South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 15, 2018

DSS

Strong Families - South Dakota's Foundation and Our Future

Table of Contents

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Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

June 15, 2018
1:00 – 3:00 PM

DDN Locations:
Sioux Falls
University Center
DDN Room FADM145
4801 North Career Avenue

Pierre
Capitol Building
DDN Room CAP A
500 East Capitol

Rapid City
Black Hills State University
DDN Room UC113
4300 Cheyenne Boulevard

Call to order

Approval of minutes of previous meeting

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Review PA forms & criteria**
  - **Review criteria for Lyrica**
  - **Review criteria for Genitourinary Smooth Muscle Relaxants**
  - **Review criteria for PCSK9 Inhibitors**
- **Review of Duzallo & Zurampic**
- **Review of Ingrezza**
- **Review PA for opioid cough suppressants**

New business
- **Review of Aimovig**

Oral presentations and comments

Next meeting date/adjournment – 9/7/18 and 12/7/18

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, March 16, 2018
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Kelley Oehlke, PharmD	X
Dana Darger, RPh		Lenny Petrik, PharmD	
James Engelbrecht, MD		Timothy Soundy, MD	
Mikal Holland, MD		Mike Jockheck, DSS Staff	X
Richard Holm, MD	X	Sarah Akers, DSS Staff	X
Bill Ladwig, RPh, Chair	X	Mary Carpenter, MD, DSS Staff	X

Administrative Business
The meeting was called to order by Ladwig at 1:06 PM. The minutes of the December meeting were presented. Holm made a motion to approve. Oehlke seconded the motion. Motion was approved unanimously.

Prior Authorization Update (PA) and Statistics
The committee reviewed the PA activity report for November 13, 2017 through December 30, 2017. There were a total of 776 PAs reviewed during this time period. There were 342 requests (44%) received via telephone and 434 requests (56%) received via fax.

Analysis of the Top 15 Therapeutic Classes and Drug Spend
The committee reviewed the top 15 therapeutic classes by total cost of claims from 10/1/2017 to 12/31/2017. The top five classes were atypical antipsychotics, insulins, respiratory and CNS stimulants, amphetamines, and anticonvulsants. The top 15 therapeutic classes make up 31.97% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 17.40% of total claims. Cystic fibrosis potentiators dropped from the top 15 therapeutic classes by total cost of claims during this quarter.

Peer-to-peer update
Jockheck provided a peer-to-peer update on prescribers with recipients utilizing opioids greater than 300 MED. Of the top ten patients; three recipients had a terminal diagnosis and two had started on a tapering schedule. For the remaining five recipients, their records were still under review to assemble a plan of action.

Review of Duzallo & Zurampic
The committee reviewed Duzallo and Zurampic clinical information and requested utilization summary of all anti-gout agents for the next meeting. In addition, committee was made aware of a drug safety communication from the FDA regarding increased risk of heart-related death with febuxostat. There was no public comment.

Review of PA Forms & Criteria
The committee reviewed all PA criteria currently in effect and requested follow up information for a more in-depth review at the next meeting:

- Non-Sedating Antihistamines – under consideration for PA removal; requested PA approval/denial information (page 33)
- Non-Sedating Antihistamines (chewable, liquid, ODT) – under consideration for PA removal; requested PA approval/denial and cost information (page 34)
- Amrix & Fexmid (cyclobenzaprine) – Committee requested utilization and PA summary (page 37)
- Genitourinary Smooth Muscle Relaxant – Holm commented on its questionable benefit and potential danger; and questioned whether criteria should these be strengthen (page 45)
- Hepatitis C – Mavyret and Vosevi are being added to criteria (page 55)
- Immunomodulator – add Kevzara to criteria (pages 64-81)
- Topical Ketoconazole – Committee inquired if a PA was warranted; under consideration for PA removal if drugs are now inexpensive (page 82)
- Topical Onychomycosis Agents – under consideration for PA removal if inexpensive (page 83)
- Lidoderm – Committee requested utilization, PA approval/denial, and cost (page 87)
- Nasal Steroids – under consideration for PA removal if inexpensive; Committee commented on many of the products' OTC status; requested utilization and pricing information (page 94)
- Topical Acne Agents – Committee requested to make sure only brand products on PA; utilization data and PA information requested (page 103)
- Proton Pump Inhibitors – Committee requested utilization of PPIs including PA approval/denial information (page 107)
- Soma 250 mg – Committee requested utilization for all soma products (page 113)
- Tramadol ER – Committee requested all tramadol utilization (page 115-116)

Pipeline & Patent Expiration
Pipeline and patent information for 1Q18 were reviewed.

FDA Advisory Committee – opioids c/c in children
Committee reviewed the FDA Pediatric Advisory Committee recommendations on the benefit/risk profile on the use of prescription opioid cough suppressants for treatment of cough in patients under 18 years of age. After reviewing utilization data of all cough/cold/allergy for recipients under 18 years old for South Dakota Medicaid recipients, committee inquired what the other State Medicaid plans are doing regarding these FDA recommendations. Committee requested a PA form be developed to review at the next meeting. Baack volunteered to provide feedback on proposed PA criteria prior to the next meeting.

Review of Ingrezza
Ingrezza clinical information was presented for review. Thom Board, representative from Neurocrine Biosciences, spoke and provided additional information highlighting the AIMS score for primary endpoint for Ingrezza. He also mentioned that utilization was mainly within the dual eligible population. Committee wanted to monitor utilization for the next meeting.

Review of Xepi
Xepi clinical information was presented for review. Committee recommended adding Xepi to step therapy with a 10 day trial of mupirocin ointment first within the last 3 months. Holm motioned adding Xepi to PA. Baack seconded the motion. The motion was approved unanimously.

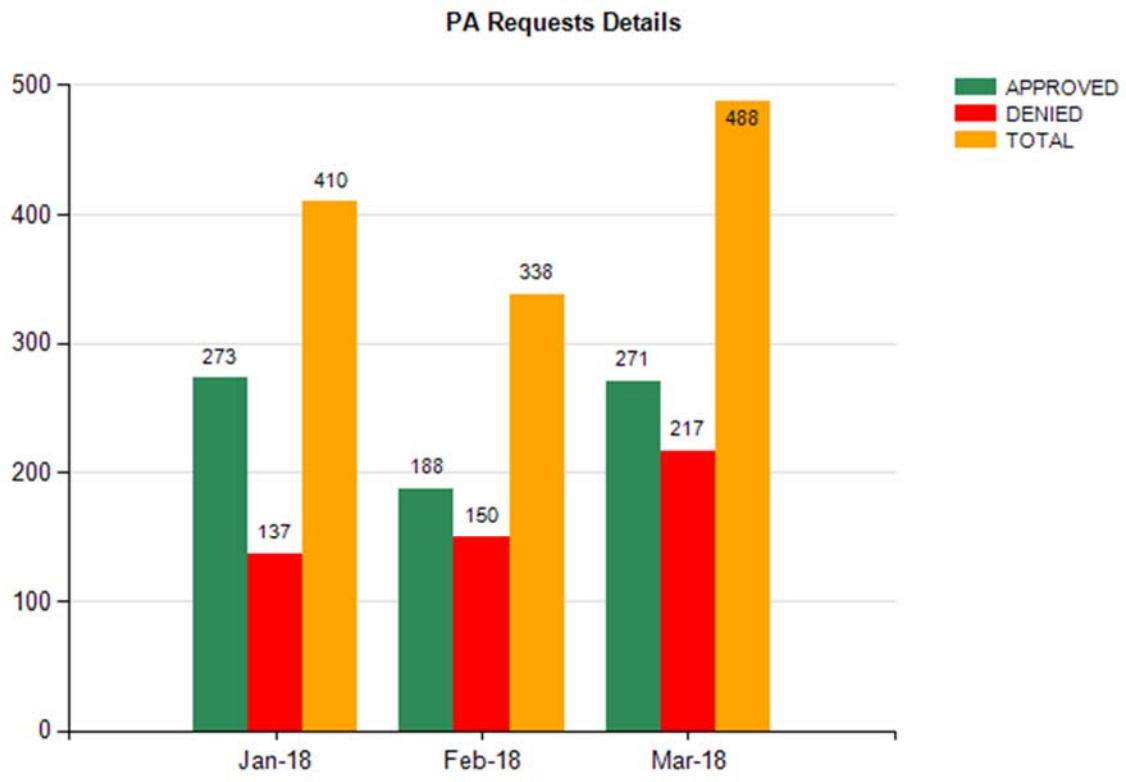
Next meeting is scheduled for 6/15/2018. Meeting dates of 9/7/2018 and 12/7/2018 were also scheduled. Baack made a motion to adjourn. Holm seconded. The meeting adjourned at 3:18 PM.

SDM - South Dakota Medicaid Quarterly Report
1/1/2018 to 3/31/2018

Priority	Total PAs	PAs Compliant Standard - 72 Hrs Urgent - 24 Hrs	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
URGENT	39	39	0	100.00%	0.00%
STANDARD	1197	1197	0	100.00%	0.00%
GRAND TOTAL	**1236**	**1236**	**0**		

Prior Authorization Initial Requests Summary

Month	Approved	Denied	Total
Jan-18	273	137	410
Feb-18	188	150	338
Mar-18	271	217	488
1Q18	732	504	1236
Percent of Total	59.22%	40.78%	



Top 5 Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
72-Anticonvulant	91	136	227	40.09%	18.37%	Lyrica, Onfi
90-Dermatologicals	85	87	172	49.42%	13.92%	Lidocaine, clindamycin/benzoyl peroxide
59-Antipsychotics/ Antimanic Agents	83	22	105	79.05%	8.50%	aripiprazole, risperidone
58-Antidepressants	84	11	95	88.42%	7.69%	duloxetine, fluoxetine
49-Ulcer Drugs	56	34	90	62.22%	7.28%	esomeprazole, Dexilant
Others	333	214	547	60.88%	44.26%	
1Q18	**732**	**504**	**1236**	59.22%		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
00 - COMPOUND & MISCELLANEOUS	0	1	1	0.00%
03 - MACROLIDES*	2	0	2	100.00%
05 - FLUOROQUINOLONES*	0	1	1	0.00%
07 - AMINOGLYCOSIDES*	3	1	4	75.00%
12 - ANTIVIRALS*	23	14	37	62.16%
15 - ANTHELMINTICS*	0	1	1	0.00%
16 - ANTI-INFECTIVE AGENTS - MISC.*	8	1	9	88.89%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	0	1	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	11	2	13	84.62%
25 - CONTRACEPTIVES*	1	1	2	50.00%
27 - ANTIDIABETICS*	9	2	11	81.82%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	9	16	25	36.00%
32 - ANTIANGINAL AGENTS*	0	1	1	0.00%
33 - BETA BLOCKERS*	5	2	7	71.43%
34 - CALCIUM CHANNEL BLOCKERS*	2	0	2	100.00%
36 - ANTIHYPERTENSIVES*	3	2	5	60.00%
39 - ANTIHYPERLIPIDEMICS*	3	3	6	50.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	2	0	2	100.00%
41 - ANTIHISTAMINES*	5	1	6	83.33%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	3	1	4	75.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	5	4	9	55.56%

45 - RESPIRATORY AGENTS - MISC.*	0	2	2	0.00%
46 - LAXATIVES*	1	0	1	100.00%
49 - ULCER DRUGS*	56	34	90	62.22%
50 - ANTIEMETICS*	14	2	16	87.50%
52 - GASTROINTESTINAL AGENTS - MISC.*	23	16	39	58.97%
54 - URINARY ANTISPASMODICS*	12	26	38	31.58%
58 - ANTIDEPRESSANTS*	84	11	95	88.42%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	83	22	105	79.05%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	1	3	4	25.00%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	42	38	80	52.50%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	19	2	21	90.48%
65 - ANALGESICS - OPIOID*	33	14	47	70.21%
66 - ANALGESICS - ANTI-INFLAMMATORY*	43	12	55	78.18%
67 - MIGRAINE PRODUCTS*	3	8	11	27.27%
68 - GOUT AGENTS*	0	1	1	0.00%
72 - ANTICONVULSANTS*	91	136	227	40.09%
75 - MUSCULOSKELETAL THERAPY AGENTS*	8	6	14	57.14%
78 - MULTIVITAMINS*	0	1	1	0.00%
82 - HEMATOPOIETIC AGENTS*	0	1	1	0.00%
83 - ANTICOAGULANTS*	31	9	40	77.50%
86 - OPHTHALMIC AGENTS*	6	18	24	25.00%
90 - DERMATOLOGICALS*	85	87	172	49.42%
94 - DIAGNOSTIC PRODUCTS*	2	1	3	66.67%
1Q18	**732**	**504**	**1236**	
Percent of Total	59.22%	40.78%		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-18	6	60.00%	4	40.00%	10
Feb-18	2	40.00%	3	60.00%	5
Mar-18	3	60.00%	2	40.00%	5
1Q18	11	55.00%	9	45.00%	20

PA Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
AMITIZA	1	2	3	33.33%
AMPHETAMINE/DEXTROAMPHETAMINE	0	1	1	0.00%
CABERGOLINE	1	0	1	100.00%
ENOXAPARIN SODIUM	0	1	1	0.00%
EPCLUSA	1	1	2	50.00%
ESOMEPRAZOLE MAGNESIUM	1	0	1	100.00%
GENOTROPIN MINIQUICK	0	1	1	0.00%
LYRICA	2	1	3	66.67%
MAVYRET	1	0	1	100.00%
MODAFINIL	0	1	1	0.00%
NUTROPIN AQ NUSPIN 10	0	1	1	0.00%
OMNITROPE	1	0	1	100.00%
ONFI	1	0	1	100.00%
RELISTOR	1	0	1	100.00%
STELARA	1	0	1	100.00%
1Q18	11	9	20	

South Dakota Medicaid

Top 15 Therapeutic Class Profile Summary by Total Cost of Claims

Therapeutic Class Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	% Total Claims
ATYPICAL ANTIPSYCHOTICS	7,319	$1,785,870.72	$244.00	3.44%
INSULINS	2,809	$1,321,706.35	$470.53	1.32%
RESPIRATORY AND CNS STIMULANTS	7,198	$1,270,894.10	$176.56	3.38%
AMPHETAMINES	6,602	$1,265,103.87	$191.62	3.10%
MISCELLANEOUS ANTICONVULS	10,598	$1,218,247.34	$114.95	4.98%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	233	$1,054,425.20	$4,525.43	0.11%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,824	$754,275.28	$85.48	4.15%
ADRENALS	6,431	$713,682.26	$110.98	3.02%
ANTINEOPLASTIC AGENTS	354	$678,393.11	$1,916.36	0.17%
SKIN AND MUCOUS MEMBRANE	492	$566,773.12	$1,151.98	0.23%
NEURAMINIDASE INHIBITORS	3,086	$519,533.69	$168.35	1.45%
IMMUNOMODULATORY AGENTS	52	$439,049.99	$8,443.27	0.02%
PROTON-PUMP INHIBITORS	6,101	$322,426.57	$52.85	2.87%
MISCELLANEOUS GI DRUGS	287	$315,704.17	$1,100.01	0.13%
HEMOSTATICS	25	$314,583.85	$12,583.35	0.01%
TOTAL TOP 15 THERAPEUTIC CLASSES	**60,411**	**$12,540,669.62**	**$207.59**	**28.39%**

Top 15 Therapeutic Class Profile Summary by Total Number of Claims

Therapeutic Class Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	11,166	$111,732.35	$10.01	5.25%
AMINOPENICILLIN ANTIBIOTICS	10,646	$148,415.43	$13.94	5.00%
MISCELLANEOUS ANTICONVULS	10,598	$1,218,247.34	$114.95	4.98%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,824	$754,275.28	$85.48	4.15%
OPIATE AGONISTS	8,752	$297,172.87	$33.95	4.11%
ATYPICAL ANTIPSYCHOTICS	7,319	$1,785,870.72	$244.00	3.44%
RESPIRATORY AND CNS STIMULANTS	7,198	$1,270,894.10	$176.56	3.38%
AMPHETAMINES	6,602	$1,265,103.87	$191.62	3.10%
ADRENALS	6,431	$713,682.26	$110.98	3.02%
SECOND GENERATION ANTIHIS	6,343	$52,435.36	$8.27	2.98%
PROTON-PUMP INHIBITORS	6,101	$322,426.57	$52.85	2.87%
THYROID AGENTS	3,658	$62,065.02	$16.97	1.72%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	3,438	$41,668.96	$12.12	1.62%
OTHER MACROLIDE ANTIBIOTICS	3,385	$74,199.37	$21.92	1.59%
MISC. CENTRAL NERVOUS SYS	3,330	$277,306.21	$83.28	1.57%
TOTAL TOP 15 THERAPEUTIC CLASSES	**103,791**	**$8,395,495.71**	**$80.89**	**48.78%**

Total Rx Claims from 01/01/2018 - 03/31/2018	**212,776**

Top 50 Drugs Based on Total Claims Cost from 1/1/2018 to 3/31/2018

Drug Brand Name	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
VYVANSE	AMPHETAMINES	3,438	$985,823.40	$286.74	1.62%
METHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	4,186	$837,378.93	$200.04	1.97%
LATUDA	ATYPICAL ANTIPSYCHOTICS	449	$511,251.67	$1,138.65	0.21%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	74	$451,064.54	$6,095.47	0.03%
INVEGA SUSTENNA	ATYPICAL ANTIPSYCHOTICS	170	$358,870.15	$2,111.00	0.08%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	2,263	$320,259.16	$141.52	1.06%
ONFI	BENZODIAZEPINES (ANTICONV	221	$293,621.01	$1,328.60	0.10%
LYRICA	MISCELLANEOUS ANTICONVULS	534	$273,743.67	$512.63	0.25%
NOVOLOG FLEXPEN	INSULINS	521	$273,371.59	$524.71	0.24%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,320	$265,095.49	$200.83	0.62%
STELARA	SKIN AND MUCOUS MEMBRANE	14	$257,653.99	$18,403.86	0.01%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,995	$248,724.54	$83.05	1.41%
KALYDECO	CYSTIC FIBROSIS (CFTR) POTENTIATORS	9	$224,561.04	$24,951.23	0.00%
ADVAIR DISKUS	SELECTIVE BETA-2-ADRENERGIC AGONISTS	519	$219,372.17	$422.68	0.24%
PULMOZYME	MUCOLYTIC AGENTS	59	$214,525.59	$3,636.03	0.03%
LANTUS SOLOSTAR	INSULINS	570	$209,967.40	$368.36	0.27%
FLOVENT HFA	ADRENALS	834	$201,746.14	$241.90	0.39%
TAMIFLU	NEURAMINIDASE INHIBITORS	822	$199,211.83	$242.35	0.39%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,596	$198,348.78	$124.28	0.75%
ATOMOXETINE	MISC. CENTRAL NERVOUS SYS	925	$190,092.30	$205.51	0.43%
ENBREL SURECLICK	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	37	$187,840.27	$5,076.76	0.02%
VIMPAT	MISCELLANEOUS ANTICONVULS	206	$167,442.02	$812.83	0.10%
RECOMBINATE	HEMOSTATICS	5	$167,328.76	$33,465.75	0.00%
BUDESONIDE	ADRENALS	440	$166,005.92	$377.29	0.21%
REVLIMID	ANTINEOPLASTIC AGENTS	9	$154,926.48	$17,214.05	0.00%
MAVYRET	HCV PROTEASE INHIBITOR ANTIVIRALS	11	$151,614.10	$13,783.10	0.01%
BANZEL	MISCELLANEOUS ANTICONVULS	63	$143,352.29	$2,275.43	0.03%
LEVEMIR FLEXTOUCH	INSULINS	297	$134,100.36	$451.52	0.14%
PREVACID SOLUTAB	PROTON-PUMP INHIBITORS	265	$133,749.30	$504.71	0.12%
NOVOLOG	INSULINS	273	$129,601.86	$474.73	0.13%
ARISTADA	ATYPICAL ANTIPSYCHOTICS	60	$129,229.72	$2,153.83	0.03%
JANUVIA	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	289	$118,128.25	$408.75	0.14%
GATTEX	MISCELLANEOUS GI DRUGS	3	$115,942.14	$38,647.38	0.00%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,937	$115,502.81	$59.63	0.91%
IMBRUVICA	ANTINEOPLASTIC AGENTS	9	$114,452.28	$12,716.92	0.00%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	16	$111,042.05	$6,940.13	0.01%
NORDITROPIN FLEXPRO	SOMATOTROPIN AGONISTS	39	$110,462.53	$2,832.37	0.02%
ACTIMMUNE	IMMUNOMODULATORY AGENTS	2	$109,256.72	$54,628.36	0.00%
INVEGA TRINZA	ATYPICAL ANTIPSYCHOTICS	16	$105,451.32	$6,590.71	0.01%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,610	$104,393.09	$64.84	0.76%
OXYCONTIN	OPIATE AGONISTS	220	$100,228.18	$455.58	0.10%
SABRIL	MISCELLANEOUS ANTICONVULS	6	$99,965.90	$16,660.98	0.00%
VICTOZA	INCRETIN MIMETICS	130	$97,010.10	$746.23	0.06%
TRACLEER	VASODILATING AGENTS (RESPIRATORY TRACT)	10	$94,733.21	$9,473.32	0.00%
TRESIBA FLEXTOUCH	INSULINS	184	$93,673.07	$509.09	0.09%
COSENTYX SENSOREADY PEN	SKIN AND MUCOUS MEMBRANE	11	$93,486.95	$8,498.81	0.01%
GENOTROPIN	SOMATOTROPIN AGONISTS	19	$92,593.36	$4,873.33	0.01%
TOBRAMYCIN	AMINOGLYCOSIDES	20	$91,725.45	$4,586.27	0.01%
SYMBICORT	ADRENALS	285	$90,972.46	$319.20	0.13%
ADVAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	229	$90,567.18	$395.49	0.11%
TOTAL TOP 50 DRUGS		**28,220**	**$10,349,461.52**	**$366.74**	**13.26%**

Top 50 Drugs Based on Number of Claims from 1/1/2018 to 3/31/2018

Drug Brand Name	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	8,643	$84,908.46	$9.82	4.06%
METHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	4,186	$837,378.93	$200.04	1.97%
FLUOXETINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,972	$40,448.41	$10.18	1.87%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,959	$30,714.74	$7.76	1.86%
SERTRALINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,671	$25,685.56	$7.00	1.73%
CETIRIZINE HCL	SECOND GENERATION ANTIHIS	3,551	$27,634.54	$7.78	1.67%
VYVANSE	AMPHETAMINES	3,438	$985,823.40	$286.74	1.62%
HYDROCODONE/ACETAMINOPHEN	OPIATE AGONISTS	3,394	$35,054.06	$10.33	1.60%
AZITHROMYCIN	OTHER MACROLIDE ANTIBIOTICS	3,258	$60,346.41	$18.52	1.53%
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	3,217	$80,845.47	$25.13	1.51%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	3,199	$36,516.13	$11.41	1.50%
LEVOTHYROXINE SODIUM	THYROID AGENTS	3,180	$43,587.70	$13.71	1.49%
GABAPENTIN	MISCELLANEOUS ANTICONVULS	3,037	$45,844.78	$15.10	1.43%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,995	$248,724.54	$83.05	1.41%
TRAZODONE HCL	SEROTONIN MODULATORS	2,861	$17,271.00	$6.04	1.34%
LISINOPRIL	ANGIOTENSIN-CONVERTING EN	2,418	$11,343.79	$4.69	1.14%
GUANFACINE ER	MISC. CENTRAL NERVOUS SYS	2,338	$58,839.92	$25.17	1.10%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	2,263	$320,259.16	$141.52	1.06%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	2,105	$15,588.07	$7.41	0.99%
AMOXICILLIN/CLAVULANATE P	AMINOPENICILLIN ANTIBIOTICS	1,997	$62,566.83	$31.33	0.94%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,937	$115,502.81	$59.63	0.91%
TRAMADOL HCL	OPIATE AGONISTS	1,882	$10,928.76	$5.81	0.88%
POLYETHYLENE GLYCOL 3350	CATHARTICS AND LAXATIVES	1,834	$44,803.79	$24.43	0.86%
CEFDINIR	3RD GENERATION CEPHALOSPORIN ANTIBIOTICS	1,815	$84,216.91	$46.40	0.85%
FLUTICASONE PROPIONATE	CORTICOSTEROIDS	1,801	$17,987.58	$9.99	0.85%
LORATADINE	SECOND GENERATION ANTIHIS	1,800	$10,779.77	$5.99	0.85%
PREDNISONE	ADRENALS	1,766	$11,285.57	$6.39	0.83%
ESCITALOPRAM OXALATE	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	1,739	$16,747.97	$9.63	0.82%
COMPOUND	-	1,667	$61,139.17	$36.68	0.78%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,610	$104,393.09	$64.84	0.76%
METFORMIN HCL	BIGUANIDES	1,600	$8,105.75	$5.07	0.75%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,596	$198,348.78	$124.28	0.75%
CLONAZEPAM	BENZODIAZEPINES (ANTICONV	1,581	$8,754.88	$5.54	0.74%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBIT	1,556	$10,766.46	$6.92	0.73%
RISPERIDONE	ATYPICAL ANTIPSYCHOTICS	1,542	$16,149.99	$10.47	0.72%
CEPHALEXIN	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	1,507	$19,532.84	$12.96	0.71%
QUETIAPINE FUMARATE	ATYPICAL ANTIPSYCHOTICS	1,500	$20,696.90	$13.80	0.70%
LAMOTRIGINE	MISCELLANEOUS ANTICONVULS	1,459	$28,122.91	$19.28	0.69%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,320	$265,095.49	$200.83	0.62%
BUPROPION HCL XL	ANTIDEPRESSANTS, MISCELLANEOUS	1,317	$44,203.21	$33.56	0.62%
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	1,307	$8,448.53	$6.46	0.61%
ONDANSETRON ODT	5-HT3 RECEPTOR ANTAGONIST	1,294	$13,092.64	$10.12	0.61%
DULOXETINE HCL	SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	1,290	$22,838.93	$17.70	0.61%
MIRTAZAPINE	ANTIDEPRESSANTS, MISCELLANEOUS	1,279	$11,823.70	$9.24	0.60%
VITAMIN D	VITAMIN D	1,271	$8,245.39	$6.49	0.60%
PREDNISOLONE SODIUM PHOSP	ADRENALS	1,268	$13,933.09	$10.99	0.60%
LEVETIRACETAM	MISCELLANEOUS ANTICONVULS	1,243	$40,275.67	$32.40	0.58%
CITALOPRAM HYDROBROMIDE	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	1,242	$6,039.85	$4.86	0.58%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYT	1,233	$7,665.06	$6.22	0.58%
CYCLOBENZAPRINE HCL	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	1,226	$5,653.28	$4.61	0.58%
TOTAL TOP 50 DRUGS		**113,164**	**$4,304,960.67**	**$38.04**	**53.18%**

Utilization and PA Data for PA Criteria Review

Time frame: 1/1/2018 – 3/31/2018

- A – Approval
- D – Denial

NSA (ST & SA)

Drug Name	Age Range	Total Rxs	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
cetirizine 5 mg tab	3-100	175	$1,877.64	$10.73	85	
cetirizine 10 mg tab	4-101	2,606	$15,005.60	$5.76	1,231	
cetirizine 5 mg chew	2-5	2	$247.48	$123.74	2	3 – A
cetirizine 10 mg chew	10	1	$131.23	$131.23	1	
cetirizine 1 mg/ml syrup	0-83	1,078	$13,172.90	$12.22	700	
desloratadin 5 mg tab	11-29	5	$79.55	$15.91	3	
fexofenadine 60 mg tab	8-84	28	$709.76	$25.35	16	
fexofenadine 180 mg tab	6-88	95	$1,630.61	$17.16	50	
fexofenadine 30 mg/3 ml susp	3-14	6	$151.55	$25.26	4	
levocetirizine 5 mg tab	9-63	25	$373.80	$14.95	13	1 – A 1 – D
levoceitirzine 2.5 mg/5 ml sol	6-57	8	$597.20	$74.65	3	
loratadine 10 mg tab	5-104	1,933	$11,588.64	$6.00	807	
Claritin 5 mg chew	4	1	$29.30	$29.30	1	1 – A
loratadine 5 mg/5 ml syrup	0-67	188	$2,273.10	$12.09	121	
cetirizine-D 5-120 mg tab (12hr)	9-74	92	$2,473.39	$26.88	51	
loratadine-D 5-120 mg tab (12hr)	10-71	26	$605.58	$23.29	15	
loratadine-D 10-240 mg tab (24hr)	5-86	72	$1,014.42	$14.09	42	
Clarinex-D 2.5-120 tab	18	3	$484.89	$161.63	1	

Amrix & Fexmid (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
cyclobenzaprine 5 mg tab	171	$825.19	$4.83	122	
cyclobenzaprine 10 mg tab	1,055	$4,828.09	$4.58	633	
Amrix 30MG	5	$5,539.00	$1,107.80	2	
Fexmid	0				
Total					

Lidoderm (SA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
Lidoderm	5	$1,069.57	$213.91	3	2 – D

Genitourinary Smooth Muscle Relaxant (SA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
oxybutynin 5 mg tab	181	$3,336.89	$18.44	77	
oxybutynin 5 mg/5ml syrup	36	$848.23	$23.56	18	
oxybutynin 5 mg tab ER	133	$2,144.18	$16.12	63	
oxybutynin 10 mg tab ER	186	$3,691.00	$19.84	78	1 – D
oxybutynin 15 mg tab ER	64	$2,005.60	$31.34	29	(qty)
tolterodine 1 mg tab	1	$102.74	$102.74	1	3 – D
tolterodine 2 mg tab	8	$807.72	$100.97	3	
tolterodine 2 mg cap ER	8	$749.80	$93.73	3	3 – A
tolterodine 4 mg cap ER	29	$1,753.44	$60.46	11	11 – D
trospium 20 mg tab	5	$265.94	$53.19	3	
trospium 60 mg cap ER	9	$1,303.45	$144.83	5	1 – D
Gelnique gel 10%	4	$925.13	$231.28	2	1 – A
Gelnique gel 10% Pump	1	$398.04	$398.04	1	
Oxytrol Dis 3.9 mg/24	3	$1,028.13	$342.71	1	
Toviaz 4 mg tab	1	$330.80	$330.80	1	1 – D
Toviaz 8 mg tab	17	$5,632.40	$331.32	6	
Vesicare 5 mg tab	29	$8,370.46	$288.64	9	5 – A
Vesicare 10 mg tab	33	$9,668.30	$292.98	11	3 – D
Enablex	0				1 – D
Myrbetriq	0				

Topical Ketoconazole (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
ketoconazole 2% cream	149	$6,550.97	$43.97	137	
ketoconazole 2% shampoo	127	$1,571.84	$12.39	102	
Extina	0				
Xolegel	0				

Topical Onychomycosis Agents (SA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
terbinafine 250 mg tab	67	$401.07	$5.99	47	
ciclopirox 8% nail solution	7	$143.93	$20.56	5	
Jublia 10% solution	1	$599.12	$599.12	1	
Kerydin	0				
Onmel	0				

Soma (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
carisoprodol 350 mg tab	110	$1,169.02	$10.63	54	
Soma 250 mg tab	0				

Topical Acne (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
adapalene 0.1% cream	11	$2,213.20	$201.20	10	9 – A
adapalene 0.1% gel	12	$1,696.36	$141.36	11	3 – D
adapalene 0.3% gel	10	$1,059.49	$105.95	9	
adapalene 0.3% gel pump	1	$219.55	$219.55	1	
Differin 0.3% gel	1	$577.61	$577.61	1	
Azelex 20% cream	1	$435.92	$435.92	1	1 – A
benzoyl peroxide 5% liq wash	3	$40.56	$13.52	3	
benzoyl peroxide 5% gel	2	$29.34	$14.67	2	
isotretinoin 20 mg cap	4	$927.84	$231.96	3	
isotretinoin 30 mg cap	26	$14,303.89	$550.15	15	
isotretinoin 40 mg cap	88	$59,723.17	$678.67	51	
tretinoin 0.025% cream	99	$11,316.47	$114.31	88	
tretinoin 0.05% cream	89	$13,196.47	$148.27	72	
tretinoin 0.1% cream	63	$10,106.38	$160.42	49	
tretinoin 0.01% gel	10	$815.25	$82.53	7	
tretinoin 0.025 % gel	20	$2,236.94	$111.85	14	
Retin-A 0.025% gel	2	$138.46	$69.23	1	
tretinoin 0.05% gel	7	$1,834.26	$262.04	5	
tretinoin micro 0.04% gel	7	$2,518.16	$359.74	6	
Retin-A micro 0.04% gel	1	$493.41	$493.41	1	
tretinoin micro 0.1% gel	5	$1,628.00	$325.60	5	
dapsone 5% gel	4	$2,017.25	$504.31	3	
Aczone 7.5% gel	4	$2,496.60	$624.15	4	2 – A
erythromycin 2% solution	7	$283.20	$40.46	7	
erythromycin 2% gel	12	$1,156.01	$96.33	12	
erythroymycin/benzoyl 5-3% gel	63	$3,148.28	$49.97	53	
adapalene/benz 0.1-2.5% gel	10	$2,986.88	$298.69	8	5 – A
Epiduo 0.1-2.5% gel	1	$382.40	$382.40	1	5 – D
Epiduo Forte 0.3-2.5% gel	7	$2,552.36	$364.62	5	
clindamycin 1% solution	47	$2,466.87	$52.49	39	
clindamycin 1% gel	269	$29,033.71	$107.93	201	
clindamycin 1% lotion	92	$6,982.99	$75.90	78	
clindamycin 1% swab	15	$476.11	$31.74	13	
clindamycin/tretinoin gel	1	$633.19	$633.19	1	1 – A
clindamycin/ben 1-5% gel	50	$10,780.70	$215.61	35	
clindamycin/ben 1.2-5% gel	12	$1,246.06	$103.84	9	
Acanya 1.2-2.5% gel	2	$1,110.24	$555.12	1	
Onexton 1.2-3.75% gel	1	$555.12	$555.12	1	

sulfacetamide 10% lotion	5	$435.50	$87.10	4	
sulfacetamide sod w/sulf 10-5% emul	2	$137.64	$68.82	1	
sulfacetamide sod w/sulf 10-5% cream	3	$900.22	$300.07	2	
sulfacetamide sod w/sulf 10-5% urea emul	2	$150.88	$75.44	1	

Proton Pump Inhibitors (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
Dexilant 30 mg cap	42	$11,969.77	$284.99	20	16 – A
Dexilant 60 mg cap	128	$39,243.93	$306.59	55	10 – D
esomeprazole 20 mg cap	51	$2,334.82	$45.78	25	12 – A
esomeprazole 40 mg cap	157	$15,088.40	$96.10	72	16 – D
Nexium 20 mg cap	3	$799.14	$266.38	1	8 – A
Nexium 40 mg cap	24	$8,419.53	$350.81	9	7 – D
Nexium 2.5 mg packet	2	$574.68	$287.34	2	
Nexium 5 mg packet	10	$2,873.40	$287.34	6	
Nexium 10 mg packet	19	$5,547.32	$291.96	9	
Nexium 20 mg packet	21	$6,922.02	$329.62	9	
Nexium 40 mg packet	28	$6,699.73	$239.28	13	
lansoprazole suspension 3mg/ml	41	$2,831.18	$69.05	20	1 – A
lansoprazole 15 mg cap	100	$6,059.23	$60.59	50	
lansoprazole 30 mg cap	4	$1,008.16	$252.04	3	
lansoprazole 30 mg cap	382	$10,012.13	$26.21	184	
Prevacid 30 mg cap*	4	$2,174.50	$543.63	2	
lansoprazole 15 mg tab	10	$4,508.18	$450.82	10	6 – A
lansoprazole 30 mg tab	1	$827.79	$827.79	1	8 – D
Prevacid 5 mg Solutab	169	$81,199.35	$480.47	92	
Prevacid 30 mg Solutab	96	$52,549.95	$547.40	46	
omeprazole 2mg/ml suspension	39	$3,182.29	$81.59	23	
omeprazole 10 mg cap	54	$886.71	$16.42	30	
omeprazole 20 mg cap	2,749	$20,422.57	$7.42	1,336	
omeprazole 40 mg cap	1,157	$9,413.54	$8.14	538	
Prilosec 2.5 mg pack	5	$4,165.00	$833.00	4	
Prilosec 10 mg pack	6	$1,083.13	$180.52	6	
pantoprazole 20 mg tab	78	$586.14	$7.51	42	
pantoprazole 40 mg tab	604	$4,757.87	$7.88	281	
Protonix pack*	3	$2,259.98	$753.33	2	
rabeprazole 20 mg tab	112	$8,128.62	$72.58	47	
Aciphex 10 mg sprinkle cap*	1	$550.15	$550.15	1	

Nasal Steroids (ST)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
flunisolide 0.025% spray	3	$191.07	$63.69	1	
fluticasone 50 mcg spray	1,801	$17,987.58	$9.99	1,264	
mometasone 50 mcg spray	60	$12,134.42	$202.24	39	
triamcinolone 55 mcg aero	2	$40.54	$20.27	2	
Beconase AQ 0.042%	5	$1,540.15	$308.03	2	
Dymista 137-50 spray	4	$755.09	$188.77	2	
Nasonex 50 mcg	1	$187.53	$187.53	1	1 – D
Omnaris spray	2	$546.04	$273.02	1	
Nasacort	0				
Qnasl	0				1 – A
Rhinocort	0				
Ticalast	0				
Veramyst	0				1 – A
Xhance	0				
Zetonna	0				

Hydrocodone (SA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
hydrocodone/APAP 10-325 tab	747	$12,213.02	$16.35	270	
Lorcet HD 10-325MG tab*	1	$9.64	$9.64	1	
hydrocodone/APAP 5-325 tab	2,428	$19,448.32	$8.01	1,521	
hydrocodone/APAP 7.5-325 tab	219	$3,392.72	$15.49	101	
hydrocodone/APAP 7.5-325 sol	285	$13,082.53	$45.90	259	
Lortab 10-300 mg elixir	7	$766.52	$109.50	6	
hydrocodone/IBU 5-200 mg tab	1	$0.00	$0.00	1	
hydrocodone/IBU 7.5-200 mg tab	27	$557.43	$20.65	14	
hydrocodone/APAP 2.5-325 mg tab	0				
hydrocodone/APAP 5-300 mg tab	0				
hydrocodone/APAP 7.5-300 mg tab	0				1 – D
hydrocodone/APAP 10-300 mg tab	0				
hydrocodone/APAP 10-500 mg tab	0				

Tramadol (SA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
tramadol 50 mg tab	1,882	$10,928.76	$5.81	857	
tramadol 200 mg ER cap	3	$994.83	$331.61	1	
tramadol 300 mg ER cap	1	$456.99	$456.99	1	
tramadol 100 mg ER tab	14	$1,412.85	$100.92	6	
tramadol 200 mg ER tab	7	$1,096.68	$156.67	3	
tramadol 300 mg ER tab	11	$2,864.52	$260.41	4	1 – A
tramadol/APAP 37.5-325 mg tab	26	$459.01	$17.65	14	

Custom Criteria Request Form

GPI CODING:	
Drug Name	
Lyrica (pregabalin) oral capsule	
Lyrica (pregabalin) oral solution	

APPROVAL DURATION:

1 year

CRITERIA FOR LYRICA

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

1) One of the following:
   a) Both of the following:
      - Diagnosis of neuropathic pain associated with postherpetic neuralgia, fibromyalgia, or diabetic peripheral neuropathy
      - Trial and failure, contraindication, or intolerance to a tricyclic antidepressant OR an immediate-release gabapentin
   b) Both of the following:
      - Diagnosis of partial onset seizure
      - Lyrica is being used as adjunctive therapy
   c) Diagnosis of neuropathic pain associated with spinal cord injury
2) Will patient receive concomitant gabapentin therapy?
3) Does patient have a diagnosis which confirms a difficulty in swallowing? (Lyrica solution)

Reauthorization Criteria and Duration:
Authorization for continued use shall be reviewed at least every 12 months when the following criteria are met:
1) Does patient have a positive clinical response to Lyrica therapy?
2) Will patient receive concomitant gabapentin therapy?
3) Does patient have a diagnosis which confirms a difficulty in swallowing? (Lyrica solution)

Criteria for South Dakota Medicaid

Genitourinary Smooth Muscle Relaxants PA

OPTUMRx®

Custom Criteria Request Form

GPI CODING:	
Drug Name	
Detrol (tolterodine tartrate), Detrol LA (tolterodine tartrate extended-release)	
Enablex (darifenacin extended-release)	
Oxytrol (oxybutynin patch)	
Gelnique (oxybutynin gel)	
Myrbetriq (mirabegron extended-release)	
Toviaz (fesoterodine extended-release)	
trospium chloride tablet, trospium chloride ER capsule	
Vesicare (solifenacin succinate)	

APPROVAL DURATION:

12 months

CRITERIA FOR GENITOURINARY SMOOTH MUSCLE RELAXANTS

GENITOURINARY SMOOTH MUSCLE RELAXANTS will be considered for coverage under the pharmacy benefit program when the following criteria are met:

Detrol, Detrol LA, Toviaz, Enablex, Myrbetriq, Vesicare, Trospium Chloride Tablet, trospium/ER

1. FDA approved diagnosis
2. Patient has had a 30-day trial of oxybutynin or oxybutynin ER

Gelnique, Oxytrol

1. FDA approved diagnosis
2. One of the following:
   a. Patient has had a 30-day trial of oxybutynin or oxybutynin ER within the last 4 months
   b. Patient has a diagnosis which confirms a difficulty in swallowing

Reauthorization Criteria and Duration for all except Gelnique and Oxytrol:
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

Reauthorization Criteria and Duration for Gelnique and Oxytrol:
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 Gelnique therapy
2. Patient has a diagnosis which confirms a difficulty in swallowing

Custom Criteria Request Form

GPI CODING:	
Drug Name	
Praluent (alirocumab)	
Repatha (evolocumab)	

APPROVAL DURATION:

12 months

CRITERIA FOR PCSK9 INHIBITORS

Medication is being prescribed by, or in consultation with, a cardiologist or endocrinologist.

One of the following:

- Patient has been receiving high dose statin therapy for at least 3 months (i.e., atorvastatin tab 40 mg, atorvastatin tab 80 mg, rosuvastatin tab 20 mg, rosuvastatin tab 40 mg)
- Patient is not a candidate for high dose statin therapy (e.g., labeled contraindication to all statins, patient has experienced rhabdomyolysis or muscle symptoms with statin treatment with creatine kinase elevations greater than 10 times upper limit of normal [ULN])

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

1. One of the following:
   - Diagnosis of heterozygous familial hypercholesterolemia (HeFH)
   - Diagnosis of hyperlipidemia in a high risk member with clinical arteriosclerotic cardiovascular disease (ASCVD)
2. Patient's baseline LDL-C level
3. Patient is 18 years of age or older

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

One of the following:

1. Both of the following:
   - Diagnosis of homozygous familial hypercholesterolemia (HoFH)
   - Patient is 13 years of age or older
2. One of the following:
   - Diagnosis of hyperlipidemia in a high risk member with clinical arteriosclerotic cardiovascular disease (ASCVD)
   - Diagnosis of heterozygous familial hypercholesterolemia (HeFH)

   AND
   - Patient is 18 years of age or older
3. Patient's baseline LDL-C level

Reauthorization Criteria and 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

REVIEW OF DUZALLO® & ZURAMPIC®

PRODUCT DETAILS	**DUZALLO®** (lesinurad/allopurinol) A combination drug containing lesinurad, a URAT1 (uric acid transporter 1) inhibitor and allopurinol (xanthine oxidase inhibitor). Lesinurad works by helping the kidney excrete uric acid by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. Allopurinol reduces the production of uric acid.	**ZURAMPIC®** (lesinurad) URAT1 (uric acid transporter 1) inhibitor
INDICATIONS & USE	Treatment of hyperuricemia associated with gout in adults not achieving target serum uric acid levels with allopurinol alone.	Indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. Zurampic is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as monotherapy.
DOSAGE & ADMINISTRA-TION	• Recommended dose is 1 tablet (containing lesinurad 200 mg; allopurinol 200 mg or 300 mg) once daily for patients who have not achieved target serum uric acid on allopurinol 300 mg/day or more. • Duzallo is not recommended for patients taking an allopurinol dose of less than 300 mg/day or for patients with asymptomatic hyperuricemia.	The dosage is 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. The maximum daily dose is 200 mg. • Failure to take Zurampic with a xanthine oxidase inhibitor may increase the risk of renal adverse reactions • Zurampic tablets should be taken in the morning with food and water • Assess renal function before initiating Zurampic
DOSAGE FORMS & STRENGTHS	Tablets: • 200 mg lesinurad/200 mg allopurinol • 200 mg lesinurad/300 mg allopurinol	Tablet: • 200 mg
CONTRA-INDICATIONS	Duzalla carries a boxed warning for risk of acute renal failure. It should not be initiated in patients with an estimated creatinine clearance (eCrCl) less than 45mL/min. Duzallo is contraindicated in patients with the following conditions: • severe renal impairment, end stage renal disease, kidney transplant recipients, or patients receiving dialysis • a known hypersensitivity to allopurinol, including previous occurrence of skin rash or serious rash	• Severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis • Tumor lysis syndrome or Lesch-Nyhan syndrome

	• tumor lysis syndrome (TLS) or Lesch-Nyhan syndrome, where the rate of uric acid formation is greatly increased	
	• Renal events • Skin rash & hypersensitivity • Hepatotoxicity • Cardiovascular events: major adverse cardiovascular events were observed with lesinurad; a causal relationship has not been established • Bone marrow suppression: bone marrow depression affecting one or more cell lines have been reported with allopurinol	• Renal events – Adverse reactions related to renal function have occurred after initiating Zurampic. A higher incidence was observed at the 400 mg dose, with the highest incidence occurring with monotherapy use. Monitor renal function at initiation and during therapy, particularly in patients with eCLcr below 60 mL/min, and evaluate for signs and symptoms of acute uric acid nephropathy. • Cardiovascular events – Major adverse cardiovascular events were observed with Zurampic; a causal relationship has not been established.
ADVERSE REACTIONS	The most common adverse reactions for lesinurad in combination with a xanthine oxidase inhibitor and more frequently than on xanthine oxidase inhibitor alone were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease. The most frequently reported adverse reaction for allopurinol is skin rash.	Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with Zurampic in combination with a xanthine oxidase inhibitor and more frequently than on a xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease.
DRUG INTERACTIONS	• *Mercaptopurine or Azathioprine:* Reduce mercaptopurine or azathioprine dose to approximately one-third to one-fourth of the usual dose and closely monitor for therapeutic response and the appearance of toxicity. • *Coumarin Anticoagulants:* Carefully monitor prothrombin time. • *Moderate Cytochrome P450 2C9 (CYP2C9) Inhibitors*: Use DUZALLO with caution. • *CYP3A Substrates*: Monitor for efficacy of the CYP3A substrate.	• Moderate CYP2C9 inhibitors – use with caution • Sensitive CYP3A substrates – monitor for efficacy of the CYP3A substrate
USE IN SPECIAL POPULATIONS	*Renal impairment*: Not recommended for patients with eCrCl below 45 mL/min. *Hepatic impairment*: Not recommended for patients with severe hepatic impairment.	*Renal impairment*: Not recommended for patients with eCrCl below 45 mL/min. *Hepatic impairment*: Not recommended for patients with severe hepatic impairment.
COST	AWP $14.84/tablet both strengths	200 mg – AWP $14.84/tablet

CLASS OVERVIEW OF ANTI-GOUT AGENTS

Medication	Manufacturer	Availability	SDM Review
colchicine/probenecid	Various	Generic: 0.5mg/500mg tablet	
Colcrys (colchicine)	Takeda	Brand: 0.6mg tablet	
Duzallo (lesinurad/allopurinol**)**	Ironwood Pharmaceuticals	Brand: 200mg/200mg, 200mg/300 mg tablets	P&T 12/2017
Krystexxa (pegloticase)	Crealta	Brand: 8mg IV infusion	
Mitigare (colchicine)	Hikma Americas	Brand: 0.6mg capsule	
probenecid	Various	Generic: 500 mg tablet	
Uloric (febuxostat)	Takeda	Brand 40mg, 80mg tablets	PA
Zurampic (lesinurad)	AstraZeneca	Brand 200mg tablet	P&T 6/2016
Zyloprim (allopurinol)	Sebela Pharmaceuticals	Brand/Generic: 100mg, 300mg tablets	

UTILIZATION

Drug Name	Total Rxs	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
allopurinol 100 mg tab	98	$696.13	$7.10	40	
allopurinol 300 mg tab	102	$891.55	$8.74	45	
colchicine 0.6 mg cap	7	$1,531.34	$218.76	4	
colchicine 0.6 mg tab	26	$5,629.56	$216.52	13	
Colcrys 0.6 mg tab	4	$1,531.93	$382.98	1	
Uloric 40 mg tab	6	$1,849.76	$308.29	3	1 – D
Uloric 80 mg tab	6	$2,023.62	$337.27	2	
probenecid	0				
Duzallo	0				
Zurampic	0				

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INTRODUCTION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks *(Newberry 2016).* The inflammation is induced by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as a serum uric acid (sUA) level > 6.8 mg/dL *(Neogi 2011).*
- Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate. Humans lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin (excreted in the urine) as the end product of purine metabolism. Hyperuricemia is a necessary but not sufficient precondition for the development of urate crystal deposition disease and should be distinguished from gout, the clinical syndrome. Most hyperuricemic individuals never experience a clinical event resulting from urate deposition *(Becker 2018).*
- Long-term success in achieving and maintaining sub-saturating sUA levels is associated with clinical benefits that include cessation of acute gout flares, resolution of tophi, and improvement in patient physical function and health-related quality of life (QOL) *(Becker 2018).*
- Lowering sUA levels can be achieved by decreasing uric acid production via xanthine oxidase inhibitors (XOIs) or by increasing excretion via uricosuric agents *(Becker 2018).*
  - The 2 XOIs available are Zyloprim (allopurinol) and Uloric (febuxostat). While both agents function as XOIs, they differ in their mechanism of action. Allopurinol acts as a purine analogue, while febuxostat occupies a channel in the xanthine oxidase (XO) dimer, impairing access to purine base substrates.
  - Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid.
  - Zurampic (lesinurad) is a uricosuric which inhibits uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4), and is used in combination with an XOI for the treatment of hyperuricemia associated with gout.
  - Colchicine is the agent of choice for acute gout attacks, but it can also be used prophylactically. The exact mechanism of action of colchicine in gout is not completely known, however, it is effective for pain associated with an acute gout attack.
  - Pegloticase is a pegylated uricase, which stimulates the breakdown of uric acid. It is reserved for refractory cases of gout and is administered via intravenous (IV) infusion every 2 weeks.
- Combination products such as Duzallo (lesinurad/allopurinol) and probenecid/colchicine are also available and are included in this class review.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are utilized as an alternative to colchicine for prophylaxis during the initiation of urate-lowering therapies *(Becker 2018)*. However, NSAIDs will not be included as part of this class review.
- Medispan class: Antigout Agent; Uric Acid Transporter 1 (URAT1) Inhibitor; Uricosuric agent; Xanthine Oxidase Inhibitor; Enzyme; Enzyme, Urate-Oxidase

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Colcrys (colchicine)†	✔
Duzallo (lesinurad/allopurinol)	-
Krystexxa (pegloticase)	-
Mitigare (colchicine)†	✔
probenecid	✔
probenecid/colchicine	✔
Uloric (febuxostat)	-
Zurampic (lesinurad)	-
Zyloprim (allopurinol)	✔

†Colcrys and Mitigare are both branded colchicine products; both have authorized generics available.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Colcrys (colchicine)	Duzallo (lesinurad/ allopurinol)	Krystexxa (pegloticase)	Mitigare (colchicine)	probenecid	probenecid/ colchicine	Uloric (febuxostat)	Zurampic (lesinurad)	Zyloprim (allopurinol)
Treatment and prophylaxis of gout flares in adults	✔			✔ ¥					
Chronic management of hyperuricemia in patients with gout							✔		
Treatment of chronic gout in adult patients refractory to conventional therapy			✔						
Treatment of hyperuricemia associated with gout		✔ *			✔			✔ **	
Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)									✔
Treatment of gouty arthritis when complicated by frequent, recurrent acute attacks of gout						✔			

*Duzallo is recommended for patients who have not achieved target sUA levels with a medically appropriate dose of allopurinol alone.
**Zurampic is recommended for patients who have not achieved target sUA levels with a XOI alone.
¥Mitigare is indicated for prophylaxis of gout flares only (not FDA-approved for the treatment of gout flares).

(*Prescribing information: Colcrys 2015, Duzallo 2017, Krystexxa 2016, Mitigare 2014, probenecid 2016, probenecid/colchicine 2016, Uloric 2018, Zurampic 2016, Zyloprim 2009*).

- 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

- Probenecid has been available since the 1950s and allopurinol and colchicine/probenecid have been available since the 1960s. Studies for these agents are therefore mainly limited to trials from the 1960s that were observational in nature. It should also be noted that there is limited literature evaluating the use of colchicine/probenecid.
- Colchicine was in use prior to the creation of the Food and Drug Administration (FDA), and therefore was "grandfathered" without receiving FDA approval. In 2006, however, colchicine was formally studied and officially approved under the brand name Colcrys. Mitigare, another brand of colchicine, was FDA-approved a few years later.
- A meta-analysis of 11 randomized controlled trials (RCTs) (n = 1258) was conducted in 2014 to assess the safety and efficacy of allopurinol (*Seth et al 2014*).
  - Moderate-quality evidence from 1 trial (n = 57) indicated that allopurinol 300 mg daily probably does not reduce the rate of gout attacks, but increases the proportion of participants achieving target sUA over 30 days.
  - In 2 studies (n = 453), there was no significant increase in withdrawals due to adverse effects (AEs) or serious AEs.
  - Low-quality evidence from 3 trials (n = 1136) indicated there may be no difference in the incidence of acute gout attacks with allopurinol up to 300 mg daily vs febuxostat 80 mg daily over 8 to 24 weeks (21% with allopurinol vs 23% with febuxostat, relative risk [RR] 0.89, 95% confidence interval [CI], 0.71 to 1.1); however more participants may achieve target sUA levels with febuxostat 80 mg daily vs allopurinol 300 mg daily (38% with allopurinol vs 70% with febuxostat, RR 0.56, 95% CI, 0.48 to 0.65).

- Colchicine's benefits and risks were examined in a meta-analysis conducted in 2014 (n = 124) (*Van Echteld et al 2014*).
  - Based upon pooled data from 2 trials, there was low-quality evidence that a greater proportion of patients receiving high-dose colchicine experienced a ≥ 50% decrease in pain from baseline up to 32 to 36 hours compared with placebo.
  - Only 1 trial included reduction of inflammation as part of a composite measure comprising pain, tenderness, swelling and erythema, each graded on a 4-point scale (none 0 to severe 3) to derive a maximum score for any 1 joint of 12. They reported the proportion of patients who achieved a 50% reduction in this composite score. Based upon 1 trial (n = 43), there was low-quality evidence that more patients in the high-dose colchicine group had a 50% or greater decrease in composite score from baseline up to 32 to 36 hours than patients in the placebo group.
- In a meta-analysis conducted in 2012, 6 febuxostat studies (n = 3978), were examined to determine the benefits and risks of febuxostat at multiple doses (*Tayar et al 2012*).
  - Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares vs placebo at 4 to 28 weeks (RR 1.7; 95% CI, 1.3 to 2.3, and RR 2.6; 95% CI, 1.8 to 3.7, respectively). No statistically significant differences were observed at febuxostat 40 mg and 80 mg. Compared to placebo, patients on febuxostat 40 mg were 40.1 times more likely to achieve sUA levels < 6.0 mg/dL at 4 weeks (95% CI, 2.5 to 639), with an absolute treatment benefit of 56% (95% CI, 37% to 71%). For febuxostat 80 mg and 120 mg, patients were 68.9 and 80.7 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit compared to placebo (95% CI, 13.8 to 343.9; 95% CI, 16.0 to 405.5, respectively).
  - When comparing allopurinol to febuxostat at 24 to 52 weeks, the number of gout flares was not significantly different between the 2 groups, except for febuxostat 240 mg (RR 2.3; 95% CI, 1.7 to 3.0). Patients on febuxostat 40 mg showed no statistically significant differences in benefits or AEs. Patients on febuxostat 80 mg and 120 mg were 1.8 and 2.2 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit, respectively, at 24 to 52 weeks.
- The combination of lesinurad with XOIs has been demonstrated to result in additive sUA lowering beyond that of XOIs alone. The Combining Lesinurad with Allopurinol in Inadequate Responders trials (CLEAR 1 and CLEAR 2) were replicate phase 3, 12-month, multicenter (MC), placebo-controlled (PC), double-blind (DB), RCTs (n = 603 and n = 610, respectively) assessing the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with a patient's current stable dose of allopurinol (≥ 300 mg daily or ≥ 200 mg daily for those with moderate renal impairment) compared to placebo plus allopurinol. The primary endpoint was the proportion of patients achieving an sUA level < 6.0 mg/dL at month 6 (*Bardin et al 2016, Saag et al 2017).*
  - Results for CLEAR 1 showed that 54.2% and 59.2% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 27.9% of the placebo plus allopurinol-treated group at month 6 (both p < 0.0001 vs placebo + allopurinol).
  - Results for CLEAR 2 similarly showed that 55.4% and 66.5% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 23.3% of the placebo plus allopurinol-treated group at month 6 (both p < 0.0001 vs placebo + allopurinol).
  - The majority of gout patients inadequately responding to allopurinol alone who were treated with lesinurad plus allopurinol achieved a target sUA level by month 1 and this was maintained throughout both 12-month studies.
  - Key secondary endpoints [frequency of gout flares requiring treatment during months 6 to 12 and complete resolution of ≥ 1 target tophi by month 12 (in patients with target tophi at baseline)] were not met, possibly due to the low gout flare rates and a low number of patients with target tophi at baseline.
  - An increase in serum creatinine (sCr) (1.5 x baseline) was more prevalent in the lesinurad 400 mg group. These sCr increases were transient and reversible.
- The Combination Treatment Study in Subjects with Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) was a third pivotal phase 3, 12-month, MC, PC, DB, RCT (n = 324) evaluating the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with febuxostat 80 mg compared to placebo plus febuxostat in treatment-naïve and treatment-experienced patients with tophaceous gout and elevated sUA levels (*Dalbeth et al 2017*).
  - Lesinurad 200 mg or 400 mg once daily in combination with febuxostat significantly increased the proportion of patients achieving sUA target (< 5.0 mg/dL) at all monthly visits from months 1 to 12, except for the lesinurad 200 mg + febuxostat group at month 6, compared to febuxostat alone in patients with tophaceous gout.
  - Although treatment with lesinurad + febuxostat resulted in a greater area of tophus resolution compared to febuxostat alone and an increase in the proportion of patients with complete resolution of ≥ 1 target tophi, these endpoints were not statistically significant.
- The FDA approval of pegloticase was based on two 6-month, replicate, MC, DB, PC, RCTs. Adult patients with chronic gout refractory to conventional therapy who were randomized to receive pegloticase 8 mg IV every 2 weeks, every 4 weeks, or placebo. The primary endpoint in both trials was the proportion of patients who achieved sUA < 6 mg/dL for at least 80% of the time during month 3 and month 6 (*Sundy et al 2011)*.

- sUA normalized within 24 hours of the first infusion in all patients receiving pegloticase, but afterward, some patients lost the urate-lowering response, whereas others maintained sUA < 6.0 mg/dL throughout the trial. Data showed that a greater proportion of patients treated with pegloticase every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. In trial 1, when pegloticase was dosed at 8 mg every 2 weeks, 47% of patients responded with sUA in the target range. When pegloticase was dosed at 8 mg every 4 weeks, 20% responded vs none in the placebo group. In trial 2, when pegloticase was dosed at 8 mg every 2 weeks, 38% of patients responded. With pegloticase 8 mg every 4 weeks, 49% of patients responded, while none of the placebo patients responded.
- Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a complete response for ≥ 1 tophi by the final visit compared with 7% of patients receiving placebo ($p = 0.002$ and $p = 0.20$, respectively). Both pegloticase dosing groups reported significant improvements in physical function and QOL compared with placebo.

CLINICAL GUIDELINES

- The American College of Physicians (ACP) published guidelines in 2016 for the management of acute and recurrent gout (*Qaseem et al 2017*).
  - Corticosteroids, NSAIDs, or colchicine (low-dose preferred) are recommended to treat patients with acute gout.
  - ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks.
  - Febuxostat (40 mg/day) and allopurinol (300 mg/day) are equally effective at decreasing sUA levels.
  - Data on the most appropriate duration of urate-lowering therapy are insufficient. However, moderate to high quality evidence suggests that urate-lowering therapy reduces the risk for acute gout attacks after 1 year, but not within the first 6 months of treatment.
- In 2012, the American College of Rheumatology (ACR) published guidelines for the management of gout. Some key points include:
  - An XOI, ie, allopurinol or febuxostat, is recommended as the first-line pharmacologic urate-lowering therapy.
  - Probenecid is recommended as an alternative first-line pharmacologic urate-lowering therapy option in the setting of contraindication or intolerance to at least 1 XOI agent.
  - sUA level should be lowered sufficiently to durably improve signs and symptoms of gout, with a target of < 6 mg/dL at a minimum, and often < 5 mg/dL.
  - Combination oral urate-lowering with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by therapeutically-appropriate doses of an XOI monotherapy.
  - If sUA target is not achieved, a uricosuric agent (titrated to maximum appropriate dose) can be added.
  - If sUA target still has not been achieved, then pegloticase can be considered. Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering options.
- A 2016 update to the European League Against Rheumatism (EULAR) 2006 guidelines for the management of gout makes the following key recommendations (*Richette et al 2016*):
  - Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitor if appropriate), oral corticosteroid, or articular aspiration and injectable corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment.
  - In patients with normal renal function, allopurinol is recommended for first-line urate-lowering therapy, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2 to 4 weeks if required, to reach the sUA target. If the sUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
  - In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor QOL, in whom the sUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.

SAFETY SUMMARY

- **Contraindications**
  - Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein or strong cytochrome P450 (CYP) 3A4 inhibitor, due to the potential for life-threatening and fatal colchicine toxicity.
  - Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.
  - Lesinurad is contraindicated in patients with severe renal impairment (creatinine clearance [Clcr] < 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis. Lesinurad should also be avoided in patients with tumor lysis syndrome or Lesch-Nyhan syndrome.

- Pegloticase is contraindicated in patients with G6PD deficiency, due to risk of hemolysis and methemoglobinemia.
- Probenecid is contraindicated in patients with known blood dyscrasias or uric acid kidney stones.

- **Boxed Warnings**
  - Lesinurad-containing products
    - Acute renal failure has occurred with lesinurad, especially when lesinurad was given alone.
    - Lesinurad should be used in combination with an XOI.
  - Pegloticase
    - Anaphylaxis may occur with any infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. Patients should be pre-medicated with anti-histamines and corticosteroids.
- **Warnings**
  - With the majority of these agents (except for colchicine), gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
  - The febuxostat product information carries a warning about cardiovascular events based on pre-approval clinical trials that showed a higher rate of cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes compared to allopurinol *(FDA 2017).*
    - The FDA issued a drug safety communication alerting the public that the preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol.
      - The preliminary results show that overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes.
  - The FDA approved a new warning for skin reactions that was added to the febuxostat product information in February 2018. Post marketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis have been reported in patients taking febuxostat. Anaphylaxis and severe allergic reactions have been reported with allopurinol (especially in patients with renal failure), pegloticase (boxed warning), and probenecid.
  - Caution should be used in patients with hepatic impairment when taking allopurinol or febuxostat.
  - Caution should also be used when administering allopurinol and lesinurad in patients with renal insufficiency.
  - Bone marrow suppression has been reported after allopurinol initiation, and blood dyscrasias have been reported at therapeutic doses of colchicine.
- **Adverse Effects**
  - Liver function abnormalities may be seen with allopurinol, febuxostat, and probenecid.
  - Rash has been noted with allopurinol and febuxostat.
  - Nausea, vomiting, gout flares, and headache are AEs that have been observed with most of the agents in this review.
- **Drug Interactions**
  - Allopurinol and febuxostat inhibit XO, which can cause an increase in azathioprine and mercaptopurine levels when given concomitantly. The dose of azathioprine or mercaptopurine will require reduction when used concomitantly with allopurinol. Concomitant use of either of these agents with febuxostat is contraindicated.
  - Increased colchicine levels can be seen when used with strong CYP 3A4 inhibitors.
  - When administered with probenecid, an increase in methotrexate and NSAID levels may be seen.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Colcrys (colchicine)	Tablets	Oral	Prophylaxis: Once or twice daily Treatment: 2 tablets at first sign of gout flare, followed by 1 tablet 1 hour later	Dosage adjustment of prophylactic dose recommended in patients with severe renal or hepatic failure
Duzallo (lesinurad/allopurinol)	Tablets	Oral	Once daily	Should be taken with food and water; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Krystexxa (pegloticase)	Injection	IV	Every 2 weeks	Should not be administered via IV push or bolus; premedication is recommended
Mitigare (colchicine)	Capsules	Oral	Once or twice daily	Dose adjustments should be considered in patients with severe renal and/or hepatic impairment
probenecid	Tablets	Oral	Twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
probenecid/colchicine	Tablets	Oral	Once daily for 1 week, then twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
Uloric (febuxostat)	Tablets	Oral	Once daily	Dose should be limited in patients with severe renal impairment
Zurampic (lesinurad)	Tablets	Oral	Once daily	Should be taken in combination with an XOI; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment
Zyloprim (allopurinol)	Tablets	Oral	In divided doses for doses > 300 mg	Dose should be adjusted in patients with renal failure; better tolerated when taken following meals

See the current prescribing information for full details

CONCLUSION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks *(Newberry 2016).* The inflammation is induced by the deposition of MSU crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as an sUA level > 6.8 mg/dL *(Neogi 2011).*
- Lowering sUA levels can be achieved by decreasing uric acid production via XOIs (ie, allopurinol or febuxostat) or by increasing excretion with agents such as probenecid and lesinurad *(Becker 2018).*
- XOIs are the preferred treatment for lowering sUA, while colchicine is the preferred treatment for acute gout attacks.
- With the majority of these agents, gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
- The FDA recently issued a drug safety communication alerting the public that preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol. Overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes (*FDA 2017).*
- Lesinurad and pegloticase carry boxed warnings for acute renal failure and anaphylaxis, respectively.
- Caution should be used when prescribing anti-gout medications, as several agents in this class have a number of potential drug-drug interactions.
- Pegloticase, the only IV anti-gout agent, should be utilized only in advanced, tophaceous, and symptomatic gout cases that are refractory to other anti-gout medications (*Becker 2018).*

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Publication Date: May 2, 2018

PRODUCT DETAILS OF INGREZZA® (valbenazine)

Neurocrine Biosciences

INDICATIONS AND USE

A vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents, predominantly antipsychotics/neuroleptics and metoclopramide.

DOSAGE AND ADMINISTRATION

Initial dose of 40 mg once daily. After 1 week, increase the dose to the recommended dose of 80 mg once daily. Continuation of 40 mg once may be considered for some patients or those with moderate to severe hepatic failure.

DOSAGE FORMS AND STRENGTHS

Capsule: 40 mg and 80 mg

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Somnolence
- QT prolongation
- Should be avoided in patients with congenital QT syndrome or with arrhythmias associated with a prolonged QT interval

ADVERSE REACTIONS

- Somnolence (10%)
- Anticholinergic effects (5%)
- Balance disorders/falls (4%)
- Headache (3%)
- Akathisia (2%)
- Vomiting (2%)
- Nausea (2%)
- Arthralgia (2%)

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. *Examples: isocarboxazid, phenelzine, selegiline*

- Concomitant use of strong Cytochrome P450 (CYP) 3A4 inducers is also not recommended, as this could lead to decreased levels of valbenazine. *Examples: rifampin, carbamazepine, phenytoin, St. John's wort*
- Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors. *Examples: CYP3A4 Inhibitors – itraconazole, ketoconazole, clarithromycin; CYP2D5 Inhibitors – paroxetine, fluoxetine, quinidine*

USE IN SPECIAL POPULATIONS

- Pregnancy: May cause fetal harm
- Lactation: Advise not to breastfeed
- Renal Impairment: No dosage adjustment is necessary for patients with mild to moderate renal impairment. Use is not recommended in patients with severe renal impairment.

OVERVIEW OF TD TREATMENT AGENTS

- Tetrabenazine, a VMAT2 inhibitor FDA-approved for Huntington's chorea, used off-label to treat TD
- Deutetrabenazine, a VMAT2 inhibitor indicated for the treatment of chorea associated with Huntington's disease; and treatment of tardive dyskinesia in adults

UTILIZATION

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	PA Requests
tetrabenazin 12.5 mg tab	2	$14,745.80	$7,372.90	1	
tetrabenazin 25 mg tab	3	$46,791.06	$15,597.02	1	
Xenazine 12.5 mg tab	3	$53,827.11	$17,942.37	1	
Xenazine 25 mg tab (COB payment) Total amount	1	$998.64 + $18,592.26 $19,590.90	$19,590.90	1	
Ingrezza 40 mg cap	3	$10,772.67	$3,590.89	3	
Ingrezza 80 mg cap	1	$4,986.89	$4,986.89	1	
Austedo	0				

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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

Custom Criteria Request Form:

GPI CODING:	
Drug Name	
OPIOID ANTITUSSIVE-ANTIHISTAMINE	

APPROVAL DURATION:

One time
Quantity limit for under 18 years old?

CRITERIA FOR OPIOID ANTITUSSIVE-ANTIHISTAMINE

OPIOID ANTITUSSIVE-ANTIHISTAMINE will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Must be 18 years and older
2. If younger than 18 years, must provide medical necessity/rationale

CRITERIA QUESTIONS

1. Is the patient 18 years and older?
Yes = Approve one time No = DENY. The plan provides coverage for the requested medication when used for a U.S. Food and Drug Administration (FDA)-approved age limit. The FDA is requiring safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. **If younger than 18 years old, must provide medical necessity/rationale.**

AIMOVIG™ (erenumab-aooe)

PRODUCT DETAILS
Erenumab-aooe is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function. A new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.

INDICATIONS AND USE
Preventive treatment of migraines in adult patients (migraine prophylaxis).

DOSAGE AND ADMINISTRATION
Given subcutaneously, the recommended dose is 70 mg once monthly. Some patients may benefit from a dose of 140 mg once monthly, administered as two consecutive subcutaneous injections of 70 mg each.

DOSAGE FORMS AND STRENGTHS
Pre-filled syringe auto injector:

- box, 1 pre-filled syringe auto injector, 1 ml erenumab 70mg/1mL, solution for injection
- box, 2 pre-filled syringe auto injector, 1 ml erenumab 70mg/1mL, solution for injection

CONTRAINDICATIONS
There are no contraindications listed in the manufacturer's prescribing information.

WARNINGS AND PRECAUTIONS
Latex hypersensitivity: the needle shield within the white cap of the auto-injector and the needle cap of the prefilled syringe may contain latex.

ADVERSE REACTIONS
The most common adverse reactions were injection site reactions, constipation and the formation of antibodies.

DRUG INTERACTIONS
There are no drug interactions listed in the manufacturer's prescribing information.

USE IN SPECIAL POPULATIONS
Renal impairment: There are no dosage adjustments provided in the manufacturer’s prescribing information. Clinical studies did not note a difference with mild to moderate renal impairment while severe renal impairment has not been studied. Renal impairment is not expected to affect the pharmacokinetics of erenumab-aooe.

Hepatic impairment: There are no dosage adjustments provided in the manufacturer’s prescribing information as clinical studies have not been conducted. Hepatic impairment is not expected to affect the pharmacokinetics of erenumab-aooe.

The effectiveness of Aimovig for the preventive treatment of migraine was evaluated in three clinical trials comparing Aimovig to placebo.

- The first study included 955 patients with a history of episodic migraine. Over the course of 6 months, Aimovig-treated patients experienced, on average, 1 to 2 fewer monthly migraine days (MMDs) than those on placebo.
- The second study included 577 patients with a history of episodic migraine. Over the course of 3 months, Aimovig-treated patients experienced, on average, 1 fewer MMD than those on placebo.
- The third study evaluated 667 patients with a history of chronic migraine. Over the course of 3 months, Aimovig-treated patients experienced, on average, 2 ½ fewer MMDs vs. those receiving placebo.

CLASS OVERVIEW

Medication	Manufacturer	Availability	SDM
Aimovig (erenumab-aooe)	Amgen	70mg/ml inj	6/15/18
Eptinezumab	Alder Biopharmaceuticals		CGRP
Fremanezumab	Teva		CGRP
Galcanezumab	Eli Lilly		CGRP

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