCTs provide moderate quality evidence that treatment with corticosteroids in patients with DMD vs. placebo improved muscle strength and function, including respiratory muscle strength and function, for 6 months. There was evidence of a continuing benefit on muscle strength and function at 1 year, but little RCT evidence concerning the longer-term effects of corticosteroids vs. placebo.
  - Not enough data were available to adequately compare the efficacy of prednisone and deflazacort, although there is very low quality data favoring deflazacort for less weight gain.

CLINICAL GUIDELINES

- DMD Care Considerations Working Group: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management *(Bushby et al 2010)*
  - Glucocorticoids are the only medications currently available that slow 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 effects (AEs). 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 AEs) 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.
  - Prednisone (prednisolone) and deflazacort are believed to work similarly and neither one has a clearly superior effect on altering the decline in motor, respiratory, or cardiac function in DMD. The choice of which glucocorticoid to use depends on legal availability, cost, formulation, and perceived AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Where available, deflazacort is more expensive and comes in fewer tablet sizes. Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.

- 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 LoA 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

- Contraindications
  - Hypersensitivity to deflazacort or to any components of the formulation.
    - Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.
- Warnings and precautions of deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi's sarcoma, risk of serious adverse events (SAEs) in infants because of benzyl alcohol preservative, thromboembolic events, and anaphylaxis.
- The most common AEs (≥ 10% and greater than placebo) with deflazacort use were Cushingoid appearance (33% with deflazacort vs. 12% with placebo), increased weight (20% vs. 6%), increased appetite (14% vs. 2%), upper respiratory

tract infection (12% vs. 10%), cough (12% vs. 6%), pollakiuria (12% vs. 2%), hirsutism (10% vs. 2%), central obesity (10% vs. 4%), and nasopharyngitis (10% vs. 6%).
  - In Study 1, at the Week 52 final assessment, the LS mean (95% CI) differences from BL in weight were 5.05 (4.08, 6.01; p < 0.0001 vs. prednisone), 5.60 (4.59, 6.61; p < 0.0001 vs. prednisone), and 8.45 (7.41, 9.49) for deflazacort 0.9 mg, deflazacort 1.2 mg, and prednisone, respectively.

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Emflaza (deflazacort)	Tablets, suspension	Oral	Daily	May be taken with or without food. No dosage adjustment in renal impairment. No dosage adjustment in mild and moderate hepatic impairment; not studied in severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Emflaza (deflazacort) tablets and oral suspension are indicated for the treatment of DMD in patients ≥ 5 years of age. Deflazacort is a corticosteroid prodrug whose active metabolite binds glucocorticoid receptors to exert immunosuppressive and anti-inflammatory effects.
- The efficacy and safety of deflazacort were demonstrated in 2 DB, PC, MC, RCTs conducted in the 1980s-90s.
  - In Study 1 (N = 196), all of the treatment groups (deflazacort 0.9 mg/kg/day or 1.2 mg/kg/day, prednisone 0.75 mg/kg/day) demonstrated statistically significant improvements in muscle strength vs. placebo from BL to Week 12. There were significant increases in weight with prednisone vs. placebo, but no significant differences between the deflazacort groups vs. placebo at Week 12 *(Griggs et al 2016)*.
  - Study 2 (N = 29) failed to yield statistically significant results for the change in muscle strength from BL to Year 2 in patients treated with an alternate regimen of deflazacort (2 mg/kg every other day) or placebo *(Angelini et al 1994)*.
- Available DMD treatment guidelines recommend the use of glucocorticoids, which are the only medications currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function *(Bushby et al 2010, Gloss et al 2016, UpToDate 2017)*.
  - Prednisone (prednisolone) and deflazacort are believed to work similarly and neither one has a clearly superior effect on altering the decline in motor, respiratory, or cardiac function in DMD.
  - The choice of which glucocorticoid to use depends on cost, formulation, and perceived AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Deflazacort is more expensive and comes in fewer tablet sizes.
  - Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.
- On the basis of extensive clinical experience, head-to-head comparisons, and available guidelines for the treatment of patients with DMD, deflazacort and prednisone appear to have similar efficacy. The selection of one agent over the other appears to rest primarily on the differences in their respective AE profiles and namely, on the limited evidence suggesting that deflazacort may be associated with a lesser increase in body weight vs. prednisone; however, this effect on weight gain may not always be undesirable among more fragile, undernourished patients with DMD.

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Publication Date: September 07, 2017

P. Monoclonal Antibody Agents

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

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

1. Coverage and Limitations

a. Xolair® (Omalizumab)

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

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

a. The recipient must be ~~12~~6 years of age or older; and

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

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

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

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

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

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

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

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

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

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

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

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

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

   e. The requested dose is:

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

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

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

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

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

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

      c. The recipient must be an appropriate age:

         1. Mepolizumab: 12 years of age or older

         2. Reslizumab: 18 years of age or older

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

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

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

g. The requested dose is appropriate:

1. Mepolizumab: 100 mg subcutaneously every four weeks.

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

2. Prior Authorization Guidelines

a. Prior Authorization approval will be for 12 months.

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

Table 1: Dosing for Xolair® (omalizumab)*

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

Xolair (omalizumab)

DRUG.00024

Override(s)	Approval Duration
Prior Authorization	1 year

Medications	Quantity Limit
Xolair (omalizumab)	N/A

APPROVAL CRITERIA

I. Individual must meet **ALL** of the following criteria:

- **a.** Diagnosis of Moderate Persistent to Severe Persistent Asthma; **AND**
- **b.** 6 years of age or older; **AND**
- **c.** Symptoms are inadequately controlled after a minimum of 3 months of combination controller therapy (medium to high dose inhaled corticosteroids plus long acting beta-2 agonists or leukotriene receptor antagonists), or cannot tolerate these medications; **AND**
- **d.** Shows a positive skin test or in vitro reactivity to a perennial aeroallergen; **AND**
- **e.** A forced expiratory volume in one second (FEV1) less than 80% predicted; **AND**
- **f.** A serum Immunoglobulin E (IgE) level is equal to or greater than 30 IU/ml.

II. Continued treatment with Xolair (omalizumab) beyond 12 months may be approved when the following criteria are met:

- **a.** Criteria for Xolair (omalizumab) therapy, as set forth above in section A, had been met at the time of initiation of therapy; **AND**
- **b.** Treatment with Xolair (omalizumab) has resulted in clinical improvement as documented by ONE OR MORE of the following:
  - **i.** Decreased utilization of rescue medications; **or**
  - **ii.** Decreased frequency of exacerbations (defined as worsening of asthma that requires increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); **or**
  - **iii.** Increase in percent predicted FEV1 from pretreatment baseline; **or**
  - **iv.** Reduction in reported asthma-related symptoms, such as, but not limited to, wheezing, shortness of breath, coughing, fatigue, sleep disturbance, or asthmatic symptoms upon awakening.

III. Xolair (omalizumab) may be approved for the treatment of chronic idiopathic urticaria (CIU) as fourth-line* therapy when **ALL** of the following criteria are met:

- **a.** 12 years of age or older; **AND**

b. When symptoms of CIU are refractory to prior treatment with antihistamines at maximal FDA-approved dosages, according to the step-care protocols for first-, second-, and third-lines of therapy, (which includes H_1 antihistamines, H_2 antihistamines and leukotriene receptor antagonists).

*__Note__: Fourth-line therapy is defined by the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology as treatment given when initial first-line therapy and subsequent therapies (second- and third-line therapy) have not been effective (Bernstein, 2014).

Xolair (omalizumab) is considered investigational and may **NOT** be approved for all other indications other than moderate to severe persistent asthma and refractory chronic idiopathic urticaria.

Note: Xolair (omalizumab) has a black box warning for anaphylaxis after administration and presents as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Anaphylaxis may occur after the first dose or beyond 1 year after beginning regularly administered treatment. Monitor individuals closely after administration and with health care providers available to manage life-threatening anaphylactic reactions. Individuals receiving treatment should be instructed on signs and symptoms of anaphylaxis and measures to take if occur.

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

Key References:

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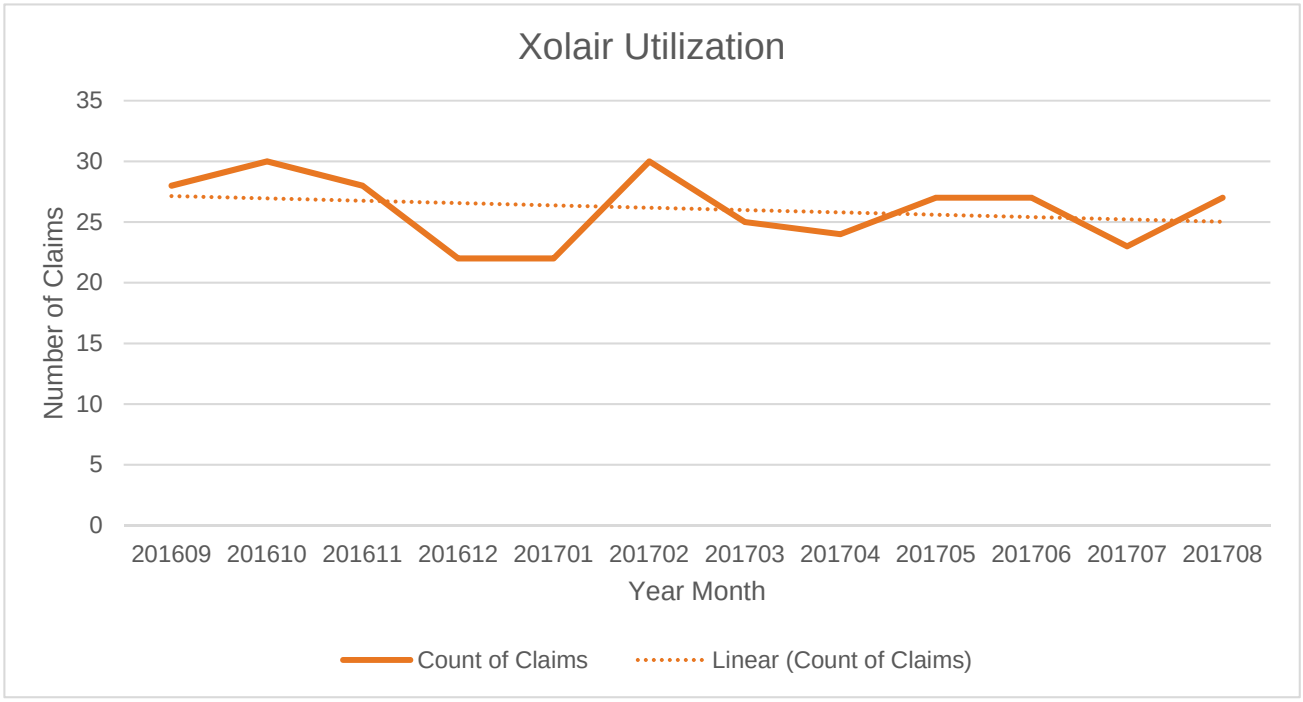
Xolair Utilization

September 1, 2016 - August 31, 2017

YearMonthFilled	Drug Name		Count of Members	Count of Claims	Sum of Days	Sum of Qty	Sum of Amt Paid
201609	XOLAIR	SOL 150MG	25	28	716	69	$ 62,831.82
201610	XOLAIR	SOL 150MG	29	30	745	82.5	$ 77,109.09
201611	XOLAIR	SOL 150MG	25	28	702	75	$ 71,138.12
201612	XOLAIR	SOL 150MG	21	22	602	61	$ 60,196.50
201701	XOLAIR	SOL 150MG	21	22	575	52.2	$ 50,424.73
201702	XOLAIR	SOL 150MG	26	30	785	69.5	$ 68,306.47
201703	XOLAIR	SOL 150MG	23	25	659	63.5	$ 58,825.55
201704	XOLAIR	SOL 150MG	22	24	617	54.5	$ 51,359.16
201705	XOLAIR	SOL 150MG	24	27	646	72	$ 73,190.54
201706	XOLAIR	SOL 150MG	22	27	605	66	$ 67,045.43
201707	XOLAIR	SOL 150MG	19	23	454	66	$ 60,176.33
201708	XOLAIR	SOL 150MG	26	27	648	67	$ 66,013.27



INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*NHLBI 2014*).
- The goal of asthma management – asthma control – can be described in the following domains (*NHLBI 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (e.g., omalizumab)
    - Leukotriene modulators
    - Long-acting β-agonists (LABAs)
    - Methylxanthines (i.e., theophylline)
  - Quick-relief medications include:
    - Anticholinergics (i.e., ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly-controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*).
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2016*).
- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 1 to 5 years (*Khan 2016, Maurer et al 2013*).

- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2016, Maurer et al 2013*).
- This monograph describes the use of Cinqair (reslizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair and Nucala are fully humanized monoclonal antibody interleukin-5 (IL-5) antagonists, each approved as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has shown to improve symptoms in patients with CIU.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

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

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

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

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

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

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

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

CLINICAL EFFICACY SUMMARY

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a step-wise manner.
  - In the 28-week study by Busse et al (N=525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; P=0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; P<0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; P=0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; P=0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N=546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; P<0.001) and steroid reduction phases (0.36 vs 0.75; P<0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N=246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; P=0.003). The percentages of patients with at least 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients ages 6 to <12 with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; relative risk (RR), 0.69; P=0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (P<0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Solèr et al 2001, Holgate et al 2004*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (i.e., all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (P=0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation

(odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies, 3,261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies, 1,889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies, 1,824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).

- A systematic review of 8 randomized, placebo-controlled trials (N=3,429) published in 2010 evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (RR, 1.8; 95% CI, 1.42 to 2.28; P=0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; P=0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; P=0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2010*).
- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly-starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly-starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly-starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients was found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo (P≤0.001) (*Saini et al 2014*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1,312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared

with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group (P<0.00001) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*).

MEPOLIZUMAB

Asthma

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

at least 24 weeks. Four studies (N=1,388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (RR, 0.49; 95% CI, 0.30 to 0.80; P=0.004) and hospitalization/emergency room visit (RR, 0.49; 95% CI, 0.33 to 0.73; P<0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2016*).

RESLIZUMAB

Asthma

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

COMPARATIVE REVIEWS

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% credible interval [CrI], 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CrI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CrI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CrI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.

CLINICAL GUIDELINES

Asthma

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

Chronic Idiopathic Urticaria

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

SAFETY SUMMARY

Cinqair:

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

Nucala:

- Contraindication: History of hypersensitivity to Nucala or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.
  - Herpes zoster infections have occurred in patients receiving Nucala. In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with Nucala compared with none in patients treated with placebo.
- The most common adverse reactions (≥5%) include headache, injection site reaction, back pain, and fatigue.

Xolair:

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established.
Nucala (mepolizumab)	SC	Every 4 weeks	• Safety and efficacy in pediatric patients younger than 12 years have not been established.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 to 4 weeks CIU: Every 4 weeks	Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). • Safety and efficacy in pediatric patients with asthma below 6 years of age have not been

Drug	Route	Usual Recommended Frequency	Comments
			established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2017, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA-approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU generally recommend treatment with Xolair in patients that are inadequately controlled with a 4-fold dose of modern second generation antihistamines and, in some cases, a leukotriene receptor antagonist (*Bernstein et al 2014, Zuberbier et al 2013, Powell et al 2015*).
- Cinqair and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, with demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014*). Both provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy (*GINA 2017*).
- There are no head-to-head trials comparing Cinqair and Nucala. In addition, the patient populations evaluated in the Cinqair and Nucala pivotal trials differed. The inclusion criteria for the Nucala trials included current use of a high-dose ICS with another controller medication. Patients were also required to have a blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL at some time during the previous year. In contrast, the Cinqair trials required that patients be on at least a medium-dose ICS with or without another controller medication. Patients were also required to have a blood eosinophil count ≥400 cells/μL.
- Compared to Nucala, Cinqair does have several limitations, including: an indication for patients aged 18 years and older (12 years and older for Nucala), IV administration (SC for Nucala), and a boxed warning for anaphylaxis.

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Publication Date: June 28, 2017

Nevada Medicaid
Codeine and Tramadol Use in Children
Pharmacy Coverage Guideline

Brand Name	Generic Name
	Codeine Codeine/APAP
Ultram	Tramadol

Indication

Pain Management	Off-label for pediatric patients

CRITERIA FOR COVERAGE/NONCOVERAGE

Codeine and tramadol will be considered for coverage under the pharmacy benefit program when the following are met:

1. The patient is 12 years of age or older
   AND
2. The patient is not obese (BMI > 30 kg/m^2)
   AND
3. The patient does not have severe lung disease or obstructive sleep apnea
   AND
4. The patient is not undergoing tonsillectomy and/or adenoidectomy.
   AND
5. The lowest effective dose for the shortest period of time is being requested

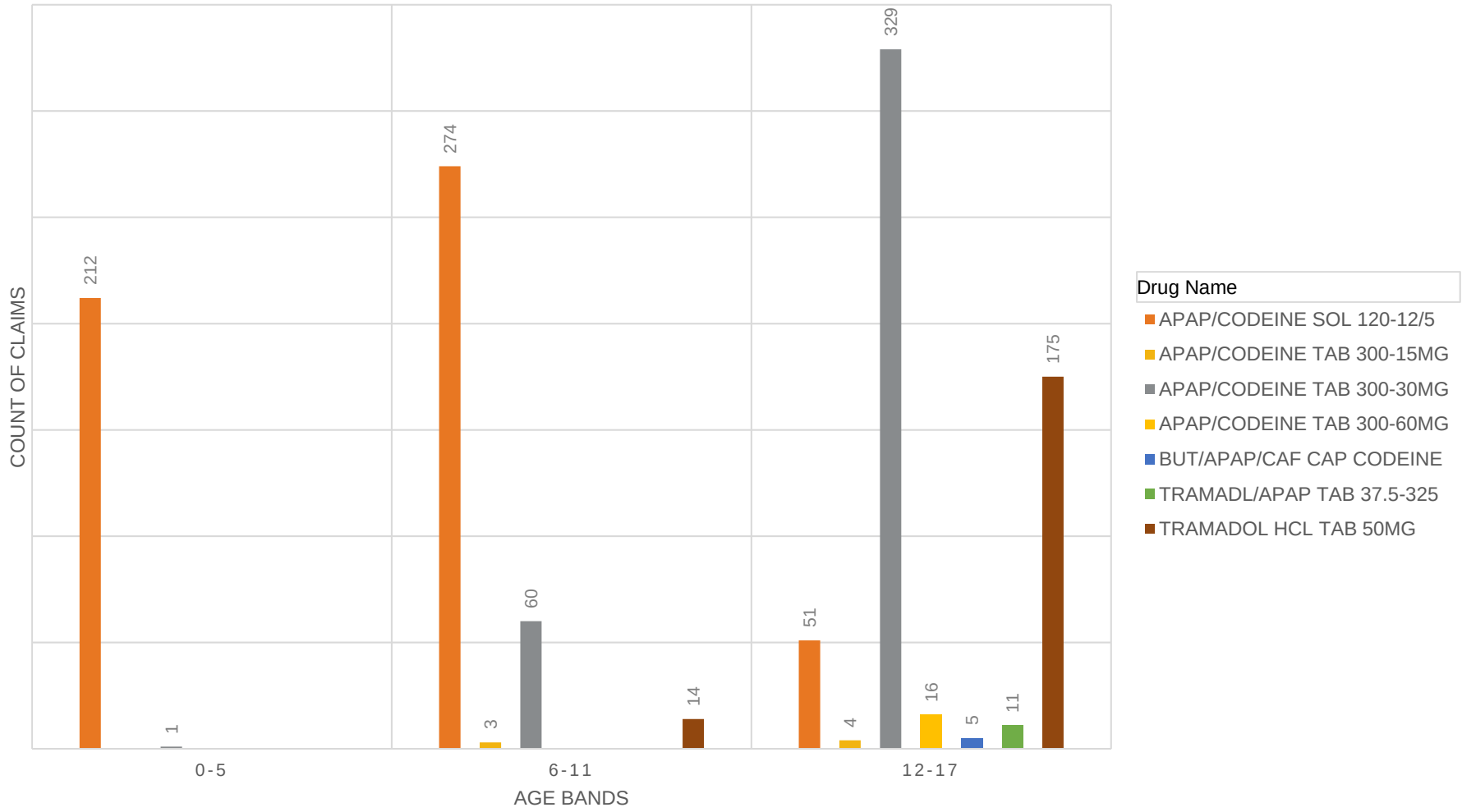
Authorization: 1 month

Note: Requests for patients under 12 years of age will not be approved. Recipients over 18 years of age are exempt from this policy.

YearMonthFilled

Sum of Count of Claims

CODEINE/TRAMADOL UTILIZATION IN CHILDREN
OCT 1, 2016 - SEPT 30, 2017

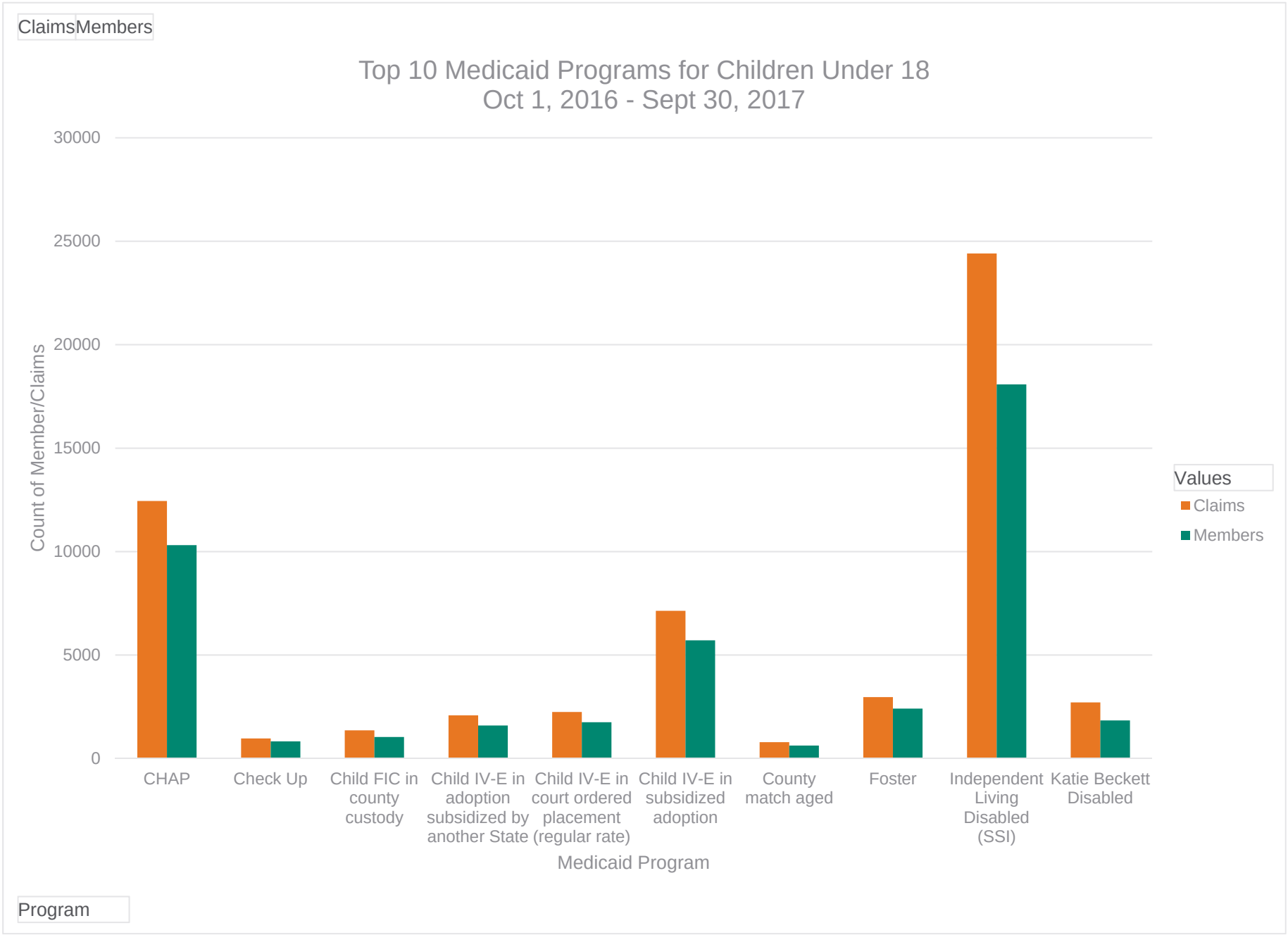


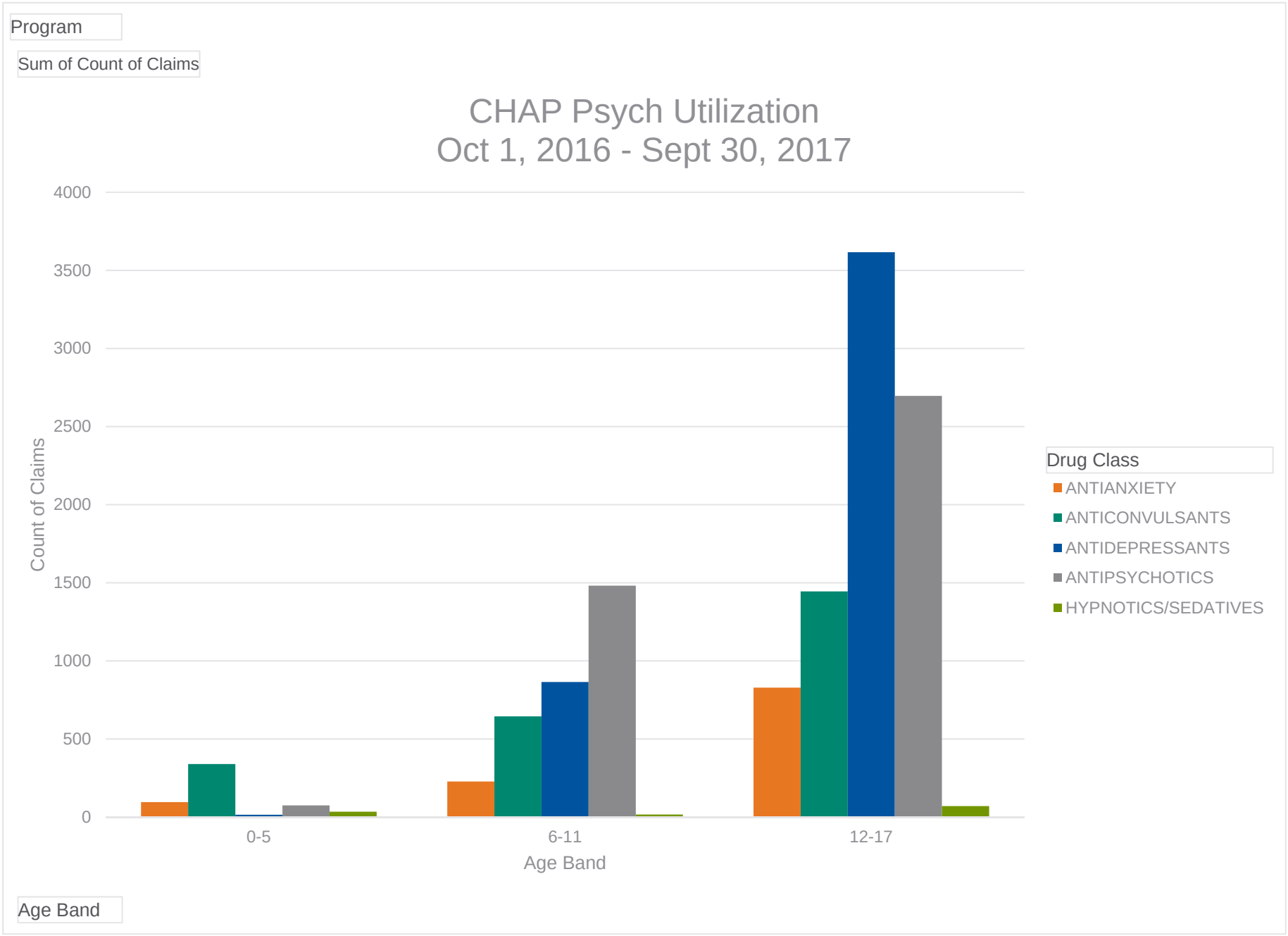
Age Band

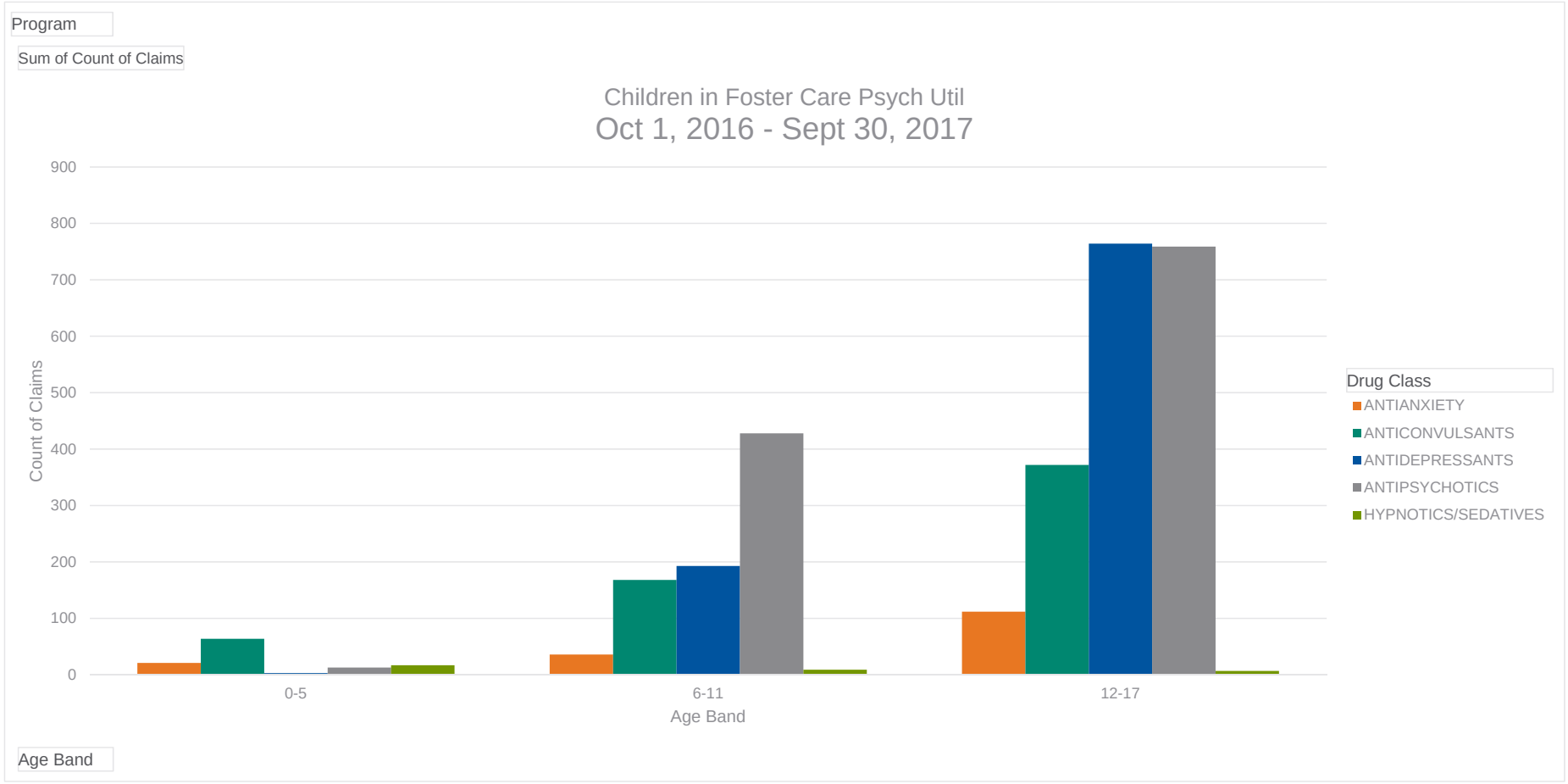
Top 25 Diagnosis of Recipients Under 18 on an Anticonvulsant

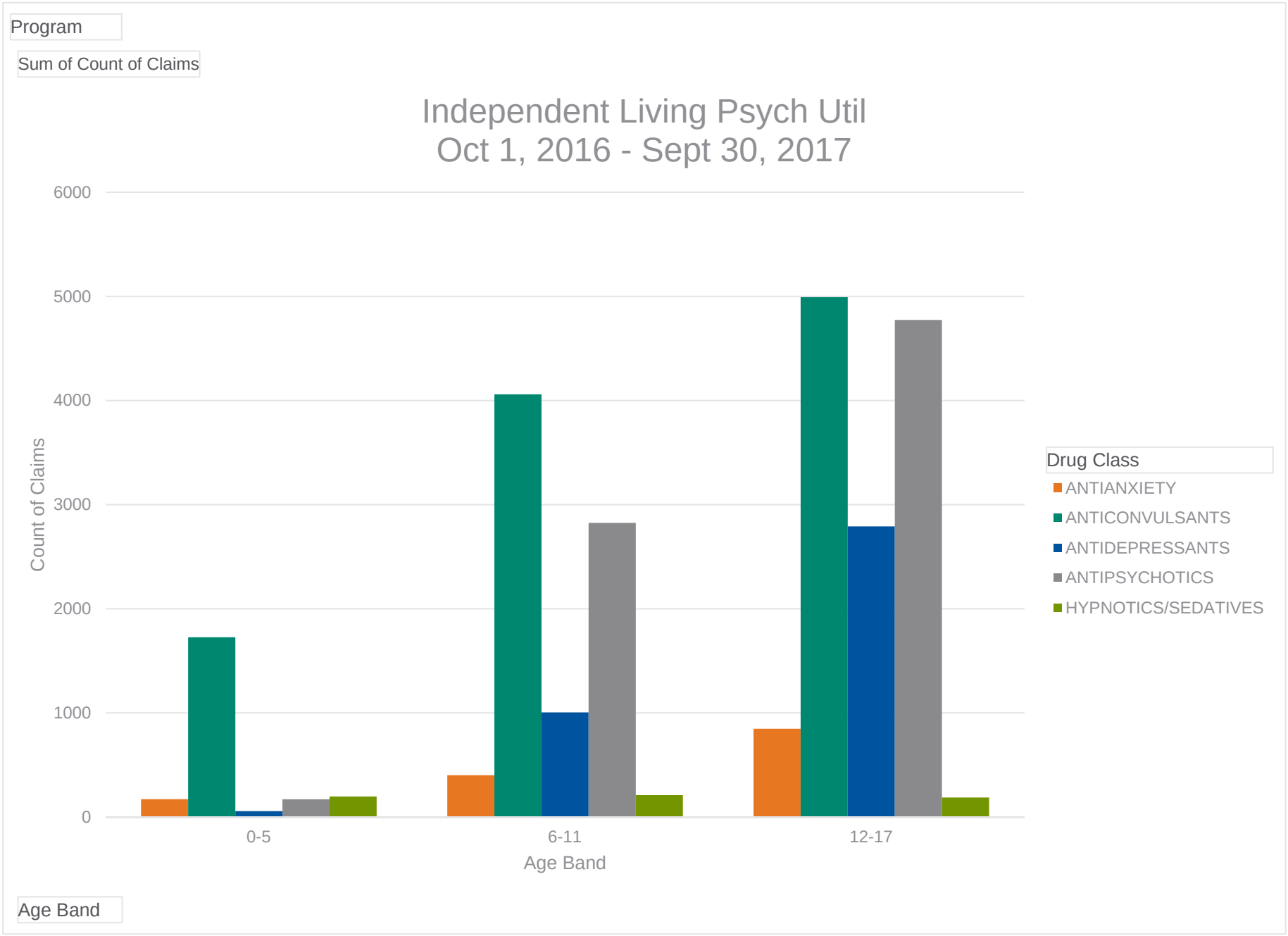
July 1, 2016 - June 30, 2017

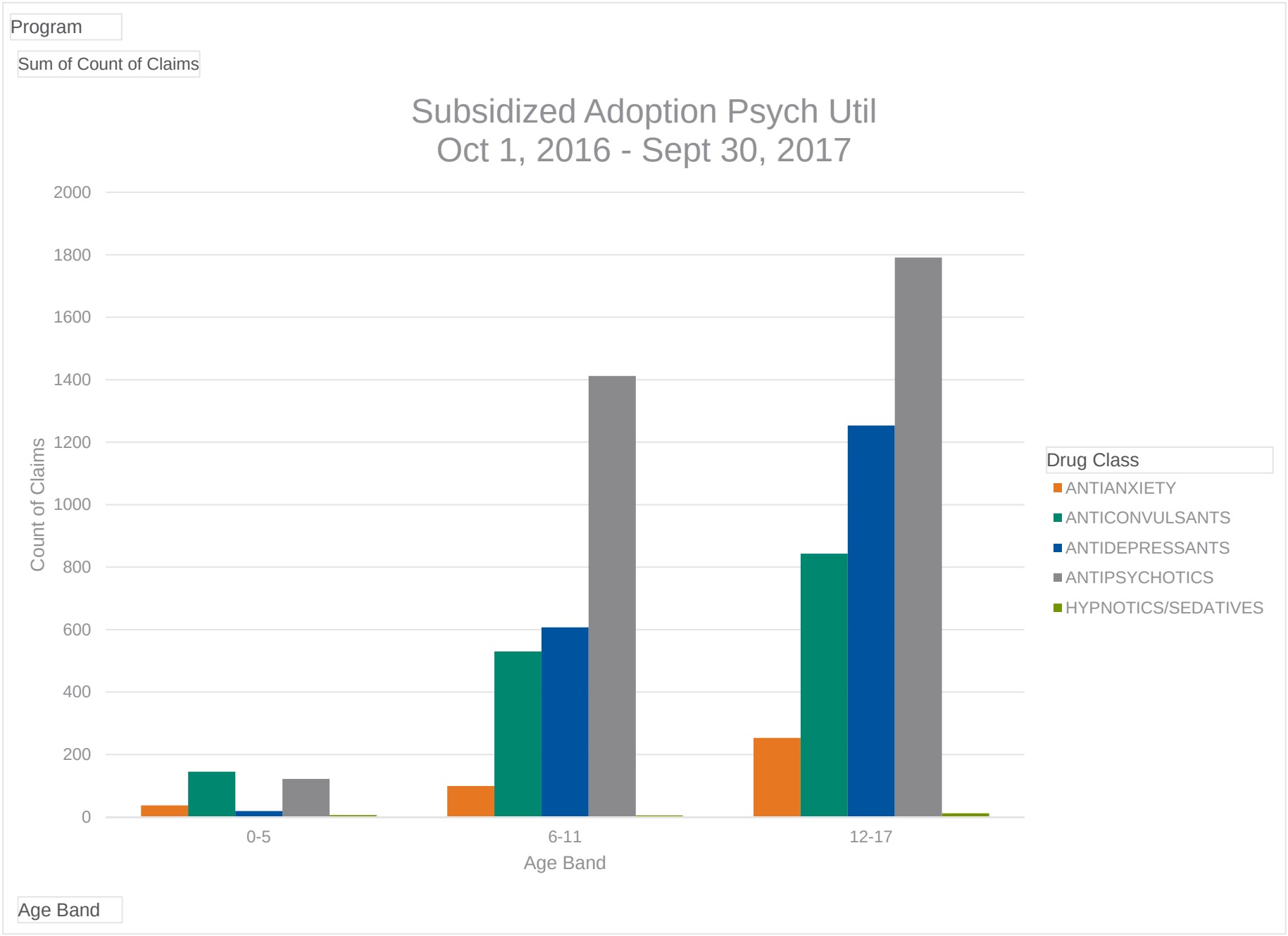
Row Labels	Count of Person ID Unencrypted
Encounter for dental examination and cleaning without abnormal findings	912
Encounter for routine child health exam without abnormal findings	622
Encounter for immunization	506
Unspecified convulsions	446
Oth specified problems related to upbringing	380
Other developmental disorders of speech & language	349
Epilepsy, unspecified, not intractable, without status epilepticus	334
Specific developmental disorder of motor function	328
Acute upper respiratory infection, unspecified	307
Unspecified mood [affective] disorder	300
Cerebral palsy, unspecified	287
Bipolar disorder, unspecified	277
Encounter for routine child health exam with abnormal findings	264
Myopia, bilateral	262
Attention-deficit hyperactivity disorder, combined type	242
Dental caries, unspecified	240
Other persistent mood [affective] disorders	230
Autistic disorder	221
Acute pharyngitis, unspecified	210
Oppositional defiant disorder	207
Cough	201
Hypermetropia, bilateral	199
Fever, unspecified	195
Local-related Sx epilepsy & epileptic syndrome w CPS, not intract w/o SE	192
Expressive language disorder	191
Grand Total	**7902**

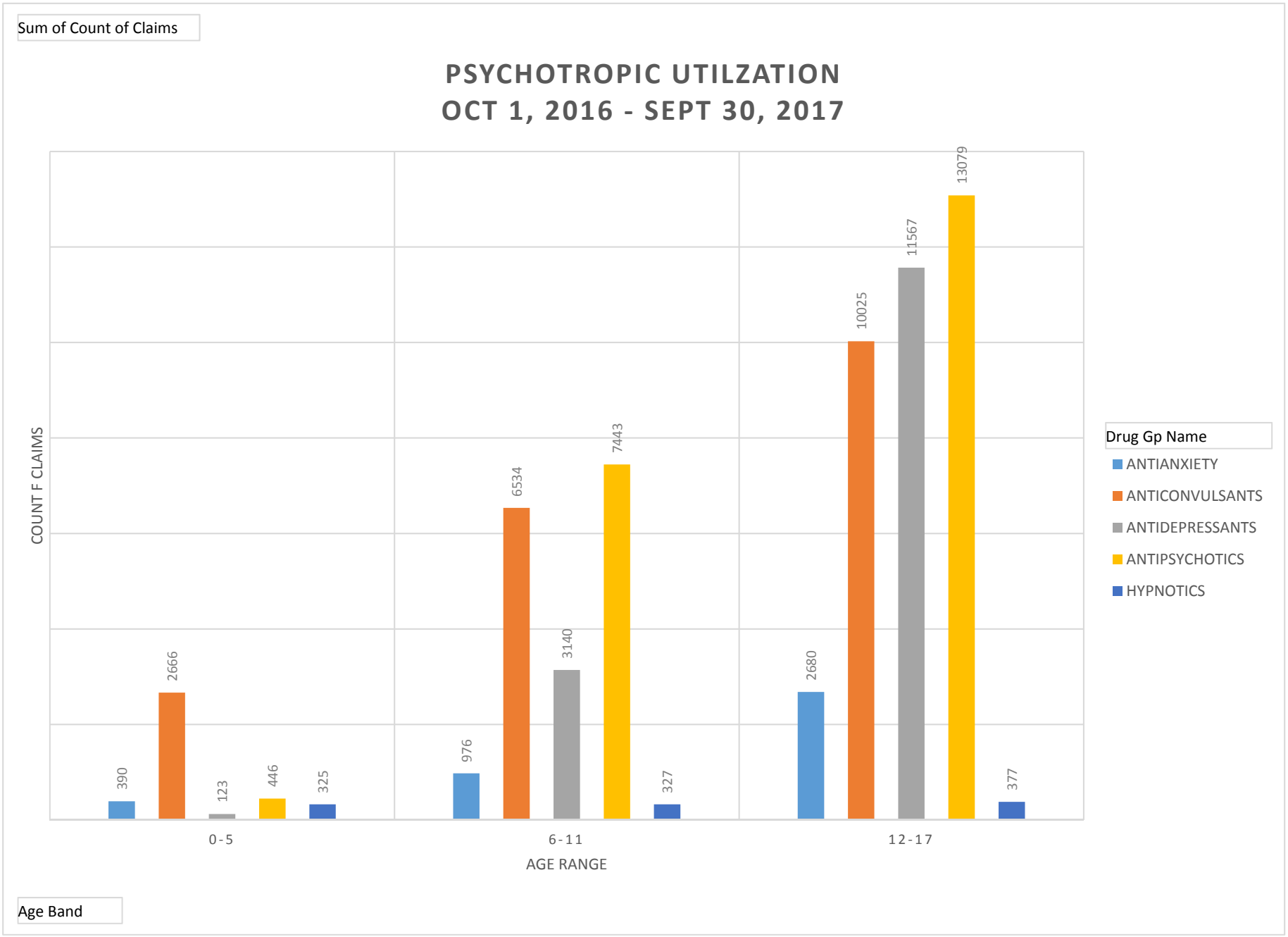

ClaimsMembers
Top 10 Medicaid Programs for Children Under 18
Oct 1, 2016 - Sept 30, 2017
30000
25000
20000
15000
10000
5000
0
Count of Member/Claims
CHAP
Check Up
Child FIC in county custody
Child IV-E in adoption subsidized by another State
Child IV-E in court ordered placement (regular rate)
Child IV-E in subsidized adoption
County match aged
Foster
Independent Living Disabled (SSI)
Katie Beckett Disabled
Medicaid Program
Values
Claims
Members
Program


Program
Sum of Count of Claims
CHAP Psych Utilization
Oct 1, 2016 - Sept 30, 2017
4000
3500
3000
2500
2000
1500
1000
500
0
Count of Claims
0-5
6-11
12-17
Age Band
Drug Class
ANTIANXIETY
ANTICONVULSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
HYPNOTICS/SEDATIVES
Age Band


Program
Sum of Count of Claims
Children in Foster Care Psych Util
Oct 1, 2016 - Sept 30, 2017
900
800
700
600
500
400
300
200
100
0
Count of Claims
0-5
6-11
12-17
Age Band
Drug Class
ANTIANXIETY
ANTICONVULSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
HYPNOTICS/SEDATIVES
Age Band


Program
Sum of Count of Claims
Independent Living Psych Util
Oct 1, 2016 - Sept 30, 2017
6000
5000
4000
3000
2000
1000
0
Count of Claims
0-5
6-11
12-17
Age Band
Drug Class
ANTIANXIETY
ANTICONVULSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
HYPNOTICS/SEDATIVES
Age Band

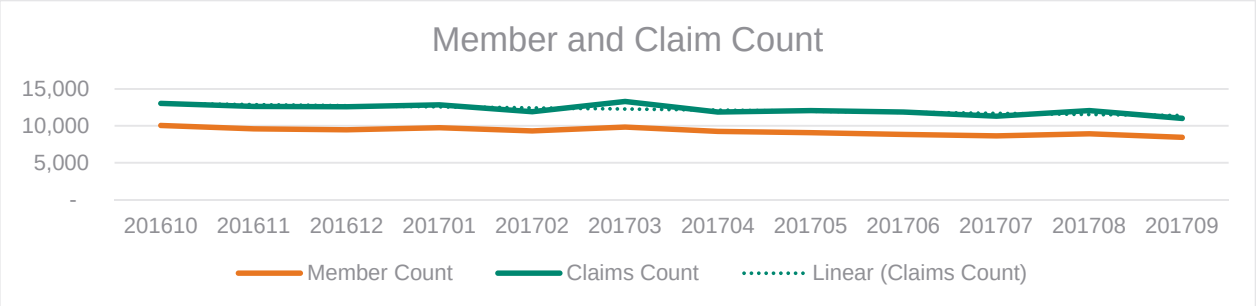

Program
Sum of Count of Claims
Subsidized Adoption Psych Util
Oct 1, 2016 - Sept 30, 2017
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Count of Claims
0-5
6-11
12-17
Age Band
Drug Class
ANTIANXIETY
ANTICONVULSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
HYPNOTICS/SEDATIVES
Age Band

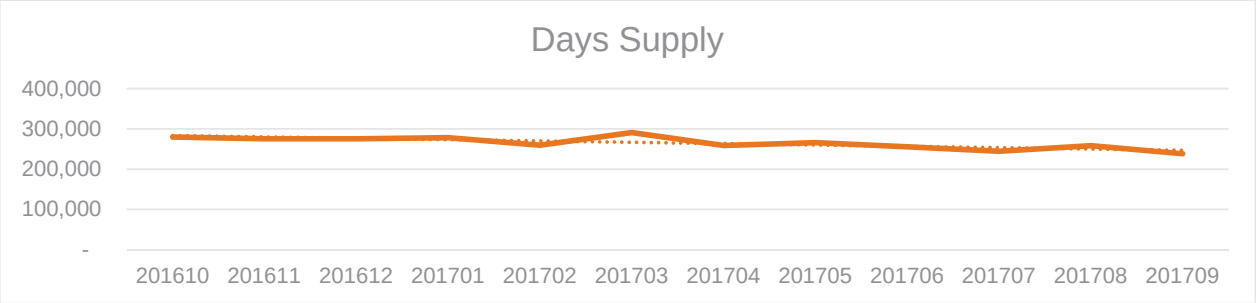

Sum of Count of Claims
PSYCHOTROPIC UTILZATION
OCT 1, 2016 - SEPT 30, 2017
COUNT F CLAIMS
390
2666
123
446
325
976
6534
3140
7443
327
2680
10025
11567
13079
377
0-5
6-11
12-17
AGE RANGE
Drug Gp Name
ANTIANXIETY
ANTICONVULSANTS
ANTIDEPRESSANTS
ANTIPSYCHOTICS
HYPNOTICS
Age Band

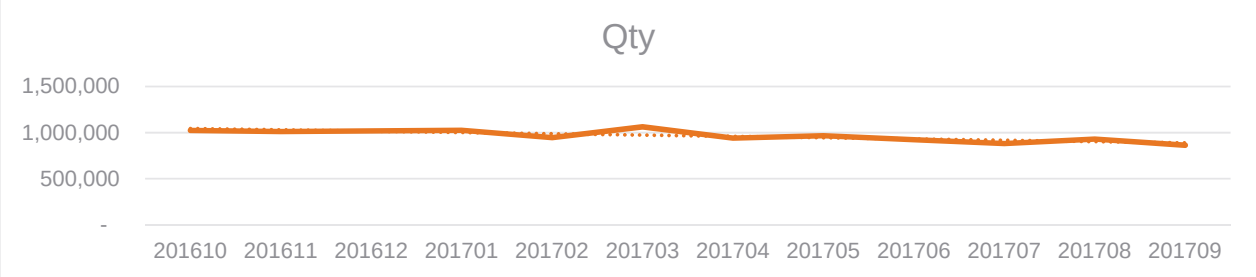
Opioid Utilization

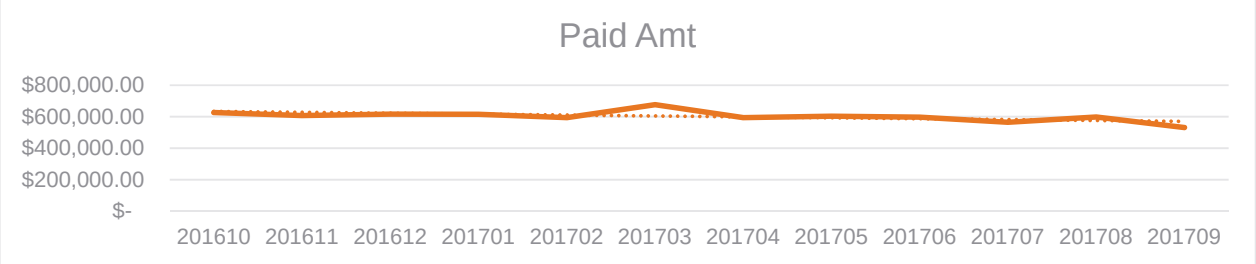
Oct 1, 2016 - Sept 30, 2017

YearMonthFilled	Member Count	Claims Count	Days Supply	Qty	Paid Amt
201610	10,058	13,047	279,813	1,023,649	$626,300.11
201611	9,603	12,639	275,270	1,011,243	$607,386.47
201612	9,461	12,584	275,275	1,018,395	$616,128.52
201701	9,745	12,841	278,303	1,026,048	$615,550.09
201702	9,311	11,913	259,460	944,694	$593,640.48
201703	9,831	13,302	290,813	1,062,292	$676,039.89
201704	9,258	11,876	258,869	939,598	$593,564.85
201705	9,084	12,061	265,723	966,721	$602,405.47
201706	8,832	11,867	255,450	922,730	$596,342.97
201707	8,653	11,315	244,279	881,154	$564,627.04
201708	8,930	12,065	258,236	929,064	$597,926.86
201709	8,444	11,015	238,249	862,589	$531,133.13









Top 10 Opioids by Qty

Oct 1, 2016 - Sept 30, 2017

Sum of MetricDecimalQty	Column Labels												
Row Labels	**201610**	**201611**	**201612**	**201701**	**201702**	**201703**	**201704**	**201705**	**201706**	**201707**	**201708**	**201709**	**Grand Total**
HYDROCO/APAP TAB 10-325MG	250,607	247,822	248,863	249,828	227,336	257,455	228,486	238,036	224,215	217,650	228,245	210,442	2,828,985
OXYCOD/APAP TAB 10-325MG	143,473	143,360	144,175	143,018	135,579	152,987	133,950	141,771	136,612	128,216	136,100	128,558	1,667,799
TRAMADOL HCL TAB 50MG	95,348	87,539	88,523	86,768	84,000	92,599	81,938	85,610	79,200	78,508	87,318	77,769	1,025,120
OXYCODONE TAB 30MG	56,284	58,645	59,265	56,678	52,454	58,509	53,090	56,427	54,617	53,355	57,239	51,965	668,528
OXYCODONE TAB 10MG	52,533	52,535	55,129	56,871	55,764	64,228	55,260	55,413	58,651	53,402	54,873	51,145	665,804
OXYCODONE TAB 15MG	61,056	59,466	54,586	56,954	51,525	58,571	52,785	55,224	53,590	50,331	54,673	51,358	660,119
HYDROCO/APAP TAB 5-325MG	55,565	52,704	52,837	53,095	48,421	54,420	48,934	46,905	44,949	42,551	44,792	39,931	585,104
HYDROCO/APAP TAB 7.5-325	49,299	46,204	44,669	48,102	43,197	47,063	44,734	44,278	41,301	39,373	41,413	37,741	527,374
METHADONE TAB 10MG	24,372	27,613	25,259	25,071	22,995	25,441	23,965	24,481	21,678	21,318	22,020	19,926	284,139
OXYCOD/APAP TAB 5-325MG	24,791	26,149	25,207	26,951	24,879	24,694	21,965	21,519	20,999	20,191	22,121	19,483	278,949
Grand Total	**813,328**	**802,037**	**798,513**	**803,336**	**746,150**	**835,967**	**745,107**	**769,664**	**735,812**	**704,895**	**748,794**	**688,318**	**9,191,921**

Top 10 Prescribers by Count of Claims

Oct 1, 2016 - Sept 30, 2017

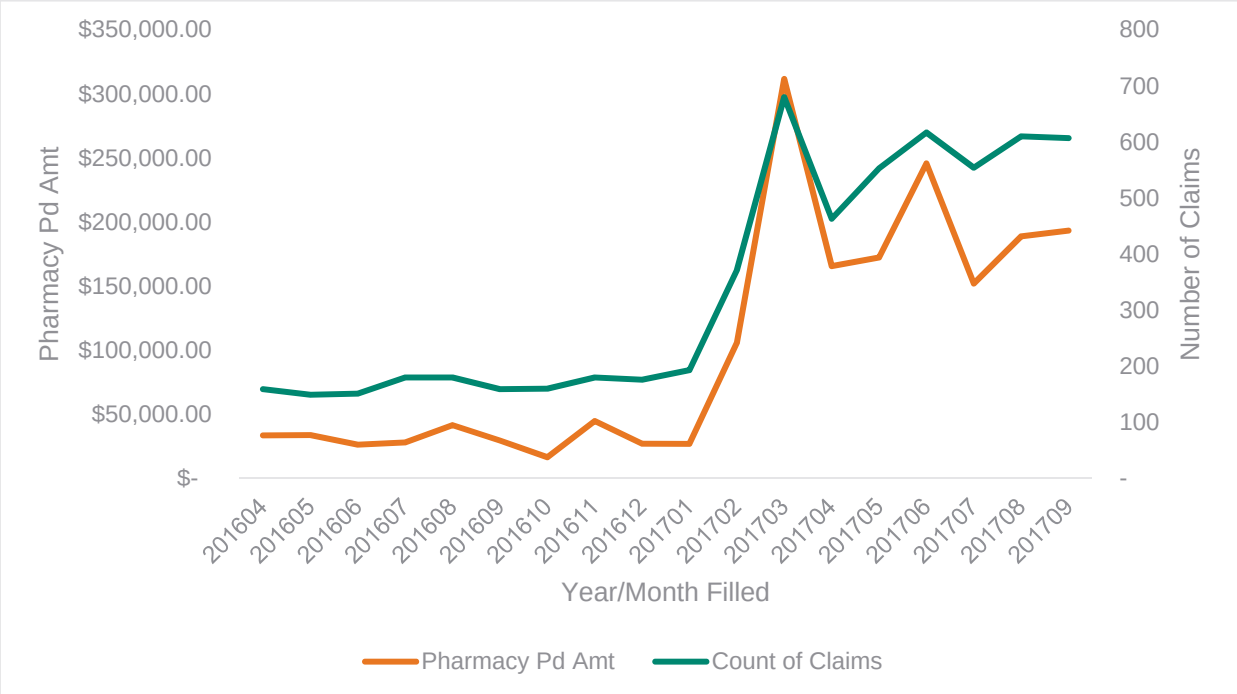
Specialty	Degree	City	Sum of Members	Sum of Claims	Sum of Days	Sum of Qty	Sum of Paid Amt
PAIN MANAGEMENT	NP	Las Vegas	2,119	2,193	64,905	205,568	$ 195,919.94
	PA	Las Vegas	1,525	1,608	47,212	182,787	$ 112,334.23
	PA	Las Vegas	1,259	1,300	38,341	115,709	$ 124,161.90
	PA	Las Vegas	1,212	1,279	36,064	125,230	$ 93,265.21
Oncology	PA	Las Vegas	1,210	1,277	35,538	124,461	$ 76,039.34
PAIN MANAGEMENT	MD	Carson City	1,069	1,204	32,714	105,283	$ 352,220.02
	PA	Las Vegas	1,103	1,133	33,419	97,989	$ 83,486.40
Oral Surgery	DDS	Reno	1,101	1,117	4,780	19,138	$ 12,620.70
PAIN MANAGEMENT	MD	Las Vegas	996	1,070	29,538	99,121	$ 39,900.88
Cardio-vascular	MD	Las Vegas	980	994	29,693	95,312	$ 84,056.81
			12,574	**13,175**	**352,204**	**1,170,598**	**$ 1,174,005.43**

90 Day Supply Utilization

Nevada Medicaid FFS

April 1, 2016 - September 30, 2017

Year Month Filled	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	193	193	19,603	17,500	$ 1,291.18	$ 26,851.94
201702	371	371	38,314	33,766	$ 2,669.62	$ 105,550.60
201703	680	680	69,787	65,588	$ 5,179.13	$ 311,698.00
201704	463	463	47,806	41,837	$ 3,345.62	$ 165,673.43
201705	553	553	55,925	57,606	$ 3,812.39	$ 172,326.13
201706	617	617	63,111	56,504	$ 4,329.65	$ 245,742.85
201707	554	554	57,998	52,059	$ 3,832.36	$ 152,027.96
201708	610	610	62,999	62,799	$ 3,978.79	$ 188,819.11
201709	607	607	62,080	66,360	$ 4,220.21	$ 193,356.66



Top 10 Drug Group by Paid Amt

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

Q2 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
85	HEMATOLOGICAL AGENTS - MISC.*	3,457	$ 10,924,453.46
12	ANTIVIRALS*	4,246	$ 7,675,577.73
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	31,299	$ 5,609,573.39
27	ANTIDIABETICS*	20,020	$ 5,235,915.50
21	ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4,240	$ 5,147,044.39
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	41,941	$ 4,762,202.79
72	ANTICONVULSANTS*	45,627	$ 3,982,719.66
74	NEUROMUSCULAR AGENTS*	337	$ 2,794,526.15
30	ENDOCRINE AND METABOLIC AGENTS - MISC.*	3,899	$ 2,601,347.46
62	PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	5,248	$ 2,268,181.85

Top 10 Drug Group by Claim Count

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

Q2 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
65	ANALGESICS - OPIOID*	57,647	$ 1,960,118.79
72	ANTICONVULSANTS*	45,627	$ 3,982,719.66
58	ANTIDEPRESSANTS*	43,789	$ 846,962.47
44	ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	41,941	$ 4,762,202.79
59	ANTIPSYCHOTICS/ANTIMANIC AGENTS*	31,299	$ 5,609,573.39
57	ANTIANXIETY AGENTS*	25,761	$ 283,662.72
49	ULCER DRUGS*	24,549	$ 1,176,384.46
36	ANTIHYPERTENSIVES*	24,325	$ 359,353.24
39	ANTIHYPERLIPIDEMICS*	24,318	$ 722,355.35
66	ANALGESICS - ANTI-INFLAMMATORY*	23,771	$ 1,871,181.95

Top 10 Drug Classes by Paid Amt

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

Q2 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
8510	ANTIHEMOPHILIC PRODUCTS**	95	$ 10,279,220.11
1235	HEPATITIS AGENTS**	343	$ 4,431,089.27
2710	INSULIN**	6,311	$ 3,446,189.72
4420	SYMPATHOMIMETICS**	28,438	$ 3,166,342.54
1210	ANTIRETROVIRALS**	2,196	$ 3,128,703.60
7260	ANTICONVULSANTS - MISC.**	33,660	$ 2,706,848.12
5907	BENZISOXAZOLES**	7,364	$ 2,091,603.88
7470	SPINAL MUSCULAR ATROPHY AGENTS (SMA)**	13	$ 2,000,132.21
2135	ANTINEOPLASTIC - ANTIBODIES**	333	$ 1,799,186.78
6240	MULTIPLE SCLEROSIS AGENTS**	304	$ 1,671,342.11

Top 10 Drug Classes by Claim Count

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 (NSAIDS)*	23,636	$ 310,226.82
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	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 (NSAIDS)*	25,202	$ 321,555.13
6510	OPIOID AGONISTS**	25,168	$ 1,063,262.89
3940	HMG COA REDUCTASE INHIBITORS**	22,722	$ 428,842.94
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	22,212	$ 270,607.46
5710	BENZODIAZEPINES**	18,734	$ 189,624.66
7510	CENTRAL MUSCLE RELAXANTS**	16,795	$ 290,601.35
2210	GLUCOCORTICOSTEROIDS**	14,370	$ 180,288.84

Q2 2017

Class	Drug Class Name	Count of Claims	Pharmacy Paid
7260	ANTICONVULSANTS - MISC.**	45,637	$ 3,667,824.50
6599	OPIOID COMBINATIONS**	43,574	$ 998,712.92
4420	SYMPATHOMIMETICS**	39,281	$ 4,329,537.64
6510	OPIOID AGONISTS**	34,049	$ 1,406,192.97
6610	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)*	32,205	$ 408,779.15
5816	SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)**	28,866	$ 360,187.39
3940	HMG COA REDUCTASE INHIBITORS**	28,068	$ 543,311.48
5710	BENZODIAZEPINES**	25,010	$ 249,237.17
7510	CENTRAL MUSCLE RELAXANTS**	21,710	$ 372,188.71
2210	GLUCOCORTICOSTEROIDS**	18,266	$ 355,741.10

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 Amount - Q2 2017

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
8510001025	ANTIHEMOPHILIC FACTOR RAHF-PFM	19	$ 4,369,916.59	99,132	14
8510002620	COAGULATION FACTOR VIIA (RECOMBINANT)	6	$ 2,620,861.02	210,000	30
1235990240	LEDIPASVIR-SOFOSBUVIR	116	$ 2,048,837.39	8	8
7470005000	NUSINERSEN	13	$ 2,000,132.21	5	21
8510001020	ANTIHEMOPHILIC FACTOR (RECOMBINANT)	12	$ 1,977,028.26	105,864	25
1235990265	SOFOSBUVIR-VELPATASVIR	118	$ 1,786,388.20	7	7
5907005010	PALIPERIDONE PALMITATE	763	$ 1,518,854.65	1	24
5940002310	LURASIDONE HCL	1,109	$ 1,186,130.47	17	15
2710400300	INSULIN GLARGINE	2,384	$ 1,115,309.42	15	34
4420101010	ALBUTEROL SULFATE	18,298	$ 1,086,491.30	36	15
9410003000	GLUCOSE BLOOD	6,959	$ 982,791.69	75	24
7260005700	PREGABALIN	2,793	$ 929,163.42	44	19
4420990270	FLUTICASONE-SALMETEROL	2,867	$ 918,205.04	43	23
6627001500	ADALIMUMAB	191	$ 881,404.72	1	9
4927002510	ESOMEPRAZOLE MAGNESIUM	3,293	$ 840,872.98	22	22
3010002000	SOMATROPIN	206	$ 765,718.19	2	10
2710400500	INSULIN LISPRO	1,029	$ 747,245.48	15	27
5925001500	ARIPIPRAZOLE	4,750	$ 733,191.61	18	17
1910002010	IMMUNE GLOBULIN (HUMAN) IV	108	$ 675,973.90	515	3
1210990429	ELVITEGRAVIR-COBICISTAT-EMTRICITABINE-TENOFOVIR ALAFENAMIDE	259	$ 633,591.95	19	19
5915307010	QUETIAPINE FUMARATE	8,209	$ 589,994.06	28	20
7460003500	ETEPLIRSEN	8	$ 582,481.36	19	6
2153253000	EVEROLIMUS	35	$ 578,474.20	12	9
4410008010	TIOTROPIUM BROMIDE MONOHYDRATE	2,113	$ 570,614.56	24	25
2710400200	INSULIN ASPART	969	$ 567,788.62	15	29
1235990230	ELBASVIR-GRAZOPREVIR	48	$ 545,144.71	14	14
4420990241	BUDESONIDE-FORMOTEROL FUMARATE DIHYDRATE	2,541	$ 540,079.03	8	24
4530402000	DORNASE ALFA	163	$ 536,405.25	47	16
7260003600	LACOSAMIDE	1,027	$ 534,377.91	51	13
8580005000	ECULIZUMAB	23	$ 525,948.00	107	1
6135303010	GUANFACINE HCL (ADHD)	1,810	$ 513,496.77	20	19
7210000700	CLOBAZAM	401	$ 498,776.01	61	14
9310002500	DEFERASIROX	67	$ 496,752.14	24	11
6110002510	LISDEXAMFETAMINE DIMESYLATE	1,872	$ 478,678.04	22	21
6240552500	DIMETHYL FUMARATE	70	$ 463,542.76	15	7
9085006000	LIDOCAINE	2,129	$ 459,717.09	85	16
8510001510	ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	22	$ 452,702.31	8,886	12
1210990230	EMTRICITABINE-TENOFOVIR DISOPROXIL FUMARATE	317	$ 442,135.71	21	21
6140002010	METHYLPHENIDATE HCL	2,391	$ 436,009.44	34	19
8240157000	PEGFILGRASTIM	79	$ 433,288.68	0	3
3090685000	IDURSULFASE	40	$ 423,739.34	8	3
6629003000	ETANERCEPT	97	$ 419,174.40	2	12
2710400600	INSULIN DETEMIR	951	$ 405,721.20	16	30
3030001000	CORTICOTROPIN	6	$ 400,263.02	2	5
9037403530	DICLOFENAC SODIUM (ACTINIC KERATOSES)	457	$ 398,615.67	217	20
2135303200	IPILIMUMAB	7	$ 376,015.51	118	1
2133502000	BEVACIZUMAB	326	$ 358,038.97	6	1
6599000220	OXYCODONE W/ ACETAMINOPHEN	10,154	$ 350,216.66	56	15
6510007510	OXYCODONE HCL	8,512	$ 347,380.03	71	18
2135304100	NIVOLUMAB	83	$ 334,212.12	138	1

Top 50 Drugs by 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

Top 50 Drugs by Claim Count - Q2 2017

Drug Code	Drug Name	Claim Count	Pharmacy Paid	Avg Qty/Rx	Avg Day Supply
6599170210	HYDROCODONE-ACETAMINOPHEN	19967	$ 317,947.99	58	15
4420101010	ALBUTEROL SULFATE	18298	$ 1,086,491.30	36	15
7260003000	GABAPENTIN	13551	$ 181,760.42	72	23
3940001010	ATORVASTATIN CALCIUM	10892	$ 112,588.26	27	26
6610002000	IBUPROFEN	10837	$ 97,499.04	43	13
5710001000	ALPRAZOLAM	10250	$ 105,012.40	50	21
6599000220	OXYCODONE W/ ACETAMINOPHEN	10154	$ 350,216.66	56	15
2810001010	LEVOTHYROXINE SODIUM	9441	$ 145,862.61	30	30
3610003000	LISINOPRIL	8945	$ 66,304.67	41	37
6510007510	OXYCODONE HCL	8512	$ 347,380.03	71	18
5915307010	QUETIAPINE FUMARATE	8209	$ 589,994.06	28	20
5812008010	TRAZODONE HCL	8131	$ 89,113.53	30	22
5025006505	ONDANSETRON HCL	7412	$ 36,721.93	4	2
4220003230	FLUTICASONE PROPIONATE (NASAL)	7377	$ 83,623.08	12	24
3400000310	AMLODIPINE BESYLATE	7273	$ 42,720.36	40	38
4450505010	MONTELUKAST SODIUM	7212	$ 110,790.63	23	22
6510005510	MORPHINE SULFATE	7026	$ 137,661.23	21	9
9410003000	GLUCOSE BLOOD	6959	$ 982,791.69	75	24
2725005000	METFORMIN HCL	6886	$ 232,635.80	77	38
5816007010	SERTRALINE HCL	6866	$ 73,542.78	28	23
6410001000	ASPIRIN	6475	$ 34,222.78	23	22
7720203200	CHOLECALCIFEROL	6183	$ 47,835.76	26	24
0120001010	AMOXICILLIN	6010	$ 62,758.77	56	6
5907007000	RISPERIDONE	5870	$ 95,601.79	36	21
4927007010	PANTOPRAZOLE SODIUM	5799	$ 53,914.30	21	20
7975001000	SODIUM CHLORIDE	5677	$ 14,969.13	469	1
4155003000	LORATADINE	5449	$ 60,149.79	32	20
5025006500	ONDANSETRON	5291	$ 56,766.01	7	3
4920002010	RANITIDINE HCL	5256	$ 67,650.17	49	24
5816004000	FLUOXETINE HCL	5207	$ 92,346.65	30	23
7510005010	CYCLOBENZAPRINE HCL	5011	$ 51,405.23	42	19
7210001000	CLONAZEPAM	4996	$ 50,998.40	44	22
6510009510	TRAMADOL HCL	4995	$ 44,401.99	56	16
2210004500	PREDNISONE	4877	$ 42,034.53	16	9
3940007500	SIMVASTATIN	4848	$ 35,080.47	33	33
5925001500	ARIPIPRAZOLE	4750	$ 733,191.61	18	17
4155002010	CETIRIZINE HCL	4716	$ 51,359.83	41	20
7250001010	DIVALPROEX SODIUM	4689	$ 182,064.27	56	20
3320003010	METOPROLOL TARTRATE	4443	$ 33,076.91	56	30
7260004000	LAMOTRIGINE	4381	$ 216,349.22	44	22
0340001000	AZITHROMYCIN	4365	$ 56,749.34	7	3
5710006000	LORAZEPAM	4293	$ 38,248.63	20	10
7720203000	ERGOCALCIFEROL	4265	$ 45,392.53	4	26
7510009010	TIZANIDINE HCL	4252	$ 94,135.97	50	20
6610005200	MELOXICAM	4235	$ 35,246.25	27	24
5816002010	CITALOPRAM HYDROBROMIDE	4146	$ 37,724.15	27	26
4920003000	FAMOTIDINE	4012	$ 32,014.24	25	15
7260004300	LEVETIRACETAM	4008	$ 176,681.52	127	20
5830004010	BUPROPION HCL	3938	$ 84,795.78	32	23
6020408010	ZOLPIDEM TARTRATE	3869	$ 37,015.76	24	24

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RXT6050D - Summarized DUR Activity Report

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

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.

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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

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

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

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

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

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

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

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

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

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

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

Client Totals:

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

DUR Information as a percent of total:

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

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

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RXT6050D - Summarized DUR Activity Report

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

DD

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

HD

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

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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

LD

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

LR

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

MN

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

MX

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

PA

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

SX

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

TD

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

TD

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

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

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

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RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

Client Totals:

Total Rxs	Plan Paid	Member Paid
702,122	$78,464,924	$0

DUR Information as a percent of total:

DUR Type	Total Rxs	Percent of Total Rxs - Paid	Cases	Rejected Rxs	Percent of Total Rxs - Rejects
Total Claims Paid	702,122	0.0%	0	0	0.0%
Cases / Rxs	508,986	72.5%	621,766	339,014	48.3%
DD - Drug-Drug Interaction	198,957	28.3%	367,009	145,228	20.7%
TD - Therapeutic Duplication	111,783	15.9%	93,854	114,296	16.3%
ID - Ingredient Duplication	58,493	8.3%	22,795	58,893	8.4%
LR - Underuse Precaution	56,332	8.0%	56,600	7,339	1.0%
LD - Low Dose Alert	33,782	4.8%	32,539	5,958	0.8%
MN - Insufficnt Duration Alert	22,872	3.3%	22,410	1,319	0.2%
HD - High Dose Alert	17,849	2.5%	17,603	3,531	0.5%
MX - Excessive Duration Alert	8,872	1.3%	8,906	2,448	0.3%
PA - Drug-Age Precaution	46	0.0%	50	2	0.0%

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

RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

DD

Curr Rank	Top Drug Drug Interaction	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	HYDROCODONE/ ACETAMINOPHEN - ALPRAZOLAM	Message Only	3,513	611	$61,411.85	$17.48	$0.00	21.73	84.35
2	SIMVASTATIN - LISINOPRIL	Message Only	2,837	684	$20,158.26	$7.11	$0.00	48.64	51.32
3	LISINOPRIL - FUROSEMIDE	Message Only	2,783	905	$19,503.44	$7.01	$0.00	50.96	60.86
4	HYDROCO/APAP - ALPRAZOLAM	Message Only	2,691	579	$24,485.03	$9.10	$0.00	25.88	60.42
5	ONDANSETRON HCL - HYDROCO/APAP	Message Only	2,325	61	$6,525.06	$2.81	$0.00	2.46	5.48
6	OXYCODONE HCL - ALPRAZOLAM	Message Only	1,995	445	$51,418.62	$25.77	$0.00	25.49	102.66
7	LISINOPRIL - IBUPROFEN	Message Only	1,926	497	$17,198.32	$8.93	$0.00	35.53	67.73
8	OXYCODONE - ALPRAZOLAM	Message Only	1,816	488	$18,172.11	$10.01	$0.00	26.26	65.85
9	OXYCODONE/ ACETAMINOPHEN - ALPRAZOLAM	Message Only	1,710	329	$57,714.91	$33.75	$0.00	21.94	86.76
10	MORPHINE SULFATE ER - GABAPENTIN	Message Only	1,604	335	$42,901.66	$26.75	$0.00	24.79	52.90
All Others			343,809	140,294	$19,623,050.59	$57.08	$0.00	29.90	56.53
Summary			**367,009**	**145,228**	**$19,942,539.85**	**$54.34**	**$0.00**	**29.85**	**56.97**

HD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ZOLPIDEM TARTRATE	GERIATRIC MAX DLY = .50UN	Message Only	453	41	$841.74	$1.86	$0.00	29.21	29.21
2	KETOROLAC TROMETHAMINE	GERIATRIC MAX DLY = 2.00UN	Message Only	395	12	$5,789.34	$14.66	$0.00	1.00	7.08
3	HYDROCODONE/ ACETAMINOPHEN	ADULT MAX DLY = 6.00 UN	Message Only	298	30	$8,002.90	$26.86	$0.00	14.99	117.91
4	MIDAZOLAM HCL	GERIATRIC MAX DLY = 3.50UN	Message Only	240	11	$645.98	$2.69	$0.00	1.00	7.92
5	GRANISETRON HCL	GERIATRIC MAX DLY = .85UN	Message Only	239	6	$4,349.48	$18.20	$0.00	1.00	1.38
6	BETAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 1.50UN	Message Only	202	1	$5,534.64	$27.40	$0.00	1.00	5.44
7	CEFTRIAXONE SODIUM	GERIATRIC MAX DLY = 4.00UN	Message Only	200	4	$9,935.91	$49.68	$0.00	1.00	172.52
8	DEXAMETHASONE SODIUM PHOS	GERIATRIC MAX DLY = 4.00UN	Message Only	191	3	$3,365.64	$17.62	$0.00	1.00	290.86
9	INVEGA SUSTENNA	ADULT MAX DLY = .05 UN	Message Only	184	129	$379,876.69	$2,064.55	$0.00	27.35	1.50
10	IBUPROFEN	ADULT MAX DLY = 4.00 UN	Message Only	174	21	$1,875.61	$10.78	$0.00	8.22	37.97
All Others				15,027	3,273	$9,186,466.36	$611.33	$0.00	16.65	376.16
HD				**17,603**	**3,531**	**$9,606,684.29**	**$545.74**	**$0.00**	**15.67**	**329.71**

RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

ID

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROVENTIL HFA	PROVENTIL AER HFA	Message Only	409	23	$39,307.30	$96.11	$0.00	27.62	8.08
2	GABAPENTIN	GABAPENTIN CAP 300MG	Message Only	247	21	$3,239.56	$13.12	$0.00	36.45	110.97
3	CLONIDINE HCL	CLONIDINE TAB 0.1MG	Message Only	204	22	$2,646.82	$12.97	$0.00	75.65	130.24
3	SERTRALINE HCL	SERTRALINE TAB 100MG	Message Only	204	12	$2,483.96	$12.18	$0.00	34.72	47.91
5	LISINOPRIL	LISINOPRIL TAB 20MG	Message Only	195	9	$2,239.60	$11.49	$0.00	78.74	90.56
6	AMLODIPINE BESYLATE	AMLODIPINE TAB 10MG	Message Only	175	17	$1,815.75	$10.38	$0.00	74.33	73.65
7	ONDANSETRON ODT	ONDANSETRON TAB 4MG ODT	Message Only	174	0	$63.13	$0.36	$0.00	1.00	1.06
7	TRAZODONE HCL	TRAZODONE TAB 50MG	Message Only	174	4	$1,936.33	$11.13	$0.00	33.84	46.23
9	METFORMIN HCL	METFORMIN TAB 500MG	Message Only	173	10	$1,909.31	$11.04	$0.00	78.01	155.55
10	TRAZODONE HCL	TRAZODONE TAB 100MG	Message Only	167	8	$1,899.19	$11.37	$0.00	36.38	50.54
All Others				20,673	58,767	$5,060,240.43	$244.78	$0.00	39.29	122.65
ID				**22,795**	**58,893**	**$5,117,781.38**	**$224.51**	**$0.00**	**39.88**	**117.43**

LD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ONDANSETRON ODT	GERIATRIC MIN DLY = 2.00UN	Message Only	1,285	18	$628.73	$0.49	$0.00	1.30	1.24
2	IPRATROPIUM BROMIDE/ ALBUT	GERIATRIC MIN DLY = 9.00UN	Message Only	935	7	$709.63	$0.76	$0.00	1.98	8.83
3	HEPARIN SODIUM	GERIATRIC MIN DLY = 4.00UN	Message Only	815	13	$2,041.66	$2.51	$0.00	1.40	2.41
4	HEPARIN SODIUM	GERIATRIC MIN DLY = 20.00UN	Message Only	751	891	$3,424.07	$4.56	$0.00	1.00	3.01
5	ALBUTEROL SULFATE	GERIATRIC MIN DLY = 9.00UN	Message Only	533	23	$1,187.65	$2.23	$0.00	5.23	26.53
6	ONDANSETRON HCL	GERIATRIC MIN DLY = 2.00UN	Message Only	529	57	$290.79	$0.55	$0.00	2.79	2.79
7	VITAMIN D	ADULT MIN DLY = .14 UN	Message Only	524	56	$5,321.45	$10.16	$0.00	37.87	4.12
8	GABAPENTIN	ADULT MIN DLY = 3.00 UN	Message Only	482	85	$4,897.75	$10.16	$0.00	33.44	55.30
9	METFORMIN HCL	ADULT MIN DLY = 1.70 UN	Message Only	379	114	$3,145.47	$8.30	$0.00	59.60	59.02
10	METFORMIN HCL	GERIATRIC MIN DLY = 1.70UN	Message Only	353	40	$624.54	$1.77	$0.00	40.10	39.11
All Others				25,953	4,654	$3,563,066.08	$137.29	$0.00	28.18	49.00
LD				**32,539**	**5,958**	**$3,585,337.82**	**$110.19**	**$0.00**	**25.01**	**41.99**

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RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

LR

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	ATORVASTATIN CALCIUM	7 DAYS LATE REFILLING	Message Only	67	5	$676.96	$10.10	$0.00	30.87	30.87
1	LEVOTHYROXINE SODIUM	7 DAYS LATE REFILLING	Message Only	67	6	$747.78	$11.16	$0.00	29.97	29.97
3	PROVENTIL HFA	12 DAYS LATE REFILLING	Message Only	65	6	$5,871.68	$90.33	$0.00	20.42	7.52
4	GABAPENTIN	7 DAYS LATE REFILLING	Message Only	61	5	$817.48	$13.40	$0.00	29.39	92.49
5	TRAZODONE HCL	7 DAYS LATE REFILLING	Message Only	60	21	$588.95	$9.82	$0.00	29.17	41.65
6	ATORVASTATIN CALCIUM	8 DAYS LATE REFILLING	Message Only	58	7	$615.40	$10.61	$0.00	32.10	32.10
6	GABAPENTIN	9 DAYS LATE REFILLING	Message Only	58	3	$637.86	$11.00	$0.00	28.93	91.76
8	ATORVASTATIN CALCIUM	9 DAYS LATE REFILLING	Message Only	56	10	$607.08	$10.84	$0.00	30.79	30.79
9	PROVENTIL HFA	11 DAYS LATE REFILLING	Message Only	55	4	$4,457.41	$81.04	$0.00	20.16	6.70
10	MONTELUKAST SODIUM	7 DAYS LATE REFILLING	Message Only	54	2	$1,174.12	$21.74	$0.00	30.00	30.56
10	LEVOTHYROXINE SODIUM	8 DAYS LATE REFILLING	Message Only	54	4	$692.71	$12.83	$0.00	30.02	30.02
All Others				55,945	7,266	$6,968,670.60	$124.56	$0.00	31.71	59.18
LR				**56,600**	**7,339**	**$6,985,558.03**	**$123.42**	**$0.00**	**31.67**	**58.94**

MN

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	IPRATROPIUM BROMIDE/ALBUT	MIN. DAYS THERAPY = 30	Message Only	1,854	240	$14,385.58	$7.76	$0.00	5.22	65.94
2	LISINOPRIL	MIN. DAYS THERAPY = 7	Message Only	940	10	$84.20	$0.09	$0.00	1.03	1.35
3	PANTOPRAZOLE SODIUM	MIN. DAYS THERAPY = 7	Message Only	808	5	$127.82	$0.16	$0.00	1.02	1.07
4	METOPROLOL TARTRATE	MIN. DAYS THERAPY = 7	Message Only	713	7	$120.75	$0.17	$0.00	1.06	1.48
5	AMLODIPINE BESYLATE	MIN. DAYS THERAPY = 7	Message Only	636	11	$73.21	$0.12	$0.00	1.04	1.16
6	LEVETIRACETAM	MIN. DAYS THERAPY = 14	Message Only	612	27	$3,268.50	$5.34	$0.00	2.60	30.25
7	KLOR-CON M20	MIN. DAYS THERAPY = 7	Message Only	586	7	$343.25	$0.59	$0.00	1.06	2.13
8	ATORVASTATIN CALCIUM	MIN. DAYS THERAPY = 7	Message Only	551	4	$157.18	$0.29	$0.00	1.06	1.16
9	CARVEDILOL	MIN. DAYS THERAPY = 7	Message Only	470	16	$27.97	$0.06	$0.00	1.01	1.37
10	CLONIDINE HCL	MIN. DAYS THERAPY = 7	Message Only	436	37	$497.64	$1.14	$0.00	1.26	3.48
All Others				14,804	955	$1,187,349.13	$80.20	$0.00	2.02	35.87
MN				**22,410**	**1,319**	**$1,206,435.23**	**$53.83**	**$0.00**	**2.08**	**30.33**

MX

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	2,421	1,766	$25,011.69	$10.33	$0.00	31.54	66.38
2	CYCLOBENZAPRINE HCL	MAX DAYS THERAPY = 21	Message Only	1,461	0	$15,094.83	$10.33	$0.00	32.20	72.54
3	FLUCONAZOLE	MAX DAYS THERAPY = 1	Message Only	500	159	$6,442.39	$12.88	$0.00	7.69	3.05
4	EPIPEN 2-PAK	MAX DAYS THERAPY = 1	Message Only	365	8	$232,394.92	$636.70	$0.00	10.83	2.27
5	AZITHROMYCIN	MAX DAYS THERAPY = 5	Message Only	265	70	$5,814.26	$21.94	$0.00	11.47	20.98
6	EPINEPHRINE	MAX DAYS THERAPY = 1	Message Only	251	10	$77,655.31	$309.38	$0.00	14.49	2.46
7	DIPHENOXYLATE/ ATROPINE	MAX DAYS THERAPY = 14	Message Only	197	7	$5,903.85	$29.97	$0.00	27.97	95.22
7	POLYETHYLENE GLYCOL 3350	MAX DAYS THERAPY = 14	Message Only	197	14	$5,836.07	$29.62	$0.00	31.45	32.09
9	SENEXON-S	MAX DAYS THERAPY = 14	Message Only	182	14	$1,717.78	$9.44	$0.00	32.14	62.90
10	MAPAP	MAX DAYS THERAPY = 10	Message Only	164	8	$1,582.96	$9.65	$0.00	26.52	135.23
All Others				2,903	392	$748,210.60	$257.74	$0.00	29.47	68.13
MX				**8,906**	**2,448**	**$1,125,664.66**	**$126.39**	**$0.00**	**27.55**	**59.70**

PA

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx	Quantity Per Rx
1	PROMETHAZINE HCL	AGE LESS THAN 4	Message Only	16	0	$183.15	$11.45	$0.00	8.12	177.75
2	PROMETHAZINE HCL PLAIN	AGE LESS THAN 4	Message Only	10	0	$57.37	$5.74	$0.00	9.60	105.00
2	NITROFURANTOIN	AGE LESS THAN 4	Message Only	10	2	$1,613.65	$161.36	$0.00	24.80	154.50
4	PROMETHAZINE/ DEXTROMETHOR	AGE LESS THAN 4	Message Only	5	0	$54.41	$10.88	$0.00	11.20	78.80
4	PROMETHAZINE-DM	AGE LESS THAN 4	Message Only	5	0	$57.57	$11.51	$0.00	11.60	126.00
6	PROMETHEGAN	AGE LESS THAN 4	Message Only	2	0	$157.63	$78.82	$0.00	3.00	8.50
7	PHENYLEPHRINE HCL	AGE LESS THAN 4	Message Only	1	0	$100.17	$100.17	$0.00	30.00	15.00
7	BENZTROPINE MESYLATE	AGE LESS THAN 4	Message Only	1	0	$13.69	$13.69	$0.00	30.00	60.00
PA				**50**	**2**	**$2,237.64**	**$44.75**	**$0.00**	**13.08**	**131.10**

TD

Curr Rank	Top Drug	Therapy / Reason	DUR Response	Paid Rxs	Rejected Rxs	Plan Paid	Plan Paid Per Rx	Member Paid Per Rx	Days Supply Per Rx
1	QUETIAPINE FUMARATE	ORAL ANTIPSYCHOTICS	Message Only	2,700	1	$41,363.12	$15.32	$0.00	29.31
2	RISPERIDONE	ORAL ANTIPSYCHOTICS	Message Only	1,653	0	$20,443.59	$12.37	$0.00	29.85
3	MORPHINE SULFATE	SHORT ACTING NARCOTIC ANALGESI	Message Only	1,577	49	$4,344.98	$2.76	$0.00	1.00
4	LISINOPRIL	ANGIOTENSIN BLOCKERS	Message Only	1,153	0	$11,780.89	$10.22	$0.00	69.99
5	GABAPENTIN	GABAPENTIN AND RELATED	Message Only	1,148	0	$18,455.19	$16.08	$0.00	35.02
6	ARIPIPRAZOLE	ORAL ANTIPSYCHOTICS	Message Only	1,079	0	$59,319.66	$54.98	$0.00	30.68
7	LEVOTHYROXINE SODIUM	THYROID HORMONES	Message Only	932	0	$16,731.01	$17.95	$0.00	49.28
8	OLANZAPINE	ORAL ANTIPSYCHOTICS	Message Only	878	0	$14,087.72	$16.05	$0.00	28.60
9	HYDROMORPHONE HCL	SHORT ACTING NARCOTIC ANALGESI	Message Only	871	48	$3,914.04	$4.49	$0.00	1.00
10	SERTRALINE HCL	SSRIS AND SNRIS	Message Only	808	0	$9,785.66	$12.11	$0.00	34.27
All Others				81,055	114,198	$14,680,252.55	$181.11	$0.00	29.45
TD				**93,854**	**114,296**	**$14,880,478.41**	**$158.55**	**$0.00**	**29.52**

RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

TD

Quantity Per Rx
41.78
49.40
1.70
75.67
112.64
35.33
47.82
37.16
2.44
42.18
75.92
71.59

RXT6050D - Summarized DUR Activity Report

Between 2017-04-01 and 2017-06-30

Selected Filters

Client(s): Nevada Medicaid - HPES

Carrier(s): NVM-NEVADA MEDICAID

Account(s): ALL

Group(s): ALL

Date Type:	Date Filled Submitted
Start Date:	2017-04-01
End Date:	2017-06-30
Relative Description:	Select Date Range
Display Report Description:	No
Top Values to Display:	10