South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 26, 2025

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA
https://sdm.pharmacy.optumrx.com

September 26, 2025
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_NDc0NzQxMmQtMTIwNi00M2M5LTkzN2ItOTZkOTI0NGU2OGM5%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
teams@optum.onpexip.com
Video Conference ID: 111 794 661 02

Join by phone
+1 952-222-7450
Phone Conference ID: 347 386 92#

Call to order

Approval of previous meeting minutes

PA update
Review of top 15 therapeutic categories/top 50 drugs

Old business
- **CGRP oral and SubQ review**
- **Antipsychotics review**
- **Opioid update**

New business
- **Stelara and biosimilar review**
- **Oxervate**
- **Cholbam**
- **Promacta**
- **Symbravo**

Public input accepted after individual topic discussion
Next meeting date December 12, 2025 (tentative) & adjournment

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

Friday, June 20, 2025
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Matthew Stanley, DO	-
Bill Ladwig, RPh	X	Brandi Tackett, PharmD	X
Sarah McGill, PharmD	X	Deidra Van Gilder, PharmD, Chair	X
Jesse Nieuwenhuis, MD	X	Clarissa Barnes, MD, DSS Staff	X
Kelley Oehlke, PharmD	X	Mike Jockheck, DSS Staff	X
Lenny Petrik, PharmD	X	Taylor Koerner, DSS Staff	X
Heather Preuss, MD	X		

Administrative Business

Van Gilder called the meeting to order at 1:02 pm. Jockheck introduced new committee members Jesse Nieuwenhuis and Sarah McGill. Petrik will be leaving the committee. Van Gilder thanked him for his years of service. The minutes of the March meeting was presented. Ladwig made a motion to approve. Baack seconded the motion. The minutes were approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from January 1, 2025, to March 31, 2025. A total of 4,548 PAs were reviewed of which 104 requests (2.3%) were received via telephone, 130 requests (2.9%) were received via fax, 1,728 requests (38%) were reviewed electronically, and 2,585 requests (56.8%) were received via ePA. There was an increase of 18.5% in PAs and increase of 31% in appeals compared to the previous quarter. This increase of PAs and appeals from 4Q to 1Q were consistent as previous years.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2025, to March 31, 2025. The top five therapeutic classes based on paid amount were atypical antipsychotics, incretin mimetics, interleukin-mediated agents, immunomodulatory agents, and tumor necrosis factor inhibitors. These top 15 therapeutic classes comprise 18.85 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid constitute 9% of total claims. The drug Oxervate was new to the Top 50 drugs by paid amount.

Van Gilder inquired if there was any public comment. There were none.

Old Business

Fleqsuvy

Committee reviewed Fleqsuvy and baclofen utilization. Nieuwenhuis asked for clarification on generic baclofen suspension pricing compared to Fleqsuvy. Van Gilder inquired if there was any public comment. There were none. Van Gilder motioned to add PA on both the solution and suspension formulation for patients without dysphagia for trial of tablets first. Baack seconded motion. The motion was approved unanimously.

Opioid Update
The committee reviewed opioid outcomes compared to the previous quarter from the opioid initiatives. There was an increase in opioid utilization and utilizers during 1Q2025 with corresponding increase in total eligibility and utilizers. The average MME/day/utilizer stayed steady. Ladwig inquired about PMPM on opioid utilization. Jockheck replied state does not track PMPM on opioids specifically.

New Business
Calcitonin gene-related peptide (CGRP) review
The committee reviewed the CGRP utilization and discussed the new guidance from the American Headache Society. Omer Aziz, Field Value, Evidence, and Outcomes Liaison from Teva, provided public comment. Van Gilder stated the current criteria is reasonable.

Antipsychotics review
Barnes provided background that monitoring for second generation antipsychotics (SGAs)s is a national metric. To improve the monitoring of SGAs, it was proposed to collect metabolic monitoring during PA reviews. Baack questioned on the delay in treatment and allowing for grace periods when prescribers do not have the requested monitoring information to submit with the PA reviews. Committee discussed extensively. Omer Aziz, Field Value, Evidence, and Outcomes Liaison from Teva, provided public comment. Stefan Luft, Senior Medical Science Liaison from Luye Pharma, provided public comment. Baack requested process and provider communication before implementing this program.

Journavx
Journavx clinical information was presented for review. Committee reviewed utilization and discussed. Taha Khan, Associate Director of HEOR, at Vertex Pharmaceuticals, provided public comment. Committee recommended monitoring utilization and review again.

Ohtuvayre
Ohtuvayre clinical information was presented for review. Van Gilder inquired if there was any public comment. There were none. Van Gilder recommended monitoring utilization and review again.

Adjournment
The next meeting is scheduled for September 26, 2025. The December and March meetings are tentatively scheduled for December 12, 2025, and March 27, 2026. All motioned and were in favor of adjourning the meeting. The meeting adjourned at 2:30 pm CT.

PA Report
4/1/2025 – 6/30/2025

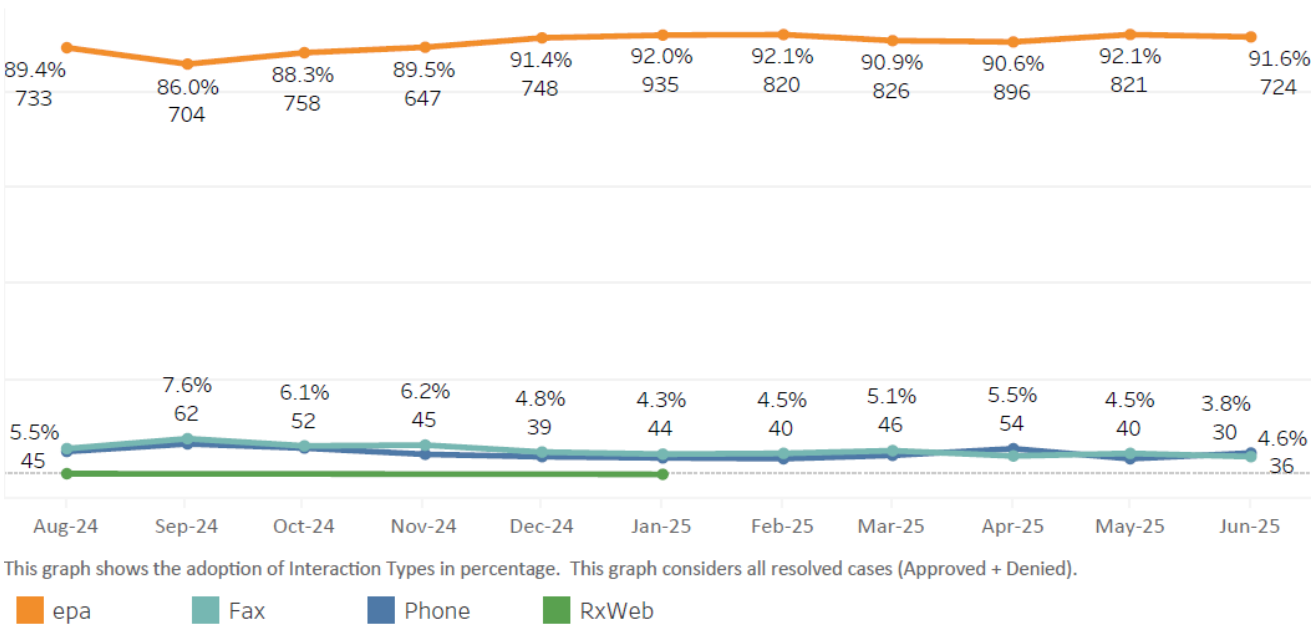
Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	3,751	3,751	0	100.00%	0.00%
Urgent	479	479	0	100.00%	0.00%
Grand Total	**4,230**	**4,230**	**0**		

Priority	Standard	Urgent
ePA	1,996	445
Fax	103	6
Phone	93	28
Real-Time	1,559	0

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**4,230**	**121**	**2.6%**	**109**	**2.9%**	**1,559**	**36.8%**	**2,441**	**57.7%**

Adoption By Interaction



PA Initial Requests Summary

Month	Approved	Denied	Total
April-25	1,236	298	1,534
May-25	1,150	255	1,405
June-25	1,066	225	1,291
2Q25	**3,452**	**778**	**4,230**
Percent of Total	**81.6%**	**18.4%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	615	57	672	91.52%	15.89%	, OZEMPIC
ANTIPSYCHOTICS/ANTIMANIC	523	35	558	93.73%	13.19%	, VRAYLAR
MEDICAL DEVICES & SUPPLIES	381	115	496	76.81%	11.73%	, DEXCOM G7 SENSOR
ANALGESICS - OPIOID	351	30	381	92.13%	9.01%	HYDROCODONE/APAP, TRAMADOL
DERMATOLOGICALS	254	59	313	81.15%	7.4%	DUPIXENT,
OTHERS -	1328	482	1810	73.37%	42.79%	
2Q25	**3,452**	**778**	**4,230**	**81.6%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
April-25	26	74.3%	9	25.7%	35
May-25	27	77.1%	8	22.9%	35
June-25	30	73.2%	11	26.8%	41
2Q25	**83**	**74.8%**	**28**	**25.2%**	**111**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	615	57	672	91.52%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	523	35	558	93.73%
97 - MEDICAL DEVICES AND SUPPLIES*	381	115	496	76.81%
65 - ANALGESICS - OPIOID*	351	30	381	92.13%
90 - DERMATOLOGICALS*	254	59	313	81.15%
58 - ANTIDEPRESSANTS*	215	34	249	86.35%
67 - MIGRAINE PRODUCTS*	211	37	248	85.08%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	78	124	202	38.61%
52 - GASTROINTESTINAL AGENTS - MISC.*	171	25	196	87.24%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	126	21	147	85.71%
66 - ANALGESICS - ANTI-INFLAMMATORY*	91	18	109	83.49%
12 - ANTIVIRALS*	43	20	63	68.25%
41 - ANTIHISTAMINES*	48	14	62	77.42%
94 - DIAGNOSTIC PRODUCTS*	13	45	58	22.41%
54 - URINARY ANTISPASMODICS*	28	25	53	52.83%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	40	11	51	78.43%
16 - ANTI-INFECTIVE AGENTS - MISC.*	39	4	43	90.70%
72 - ANTICONVULSANTS*	32	9	41	78.05%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	22	7	29	75.86%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	11	14	25	44.00%
33 - BETA BLOCKERS*	15	8	23	65.22%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	22	1	23	95.65%
83 - ANTICOAGULANTS*	15	7	22	68.18%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	20	0	20	100.00%
28 - THYROID AGENTS*	15	5	20	75.00%
75 - MUSCULOSKELETAL THERAPY AGENTS*	8	12	20	40.00%
39 - ANTIHYPERLIPIDEMICS*	11	5	16	68.75%
34 - CALCIUM CHANNEL BLOCKERS*	5	9	14	35.71%
50 - ANTIEMETICS*	6	5	11	54.55%
36 - ANTIHYPERTENSIVES*	8	0	8	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	6	7	14.29%
82 - HEMATOPOIETIC AGENTS*	6	0	6	100.00%
02 - CEPHALOSPORINS*	5	0	5	100.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	5	0	5	100.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	3	2	5	60.00%
03 - MACROLIDES*	3	1	4	75.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	3	1	4	75.00%
45 - RESPIRATORY AGENTS - MISC.*	3	1	4	75.00%
64 - ANALGESICS - NONNARCOTIC*	0	3	3	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	2	1	3	66.67%
11 - ANTIFUNGALS*	1	1	2	50.00%
22 - CORTICOSTEROIDS*	2	0	2	100.00%
57 - ANTIANXIETY AGENTS*	0	2	2	0.00%
01 - PENICILLINS*	0	1	1	0.00%
07 - AMINOGLYCOSIDES*	0	1	1	0.00%
74 - NEUROMUSCULAR AGENTS*	0	1	1	0.00%
79 - MINERALS & ELECTROLYTES*	1	0	1	100.00%
86 - OPHTHALMIC AGENTS*	0	1	1	0.00%
2Q25	**3,452**	**778**	**4,230**	
Percent of Total	**81.6%**	**18.4%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	5	1	6	83.33%
LYBALVI	4	1	5	80.00%
FREESTYLE LIBRE 3	5	4	9	55.55%
NORDITROPIN FLEXPRO	2	2	4	50.00%
VRAYLAR	2	2	4	50.00%
WEGOVY	3	1	4	75.00%
BELSOMRA	1	2	3	33.33%
BIMZELX	3	0	3	100.00%
DEXCOM G7	3	1	4	75.00%
ENOXAPARIN SODIUM	3	0	3	100.00%
HUMIRA PEN	1	2	3	33.33%
DEXMETHYLPHENIDATE HCL ER	1	1	2	50.00%
LUBIPROSTONE	1	1	2	50.00%
MAVYRET	2	0	2	100.00%
MODAFINIL	0	2	2	0.00%
MOTEGRITY	1	1	2	50.00%
ONETOUCH VERIO TEST STRIPS	2	0	2	100.00%
REPATHA SURECLICK	2	0	2	100.00%
REZDIFFRA	1	1	2	50.00%
RINVOQ	2	0	2	100.00%
SKYRIZI PEN	1	1	2	50.00%
SOFOSBUVIR/VELPATASVIR	2	0	2	100.00%
SYNTHROID	2	0	2	100.00%
TALTZ	1	1	2	50.00%
UZEDY	2	0	2	100.00%
ACETAMINOPHEN/CODEINE	1	0	1	100.00%
AIMOVIG	1	0	1	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
ARIKAYCE	1	0	1	100.00%
CYCLOBENZAPRINE HYDROCHLORIDE	1	0	1	100.00%
DEXCOM G6	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
EBGLYSS	1	0	1	100.00%
EMGALITY	1	0	1	100.00%
ENBREL SURECLICK	1	0	1	100.00%
EVRYSDI	1	0	1	100.00%
FABHALTA	1	0	1	100.00%
FINTEPLA	1	0	1	100.00%
GEMTESA	1	0	1	100.00%
HUMIRA PEDIATRIC CROHNS DISEASE STARTER PACK	1	0	1	100.00%
HYRIMOZ PEDIATRIC CROHN'SDISEASE STARTER PACK	1	0	1	100.00%
IBSRELA	1	0	1	100.00%
LANSOPRAZOLE ODT	1	0	1	100.00%
LISDEXAMFETAMINE DIMESYLATE	0	1	1	0.00%
METHADONE HYDROCHLORIDE	1	0	1	100.00%
MIRABEGRON ER	0	1	1	0.00%
MOUNJARO	1	0	1	100.00%
NUCALA	1	0	1	100.00%
NURTEC	1	0	1	100.00%
OLANZAPINE	1	0	1	100.00%
OLANZAPINE ODT	1	0	1	100.00%
OZEMPIC	1	0	1	100.00%
PALIPERIDONE ER	1	0	1	100.00%

Drug Class	Approved	Denied	Total	Approval Rate
QELBREE	0	1	1	0.00%
QUVIVIQ	1	0	1	100.00%
SKYTROFA	1	0	1	100.00%
STELARA	1	0	1	100.00%
UBRELVY	1	0	1	100.00%
VOQUEZNA	1	0	1	100.00%
ZEPBOUND	0	1	1	0.00%
2Q25	**83**	**28**	**111**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2025 – 6/30/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	18,526	$249,438.22	$13.46	5.96%
2	ATYPICAL ANTIPSYCHOTICS	13,054	$5,065,310.34	$388.03	4.20%
3	PROTON-PUMP INHIBITORS	9,771	$237,943.13	$24.35	3.14%
4	RESPIRATORY AND CNS STIMULANTS	9,729	$1,101,626.55	$113.23	3.13%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	9,299	$502,161.85	$54.00	2.99%
6	AMPHETAMINES	9,291	$884,955.10	$95.25	2.99%
7	SECOND GENERATION ANTIHISTAMINES	8,887	$95,647.09	$10.76	2.86%
8	GABA-MEDIATED ANTICONVULSANTS	8,727	$251,021.59	$28.76	2.81%
9	OPIOID AGONISTS	8,270	$239,720.38	$28.99	2.66%
10	ADRENALS	8,249	$1,116,386.93	$135.34	2.65%
11	SEROTONIN MODULATORS	7,609	$211,870.73	$27.84	2.45%
12	ANTICONVULSANTS, MISCELLANEOUS	7,489	$958,285.61	$127.96	2.41%
13	HMG-COA REDUCTASE INHIBITORS	7,114	$85,096.48	$11.96	2.29%
14	AMINOPENICILLIN ANTIBIOTICS	7,106	$108,273.42	$15.24	2.28%
15	BETA-ADRENERGIC BLOCKING AGENTS	6,252	$99,541.24	$15.92	2.01%
Total		**139,373**	**$11,207,278.66**	**$80.41**	**44.81%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2025 – 6/30/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	13,054	$5,065,310.34	$388.03	4.20%
2	IMMUNOMODULATORY AGENTS	934	$4,057,842.44	$4,344.59	0.30%
3	INCRETIN MIMETICS	3,654	$3,572,271.61	$977.63	1.17%
4	INTERLEUKIN-MEDIATED AGENTS, MISC	233	$2,727,515.18	$11,706.07	0.07%
5	TUMOR NECROSIS FACTOR INHIBITORS, MISC	317	$2,580,910.85	$8,141.67	0.10%
6	ANTINEOPLASTIC AGENTS	431	$1,894,591.90	$4,395.80	0.14%
7	CYSTIC FIBROSIS (CFTR) CORRECTORS	74	$1,697,706.47	$22,941.98	0.02%
8	HEMOSTATICS	61	$1,395,520.64	$22,877.39	0.02%
9	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	344	$1,321,440.54	$3,841.40	0.11%
10	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	2,029	$1,122,058.85	$553.01	0.65%
11	ADRENALS	8,249	$1,116,386.93	$135.34	2.65%
12	RESPIRATORY AND CNS STIMULANTS	9,729	$1,101,626.55	$113.23	3.13%
13	CALCITONIN GENE-RELATED PEPTIDE ANTAG.	1,031	$964,704.29	$935.70	0.33%
14	ANTICONVULSANTS, MISCELLANEOUS	7,489	$958,285.61	$127.96	2.41%
15	AMPHETAMINES	9,291	$884,955.10	$95.25	2.99%
Total		**56,920**	**$30,461,127.30**	**$535.16**	**18.30%**

Total Rx Claims from 4/1/2025 – 6/30/2025	**311,062**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2025 – 6/30/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Antidepressants	FLUOXETINE	6,310	$79,394.43	$12.58	2.03%
2	Anticonvulsants - 2nd Generation	GABAPENTIN	5,901	$88,633.24	$15.02	1.90%
3	Antidepressants	**SERTRALINE**	5,845	$76,757.83	$13.13	1.88%
4	Proton Pump Inhibitors	OMEPRAZOLE	5,721	$67,762.44	$11.84	1.84%
5	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,636	$187,382.49	$33.25	1.81%
6	ADHD & Narcolepsy Medications	METHYLPHENIDATE	5,164	$260,407.19	$50.43	1.66%
7	Antidepressants	TRAZODONE	5,156	$61,212.83	$11.87	1.66%
8	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	4,819	$149,758.02	$31.08	1.55%
9	Penicillins	AMOXICILLIN	4,800	$64,020.20	$13.34	1.54%
10	Thyroid Hormones	LEVOTHYROXINE	4,738	$54,263.76	$11.45	1.52%
11	Antidepressants	ESCITALOPRAM	4,595	$57,948.41	$12.61	1.48%
12	Antihistamines	**CETIRIZINE**	4,595	$47,017.16	$10.23	1.48%
13	Antidepressants	**BUPROPION**	4,399	$87,919.36	$19.99	1.41%
14	ACE Inhibitors & Combos	**LISINOPRIL**	4,224	$43,442.48	$10.28	1.36%
15	Biguanides & Combos	**METFORMIN**	4,150	$52,352.82	$12.62	1.33%
16	Statins & Combos	ATORVASTATIN	4,112	$48,567.58	$11.81	1.32%
17	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	3,763	$527,057.62	$140.06	1.21%
18	Antidepressants	**DULOXETINE**	3,329	$51,994.88	$15.62	1.07%
19	Antianxiety Agents	**HYDROXYZINE**	3,232	$42,525.65	$13.16	1.04%
20	ADHD & Narcolepsy Medications	GUANFACINE	3,178	$50,526.94	$15.90	1.02%
21	Opioid Agonists & Combos	HYDROCODONE BITARTRA/AC	3,120	$53,469.56	$17.14	1.00%
22	Leukotriene Modulators	MONTELUKAST	3,114	$39,167.73	$12.58	1.00%
23	Antiadrenergic Antihypertensives	CLONIDINE	2,937	$29,773.30	$10.14	0.94%
24	Antianxiety Agents	**BUSPIRONE**	2,775	$37,048.59	$13.35	0.89%
25	Atypical Antipsychotics	ARIPIPRAZOLE	2,766	$39,977.97	$14.45	0.89%
26	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	2,679	$30,999.83	$11.57	0.86%
27	Calcium Channel Blockers	AMLODIPINE	2,551	$27,045.28	$10.60	0.82%
28	Glucocorticosteroids	PREDNISONE	2,496	$25,306.95	$10.14	0.80%
29	Antiemetics	ONDANSETRON ODT	2,468	$35,186.63	$14.26	0.79%
30	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,440	$32,896.21	$13.48	0.78%
31	Atypical Antipsychotics	QUETIAPINE	2,365	$32,540.67	$13.76	0.76%
32	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,333	$24,491.53	$10.50	0.75%
33	Penicillins	AMOXICILLIN/CLAVULANATE	2,294	$41,635.33	$18.15	0.74%
34	Statins & Combos	ROSUVASTATIN	2,264	$27,305.98	$12.06	0.73%
35	Antihistamines	**LORATADINE**	2,235	$23,982.42	$10.73	0.72%
36	Proton Pump Inhibitors	PANTOPRAZOLE	2,233	$27,269.88	$12.21	0.72%
37	Beta Blockers & Combos	METOPROLOL SUCCINATE ER	2,211	$28,697.12	$12.98	0.71%
38	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,100	$26,250.41	$12.50	0.68%
39	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	2,020	$21,711.62	$10.75	0.65%
40	Anticonvulsants - 2nd Generation	CLONAZEPAM	2,004	$23,002.46	$11.48	0.64%
41	Cephalosporins	CEPHALEXIN	2,001	$28,789.72	$14.39	0.64%
42	Atypical Antipsychotics	RISPERIDONE	1,929	$26,793.74	$13.89	0.62%
43↓	Macrolides	AZITHROMYCIN	1,914	$28,201.55	$14.73	0.62%
44	Antidepressants	**VENLAFAXINE**	1,911	$29,313.11	$15.34	0.61%
45	Nasal Steroids	FLUTICASONE PROPIONATE	1,897	$33,174.51	$17.49	0.61%
46	Antidepressants	MIRTAZAPINE	1,862	$25,381.95	$13.63	0.60%
47↑	Opioid Agonists & Combos	OXYCODONE	1,834	$27,241.42	$14.85	0.59%
48↑	GLP-1 Receptor Agonists	MOUNJARO	1,783	$1,802,240.72	$1,010.79	0.57%
49	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,764	$24,632.47	$13.96	0.57%
50↑	Diuretics & Combos	SPIRONOLACTONE	1,746	$25,179.73	$14.42	0.56%
	Total Top 50 Drugs		**161,693**	**$4,777,247.23**	**$29.55**	**52.01%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2025 – 6/30/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	DUPIXENT	605	$2,448,979.30	$4,047.90	0.19%
2	GLP-1 Receptor Agonists	MOUNJARO	1,783	$1,802,240.72	$1,010.79	0.57%
3	Chronic Inflammatory Disease	**HUMIRA/PEN/CD/UC/HS/UV**	208	$1,797,490.79	$8,641.78	0.07%
4	Cystic Fibrosis	TRIKAFTA	72	$1,640,876.93	$22,789.96	0.02%
5	Atypical Antipsychotics	**INVEGA SUSTENNA/HAFYERA/TRINZA**	480	$1,598,726.38	$3,330.68	0.15%
6	GLP-1 Receptor Agonists	OZEMPIC	1,527	$1,458,787.37	$955.33	0.49%
7	Atypical Antipsychotics	VRAYLAR	863	$1,175,437.70	$1,362.04	0.28%
8	Chronic Inflammatory Disease	**SKYRIZI/PEN**	54	$1,152,801.07	$21,348.17	0.02%
9	Chronic Inflammatory Disease	STELARA	44	$1,133,325.38	$25,757.40	0.01%
10	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY/UNOREADY**	92	$977,630.36	$10,626.42	0.03%
11	HIV-Multiclass Combo	BIKTARVY	233	$951,769.61	$4,084.85	0.07%
12	SGLT-2 Inhibitors & Combos	JARDIANCE	1,319	$780,243.47	$591.54	0.42%
13	Chronic Inflammatory Disease	**ENBREL/SURECLICK/MINI**	78	$588,576.77	$7,545.86	0.03%
14	Diabetes Monitoring and Testing	**DEXCOM**	**1,560**	**$552,244.43**	$354.00	0.50%
15	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE DIMESYLA	3,763	$527,057.62	$140.06	1.21%
16	Atypical Antipsychotics	ARISTADA	180	$519,366.44	$2,885.37	0.06%
17	Oral Anticoagulants	ELIQUIS	917	$511,578.90	$557.88	0.29%
18	Anticonvulsants - 2nd Generation	EPIDIOLEX	186	$495,931.18	$2,666.30	0.06%
19	Chronic Inflammatory Disease	TALTZ	62	$456,833.46	$7,368.28	0.02%
20↑	Chronic Inflammatory Disease	RINVOQ	66	$444,210.89	$6,730.47	0.02%
21	Atypical Antipsychotics	**ABILIFY MAINTENA/ASIMTUFII**	132	$440,313.74	$3,335.71	0.04%
22	Atypical Antipsychotics	REXULTI	306	$427,642.44	$1,397.52	0.10%
23	Antihemophilic Products	HEMLIBRA	12	$391,856.82	$32,654.74	0.00%
24	Oncology	KISQALI	26	$386,460.55	$14,863.87	0.01%
25↑	Hepatitis C	MAVYRET	30	$385,273.59	$12,842.45	0.01%
26↑	Chronic Inflammatory Disease	BIMZELX	14	$380,446.19	$27,174.73	0.00%
27	Movement Disorder Drug Therapy	INGREZZA	51	$371,594.15	$7,286.16	0.02%
28	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	542	$350,258.48	$646.23	0.17%
29	Atypical Antipsychotics	CAPLYTA	221	$349,033.21	$1,579.34	0.07%
30↓	Rett Syndrome Agent	DAYBUE	5	$330,140.71	$66,028.14	0.00%
31	Metabolic Modifiers	PALYNZIQ	6	$328,413.30	$54,735.55	0.00%
32	Anti-Infective Agents - Misc.	XIFAXAN	100	$298,780.75	$2,987.81	0.03%
33	Irritable Bowel Syndrome (IBS) Agt	LINZESS	546	$283,857.82	$519.89	0.18%
34	Migraine Products	NURTEC	256	$283,327.27	$1,106.75	0.08%
35↓	Growth Hormones	NORDITROPIN FLEXPRO	66	$280,435.12	$4,249.02	0.02%
36	Movement Disorder Drug Therapy	**AUSTEDO XR/TITRATION**	25	$272,919.62	$10,916.78	0.01%
37	ADHD & Narcolepsy Medications	METHYLPHENIDATE HYDROCHLO	5,164	$260,407.19	$50.43	1.66%
38	Hepatitis C	SOFOSBUVIR/VELPATASVIR	32	$256,337.60	$8,010.55	0.01%
39↓	Antihemophilic Products	NOVOSEVEN RT	3	$252,931.65	$84,310.55	0.00%
40	Cystic Fibrosis	PULMOZYME	48	$240,304.76	$5,006.35	0.02%
41	Platelet Receptor Agonists	PROMACTA	16	$232,702.57	$14,543.91	0.01%
42↑	Antihemophilic Products	XYNTHA SOLOFUSE	4	$218,391.49	$54,597.87	0.00%
43↑	Antihemophilic Products	ALPROLIX	7	$217,307.01	$31,043.86	0.00%
44↑	Oncology	VERZENIO	14	$215,017.98	$15,358.43	0.00%
45↑	Angiotensin II Receptor & Neprilysin Inhibitor (ARNI)	ENTRESTO	333	$213,903.13	$642.35	0.11%
46	ADHD & Narcolepsy Medications	AZSTARYS	534	$211,544.23	$396.15	0.17%
47*	Metabolic Modifiers	VYKAT XR	5	$211,396.75	$42,279.35	0.00%
48↑	Migraine Products	UBRELVY	202	$208,963.37	$1,034.47	0.06%
49	ADHD & Narcolepsy Medications	JORNAY PM	469	$204,720.60	$436.50	0.15%
50↓	Oncology	REVLIMID	11	$193,582.50	$17,598.41	0.00%
	Total Top 50 Drugs		**23,271**	**$29,737,171.24**	**$1,277.86**	**7.48%**

Old Business

CGRP Oral and SubQ review

CGRP Utilization
Time frame: 4/1/2025 to 6/30/2025

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Aimovig (erenumab)	156	$109,324.92	$700.80	1 per 29 days	64	14 – 63
Ajovy (fremanezumab)	105	$77,384.29	$736.99	1.5 per 29.7 days	43	21 – 62
Emgality (galcanezumab)	186	$146,289.98	$786.51	1.1 per 29.2 days	74	18 – 64
Nurtec ODT (rimegepant)	256	$283,327.27	$1,106.75	8.9 per 24.9 days	137	15 – 64
Qulipta (atogepant)	120	$132,829.18	$1,106.91	30 per 30 days	50	18 – 60
Ubrelvy (ubrogepant)	202	$208,963.37	$1,034.47	9.9 per 26.2 days	116	17 – 64
Zavzpret (zavegepant)	6	$6,585.28	$1,097.55	6 per 26 days	3	25 – 43
Reyvow (lasmiditan)	4	$2,881.27	$720.32	8 per 30 days	3	32 – 51

*excludes IHS

Indications

Drug & Indications	Acute treatment of migraine with or without aura	Preventive treatment of migraine	Preventive treatment of episodic migraine	Treatment of episodic cluster headache
Aimovig (erenumab)		✔		
Ajovy (fremanezumab)		✔	✔	
Emgality (galcanezumab)		✔		✔
Nurtec ODT (rimegepant)	✔		✔	
Qulipta (atogepant) tab		✔	✔	
Ubrelvy (ubrogepant) tab	✔			
Zavzpret (zavegepant) nasal spray	✔			
Reyvow (lasmiditan) tab	✔			

CGRP Oral and SubQ Review
Time frame: 4/1/2025 to 6/30/2025

Initial review: 73 utilizers (includes IHS)
In-depth review: 54 utilizers

• Aimovig + Nurtec ODT	2 utilizers	age range 38 – 61	1 female, 1 male
• Aimovig + Ubrelvy	6 utilizers	age range 17 – 62	all female
• Ajovy + Nurtec ODT	6 utilizers	age range 26 – 48	all female
• Ajovy + Nurtec ODT or Zavzpret	1 utilizer	age range 25	female
• Ajovy + Ubrelvy	6 utilizers	age range 25 – 49	5 females, 1 male
• Ajovy + Qulipta + Ubrelvy	1 utilizer	age range 22	female
• Emgality + Nurtec ODT	8 utilizers	age range 22 – 57	7 female, 1 male
• Emgality + Nurtec ODT or Reyvow	1 utilizer	age range 32	female
• Emgality + Ubrelvy	7 utilizers	age range 23 – 64	all females
• Emgality + Ubrelvy + Zavzpret	1 utilizer	age range 35	female
• Nurtec ODT + Qulipta	6 utilizers	age range 31 – 64	5 females, 1 male
• Nurtec ODT + Qulipta + Ubrelvy	2 utilizers	age range 53 – 55	all females
• Nurtec ODT + Zavzpret	1 utilizer	age range 43	female
• Qulipta + Ubrelvy	6 utilizers	age range 28 – 55	all females

South Dakota Department of Social Services

Please note: All information below is required to process this request.
Fax to 1-844-403-1029
Mon-Sat: 7am to 7pm Central

Atypical Antipsychotics Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)

Member Name:		
Insurance ID#:		
Date of Birth:		
Street Address:		
City:	State:	Zip:
Phone:		

Provider Information (required)

Provider Name:		
NPI#:	Specialty:	
Office Phone:		
Office Fax:		
Office Street Address:		
City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength: / Dosage Form:
❑ Check if requesting **brand**	Directions for Use:
❑ Check if request is for **continuation of therapy**	

Biometric Screening Information (required beginning 1/1/2027)

Date of Screening: ____/____/_____

Blood Pressure: ☐☐☐/☐☐☐ (Systolic / Diastolic)

BMI: ☐☐.☐

A1C: ☐.☐

Total Cholesterol: ☐☐☐

HDL: ☐☐☐

LDL: ☐☐☐

Triglycerides: ☐☐☐

Clinical Information (required)

Continuation of therapy:

Is this for a continuation of a second generation atypical antipsychotic agent? ❑ **Yes** ❑ **No**

Is the patient being discharged from an in-patient psychiatric facility? ❑ **Yes** ❑ **No**

What is the patient's diagnosis for the medication being requested? (Mandatory) _____

_____

ICD-10 Code(s) (Mandatory): _____

Clinical Information:

For patients with a diagnosis of depression, has the patient tried and failed 2 different antidepressants? ❑ **Yes** ❑ **No**

For patients younger than 6 years of age, is a psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care? ❑ **Yes** ❑ **No**

For alternative dosage forms (e.g., rapid dissolve tablets, injectables, extended-release), also answer the following:

Is the patient unable to swallow? ❑ **Yes** ❑ **No**

Has the patient failed a standard dosage form from this drug class in the last 30 days? ❑ **Yes** ❑ **No**

Quantity limit requests:

What is the quantity requested per DAY? _____

What is the reason for exceeding the plan limitations?

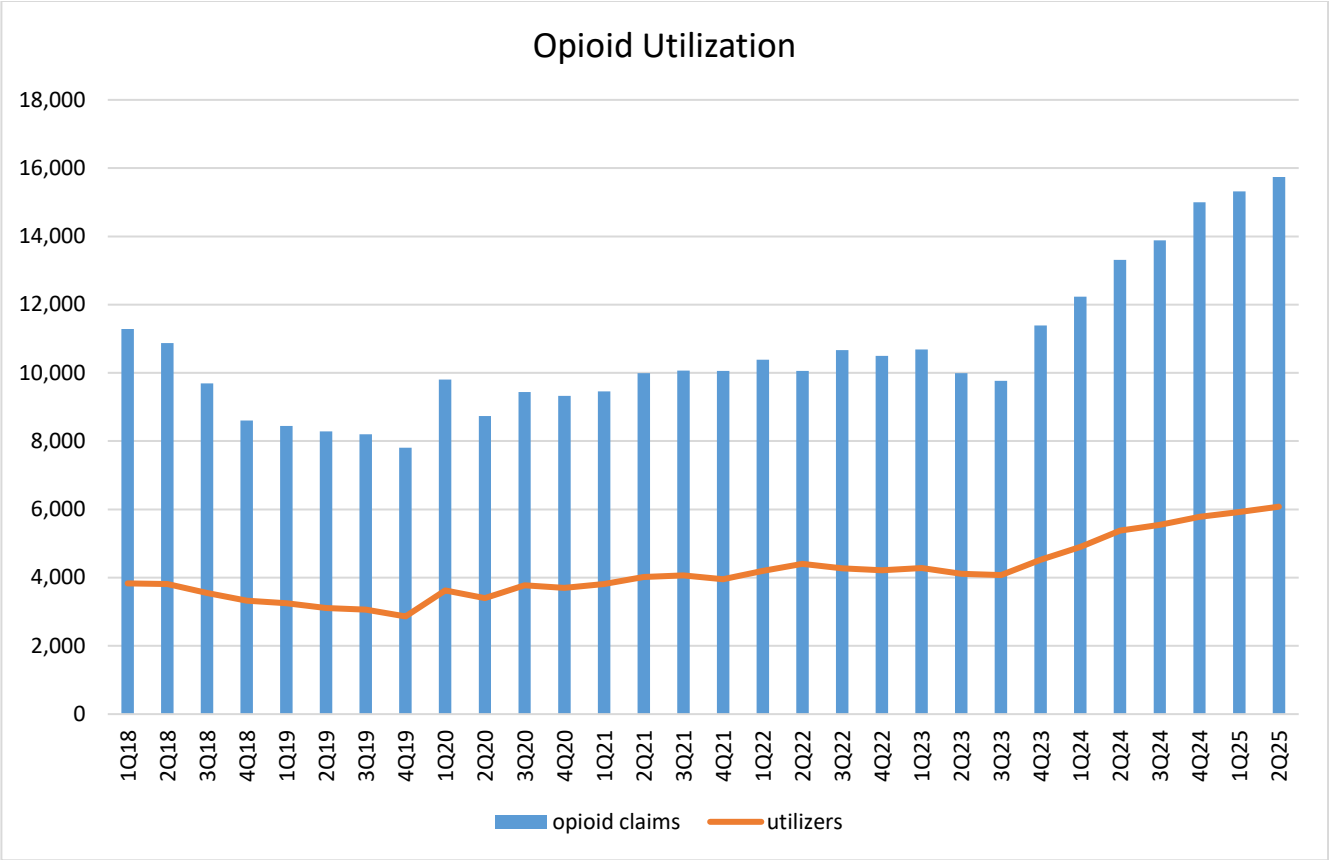
- ❑ Titration or loading dose purposes
- ❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
- ❑ Requested strength/dose is not commercially available
- ❑ Other: _____

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

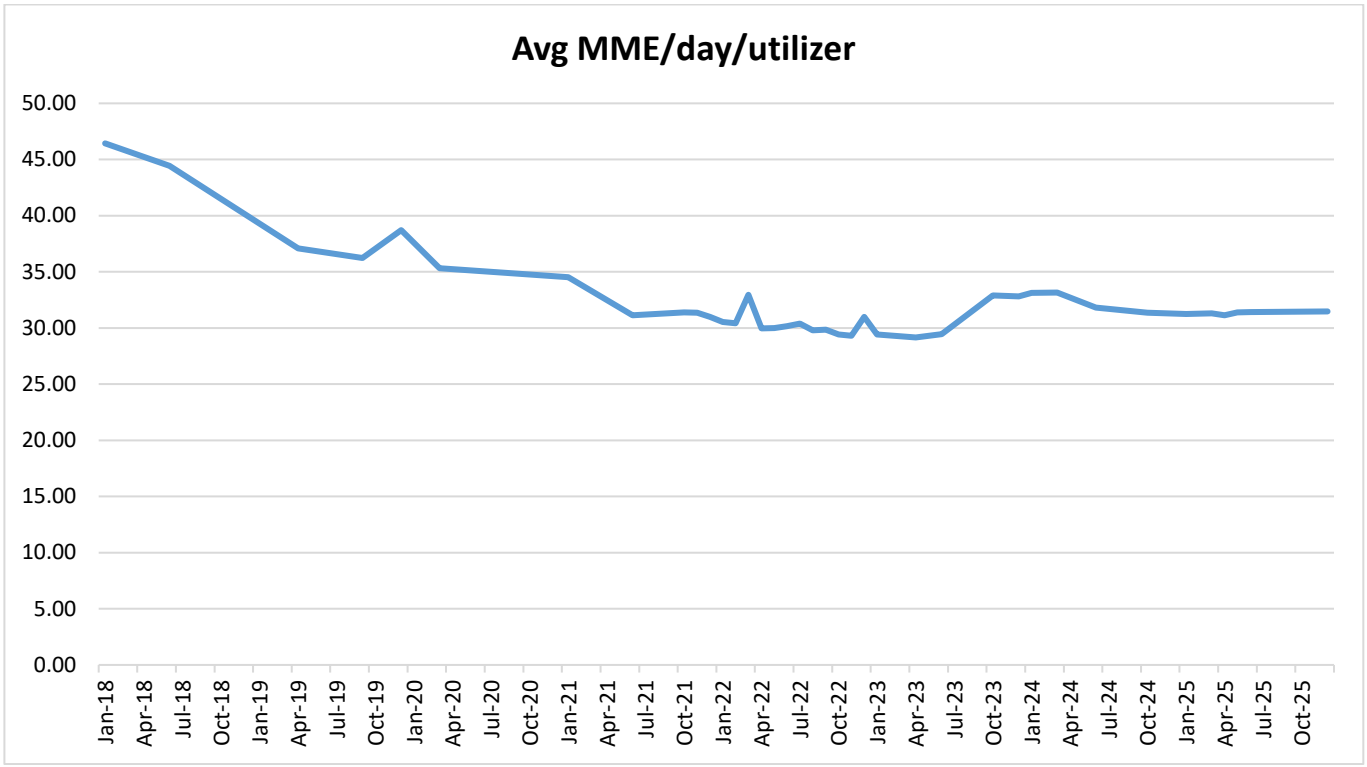
_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-844-403-1029.

Opioid Summary



- 1Q18 to 4Q19 excludes IHS
- 1Q20 to current includes IHS
- March 13, 2020 – Pandemic Closure



Opioid Initiatives:

1. June 1, 2018 – early refill threshold for controlled substance changed from 75% to 85%
2. July 1, 2028 – PA for more than one LAO and one SAO
3. August 1, 2018 – opioid Naïve PA (initial 7-day supply and 60 MED limit)
4. October 1, 2018 to October 1, 2019 – decrease from 300 MED to 90 MED (cancer diagnosis excluded)

Other Initiatives:

- Buprenorphine PA (Bunavail/Suboxone/Zubsolv/Subutex) and ST (Belbuca/Butrans) removed 10/14/2019
- Lidoderm PA removed 8/1/2020

Total Eligibles and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%
3Q2023	131,292	26,218	19.9%
4Q2023	134,270	29,320	21.8%
1Q2024	141,162	32,891	23.3%
2Q2024	149,613	32,686	21.8%
3Q2024	159,160	35,263	22.2%
4Q2024	162,163	36,468	22.5%
1Q2025	164,446	38,367	23.3%
2Q2025	161,372	34,446	21.3%

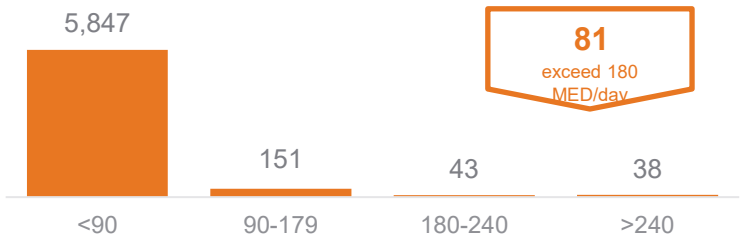
Opioid Utilization Snapshot

SDM 2Q2025
Mar 25 to Jun 25

Opioid Claims **15,744**
3.3% prescription claims filled for an opioid
1.5% higher than Medicaid FFS benchmark

Utilizers **6,079**
32.4% are high utilizers [1]
6% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]
Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
88 opioid utilizing members with 3+ pharmacies

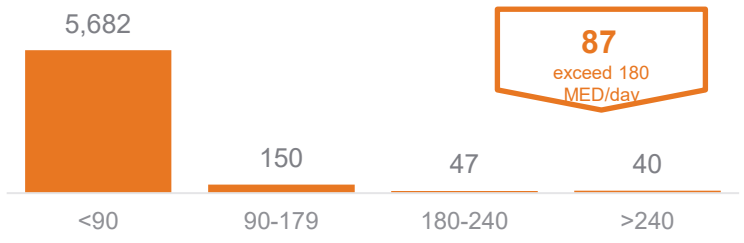
564 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

1Q2025
Dec 24 to Mar 25

Opioid Claims **15,321**
3.1% prescription claims filled for an opioid
1.3% higher than Medicaid FFS benchmark

Utilizers **5,919**
32.1% are high utilizers [1]
4.9% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]
Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy
80 opioid utilizing members with 3+ pharmacies

533 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

OPTUMRx®

[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization

SDM 2Q2025
Opportunities date range: Mar - Jun 2025
Benchmark: MEDICAID FEE FOR SERVICE

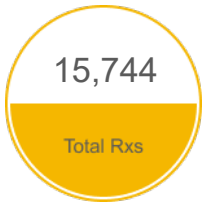
Utilizers: 6,079

3.3% of all Rx claims are filled for an Opioid

Opioid dependence can start in just a few days, and the risk of chronic opioid use increases with each additional day of opioid supplied, starting with the third day. Our Opioid Risk Management program, which includes point of sale, utilization management and retrospective drug utilization edits, are tightly aligned with CDC opioid prescribing guidelines which can help reduce exposure to excessive doses and prevent more members from transitioning from acute to chronic use.

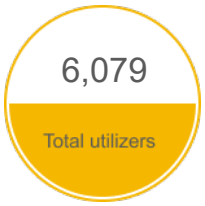
- Opioid prescriptions account for 3.3% of all prescriptions this period, which is 1.5% higher than the benchmark
- 1,970 high opioid utilizers were identified this period, which is 6.0% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
11.9%

Opioid utilizers

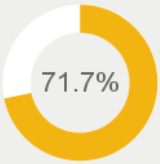


HIGH UTILIZERS
32.4%
1,970 high utilizers

6.0% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

71.7% of all opioid Rxs were filled for short acting opioids. **3,439** Rxs were for medication assisted therapy (MAT) and **152** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT – view definition
Overdose rescue therapy – view definition
MME – view definition

Utilizers by cumulative MED

81 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	5,847	151	43	38

MED – view definition

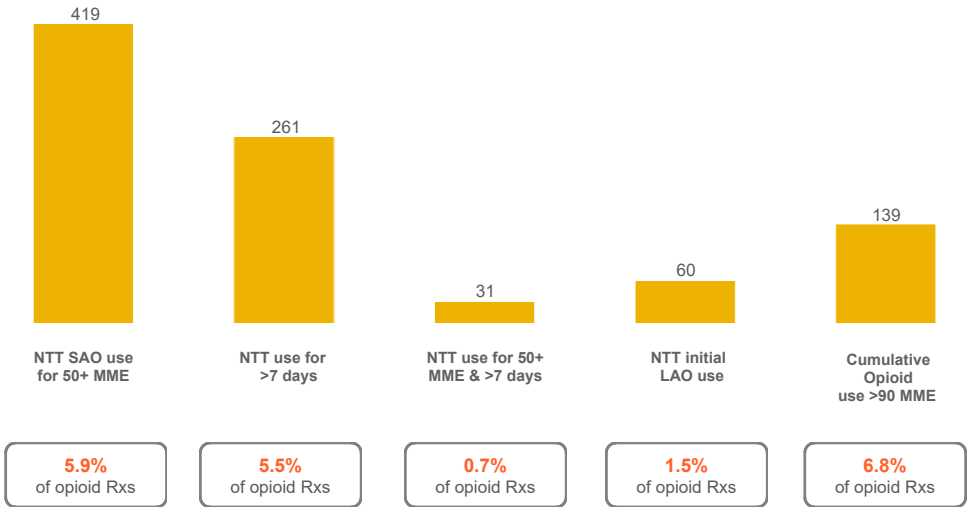
Opioid Opportunity Assessment

SDM 2Q2025
Opportunities date range: Mar - Jun 2025
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.9%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - view definition | SAO - view definition | LAO - view definition | MME - view definition

DID YOU KNOW?

88 opioid utilizing members use 3 or more pharmacies and 564 opioid utilizing members use 3 or more prescribers.

Identification, management and prevention of fraudulent or potential abuse of opioid medications are monitored and addressed by OptumRx through various means in pharmacy network audit capabilities and high touch clinical programs that include care coordination with opioid prescribers.

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
1,312	834	1,210	690	153

Anticonvulsants –view definition

New Business

Stelara and Biosimilar Review
Time frame: 4/1/2025 to 6/30/2025

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Mbr	Age Range	Net Price
Steqeyma 45mg/0.5ml ustekinumab-STBA							$
Steqeyma 90mg/ml ustekinumab-STBA							$
Stelarsdi 90mg/0.5ml ustekinumab-AEKN							$
Stelarsdi 90mg/ml ustekinumab-AEKN	7	$29,308.86	$4,186.98	1 per 34 days	6	33 – 61	$$
Pyzchiva 45mg/0.5ml ustekinumab-TTWE							$
Pyzchiva 90mg/ml ustekinumab-TTWE							$$
Yesintek 45mg/0.5ml ustenkinumab-KFCE							$
Yesintek 90mg/ml ustenkinumab-KFCE							$$
Otulfi 45mg/0.5ml ustekinumab-AAUZ							$$
Otulfi 90mg/ml ustekinumab-AAUZ							$$
Ustekinumab 45mg/0.5ml							$$
Ustekinumab 90mg/ml							$$$
Ustekinumab-AEKN 45mg/0.5ml							$$
Ustekinumab-AEKN 90mg/ml							$$$
Starjemza 45mg/0.5ml ustekinumab-HMNY							N/A
Starjemza 90mg/1ml ustekinumab-HMNY							N/A
Imuldosa 45mg/0.5ml ustekinumab-SRLF							$$$
Imuldosa 90mg/ml ustekinumab-SRLF							$$$$
Ustekinumab-TTWE 45mg/0.5ml							$$$
Ustekinumab-TTWE 90mg/ml							$$$$
Wezlana 45mg/0.5ml ustenkinumab -AAUB							$$$$
Wezlana 90mg/ml ustenkinumab -AAUB							$$$$$
Stelara 45mg/0.5ml	6	$84,956.89	$14,159.48	0.5 per 84 days	5	8 – 40	$$$$
Stelara 90mg/ml	38	$1,048,368.49	$27,588.64	1 per 47 days	20	13 – 53	$$$$$

*All drugs are on PA

Oxervate (cenegermin-bkbj)

Time frame: 1/1/2025 to 8/20/2025
Indication: for the treatment of neurotropic keratitis (ICD-10 code **H16.231**) – rare degenerative eye disease that affects the cornea, leading to a reduction in corneal sensitivity

	Jan-Mar 2025					Apr-Aug 2025				
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Mbr**	**Age Range**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Mbr**	**Age Range**
Oxervate	9	$288,469.4	$32,052.15	2	51, 63	4	$230,775.52	$57,693.88	2	24, 51

Utilizer	Demographics	Prescribed by	Treatment	Diagnosis
Member 1	female, 63 yrs	Optometrist	8 weeks 112 ml $230,860	**H16.231** neurotropic keratitis H16.232 neurotrophic keratoconjunctivitis, left eye H16.233 neurotrophic keratoconjunctivitis, bilateral
Member 2	male, 51 yrs	Ophthalmology	8 weeks 112 ml $230,818	**H16.231** neurotropic keratitis H16.233 neurotrophic keratoconjunctivitis, bilateral
Member 3	male, 24 yrs	Student	6 weeks~ 84 ml $173,113	H16.239 neurotrophic keratoconjunctivitis, unspecified eye

PA Criteria for Consideration

State A

1. Member is 2 years of age and older
2. Diagnosis of neurotrophic keratitis
3. Prescribed by, or in consultation with, an ophthalmologist
4. Member has not received 8 weeks or more of prior cenegermin treatment for the affected eye
5. Approval length: 8 weeks per eye, per lifetime

State B

1. Patient is 2 years of age or older
2. Diagnosis of moderate to severe (stage 2 or stage 3) neurotrophic keratitis (NK)
3. Prescribed by or in consultation with an ophthalmologist
4. Prescriber attests that patient or caregiver has been counseled on proper administration technique

Commercial

1. Diagnosis of neurotrophic keratitis
2. Trial and failure or intolerance to at least one over-the-counter ocular lubricant used at an optimal dose and frequency for at least two weeks (e.g., artificial tears, lubricating gels/ointments, etc)
3. Prescribed by or in consultation with an ophthalmologist
4. Approval length: 8 weeks (coverage is limited to 112 ml per lifetime)

Cholbam (cholic acid)

Time frame: 1/1/2023 to 6/30/2025
Indication: for the treatment of bile acid synthesis disorders due to single enzyme defects and the adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders (E71.510)

Date	Total Rx	Paid Amount	Paid/Rx	Avg Days Supply	Utilizers	Age
Jan-Mar 2023	3	$74,731.65	$24,910.55	30 per 30 days	1	6
Apr-Jun 2023	3	$74,731.65	$24,910.55	30 per 30 days	1	6
July-Sep 2023	4	$99,642.20	$24,910.55	30 per 30 days	1	6
Oct-Dec 2023	6	$124,413.30	$20,735.55	45 per 30 days	2	4, 6
Jan-Mar 2024	4	$86,421.54	$21,605.39	45 per 30 days	2	4, 6
Apr-Jun 2024	6	$131,873.31	$21,978.89	45 per 30 days	2	4, 7
July-Sep 2024	6	$111,719.62	$18,619.94	50 per 30 days	2	5, 7
Oct-Dec 2024	9	$167,705.94	$18,633.99	40 per 30 days	2	5, 7
Jan-Mar 2025	11	$279,383.36	$25,398.49	60 per 30 days	2	5, 8
Apr-Jun 2025	7	$167,600.50	$23,942.93	60 per 30 days	2	5, 8

Utilizer	Demographics	Prescribed by	Diagnosis
Member 1	female, 5 yrs	Physician Assistant	E78.70 Disorder of bile acid and cholesterol metabolism, unspecified E78.79 Other disorders of bile acid and cholesterol metabolism E80.6 Other disorders of bilirubin metabolism
Member 2	female, 8 yrs	Pediatrics	E78.70 Disorder of bile acid and cholesterol metabolism, unspecified E78.79 Other disorders of bile acid and cholesterol metabolism E78.89 Other lipoprotein metabolism disorders E80.6 Other disorders of bilirubin metabolism

PA Criteria for Consideration

State A

1. Diagnosis of a bile acid synthesis disorder
2. It is due to single enzyme defects

State B

1. One of the following:
   - Used for the treatment of bile acid synthesis disorders due to single enzyme defects
   - Used as adjunctive treatment of manifestations of peroxisomal disorders (PDs) including Zellweger spectrum disorders
2. Prescribed by a hepatologist or gastroenterologist

State C

1. Diagnosis of a bile acid synthesis disorder due to a single enzyme defect based on one of the following:
   - An abnormal urinary bile acid analysis by mass spectrometry
   - Molecular genetic testing consistent with the diagnosis
2. Prescribed by one of the following:
   - Hepatologist
   - Medical geneticist
   - Pediatric gastroenterologist
   - Other specialist that treats inborn errors of metabolism

Promacta (eltrombopag)

Time frame: 1/1/2023 to 6/30/2025
Indications:

- for treatment of thrombocytopenia in patients with persistent or chronic immune thrombocytopenia (ITP)
- for treatment of severe aplastic anemia
- for the treatment of refractory severe aplastic anemia
- for chronic hepatitis C infection-associated thrombocytopenia

Date	Total Rx	Paid Amount	Paid/Rx	Avg Days Supply	Utilizers	Age
Jan-Mar 2023	2	$40,282.36	$20,141.18	90 per 30 days	1	6
Apr-Jun 2023	2	$40,282.36	$20,141.18	90 per 30 days	1	6
July-Sep 2023	4	$43,648.73	$10,912.18	37 per 20 days	2	6, 42
Oct-Dec 2023	4	$43,180.18	$10,795.05	30 per 30 days	1	42
Jan-Mar 2024	1	$13,124.68	$13,124.68	30 per 30 days	1	42
Apr-Jun 2024	1	$13,124.68	$13,124.68	30 per 30 days	1	16
July-Sep 2024	4	$52,498.72	$13,124.68	30 per 30 days	1	16
Oct-Dec 2024	10	$151,607.98	$15,160.80	30 per 30 days	4	3 – 57
Jan-Mar 2025	15	$234,981.89	$15,665.46	36 per 30 days	5	3 – 57
Apr-Jun 2025	17	$249,460.74	$14,674.16	33.5 per 30 days	7	3 – 57

- Prescribed by:
  - Pediatrics
  - Hematology & Oncology
  - Hematology & Oncology, Pediatric
  - Medical Oncology
  - Nurse Practitioner
  - Student

	Jan-Mar 2025				Apr-Jun 2025			
Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbr	Total Rx	Paid Amount	Paid/Rx	Mbr
eltrombopag 75mg tab	0				1	$16,758.17	$16,758.17	1
Promacta 25mg PAK	2	$22,341.95	$11,170.98	2	0			
Promacta 25mg POW	4	$39,176.15	$9,794.04	2	3	$54,840.28	$10,968.06	2
Promacta 50mg tab	4	$68,760.24	$17,190.06	2	5	$71,585.04	$14,317.01	3
Promacta 75mg tab	5	$104,703.55	$26,175.89	2	5	$106,277.25	$21,255.45	3

PA Criteria for Consideration

State A

Persistent or Chronic Immune Thrombocytopenia (ITP):

1. Diagnosis of one of the following:
    - Persistent ITP
    - Chronic ITP
    - Relapsed/refractory ITP
2. Baseline platelet count is less than 30,000/mcL
3. Trial and failure, contraindication, or intolerance to one of the following:
    - Corticosteroids
    - Immunoglobulins
    - Splenectomy
4. Patient's degree of thrombocytopenia and clinical condition increase the risk of bleeding
5. Prescribed by or in consultation with a hematologist/oncologist

First-Line for Severe Aplastic Anemia:

1. Diagnosis of severe aplastic anemia
2. Used for first-line treatment (i.e., patient has not received prior immunosuppressive therapy with any equine antithymocyte globulin plus cyclosporine, alemtuzumab, or high dose cyclophosphamide) [1]
3. Patient meets at least TWO of the following:
    - Absolute neutrophil count < 500/mcL
    - Platelet count < 20,000/mcL
    - Absolute reticulocyte count < 60,000/mcL
4. Used in combination with standard immunosuppressive therapy (e.g., Atgam [antithymocyte globulin equine] and cyclosporine)
5. Prescribed by or in consultation with a hematologist/oncologist

Refractory Severe Aplastic Anemia:

1. Diagnosis of refractory severe aplastic anemia
2. Trial and failure, contraindication, or intolerance to immunosuppressive therapy with antithymocyte globulin (ATG) and cyclosporine
3. Patient has thrombocytopenia defined as platelet count less than 30,000/mcL
4. Prescribed by or in consultation with a hematologist/oncologist

Chronic Hepatitis C-Associated Thrombocytopenia:

1. Diagnosis of chronic hepatitis C-associated thrombocytopenia
2. One of the following:
    2.1 Planning to initiate and maintain interferon-based treatment
    2.2 Currently receiving interferon-based treatment
3. Prescribed by or in consultation with one of the following:
    - Hematologist/oncologist
    - Hepatologist
    - Gastroenterologist
    - Infectious disease specialist
    - HIV specialist certified through the American Academy of HIV Medicine

State B

Chronic or Persistent Thrombocytopenia Purpura:

1. Diagnosis of Chronic or Persistent Thrombocytopenia Purpura
2. Patient is 1 year of age or older
3. Patient's thrombocytopenia and clinical condition put them at increased risk of bleeding
4. One of the following:
   4.1. Patient has failed or had insufficient response to adequate treatment with BOTH of the following:
      - Corticosteroid
      - immunoglobulins
   4.2. Patient has had an ITP related splenectomy

Thrombocytopenia in patient with chronic Hepatitis C:

1. Diagnosis of Thrombocytopenia in patient with chronic Hepatitis C
2. Patient is receiving (or planning to initiate) interferon-based antiviral therapy

Severe aplastic anemia:

1. Diagnosis of severe aplastic anemia
2. Patient has tried and failed or has intolerance to immunosuppressive therapy

State C

Must meet one of the following:

1.1. All of the following:
   1.1.1. Diagnosis of chronic immune thrombocytopenia (ITP) whose degree of thrombocytopenia and clinical condition increases the risk of bleeding
   1.1.2. Member has had an insufficient response to corticosteroids, immunoglobulins, or splenectomy (documentation of therapies) trialed must be submitted)
   1.1.3. Member is 1 year of age or older

1.2. All of the following:
   1.2.1. Diagnosis of thrombocytopenia in members with chronic hepatitis C requiring initiation and/or maintenance of interferon-based therapy
   1.2.2. Prescriber attests to both of the following:
      - Member is currently on interferon-based therapy or will be initiated on interferon-based therapy
      - Prescriber will discontinue Promacta (eltrombopag olamine) if interferon-based therapy is terminated
   1.2.3. Member is 18 years of age or older

1.3. All of the following:
   1.3.1. Diagnosis of severe aplastic anemia
   1.3.2. One of the following:
      - Member is 2 years of age or older and will be using Promacta (eltrombopag olamine) in combination with standard immunosuppressive therapy*
      - Member is 18 years of age or older, will be using Promacta (eltrombopag olamine) as monotherapy, and has had an insufficient response to immunosuppressive therapy (e.g., anti-thymocyte globulin, cyclosporine) (documentation of therapy(ies) trialed must be submitted)

Symbravo (meloxicam 20mg/rizatriptan 10mg) tab
Time frame: 4/1/2025 to 6/30/2025
Indication: for the treatment of migraine with or without aura

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Symbravo	0					
meloxicam 15mg tab	1,539	$15,289.37	$9.93	29.9 per 29.4 days	903	14 – 80
meloxicam 7.5mg tab	473	$4,844.13	$10.24	36 per 28 days	306	10 – 64
meloxicam 5mg cap	8	$1,578.12	$197.27	14.8 per 14.8 days	2	60, 65
rizatriptan 10mg	129	$1,941.63	$15.05	11 per 25.6 days	81	12 – 64
rizatriptan 10mg ODT	94	$1,486.24	$15.81	10.5 per 28 days	62	10 – 62

*IHS excluded

PA Criteria
State A

1. Diagnosis of migraine headaches with or without aura
2. Prescribed by or in consultation with one of the following:
    - Neurologist
    - Pain management specialist
3. Patient is currently receiving prophylactic therapy with at least ONE of the following:
    3.1. Amitriptyline (Elavil)
    3.2. One of the following beta-blockers:
        - atenolol
        - metoprolol
        - nadolol
        - propranolol
        - timolol
    3.3. Divalproex sodium (Depakote/Depakote ER)
    3.4. OnabotulinumtoxinA (Botox)
    3.5. Topiramate (Topamax)
    3.6. Venlafaxine (Effexor/Effexor XR)
    3.7. Calcitonin gene-related peptide (CGRP) receptor antagonists [e.g., Aimovig (erenumab), Emgality (galcanezumab)]
4. One of the following:
    4.1. Higher dose or quantity is supported in the dosage and administration section of the manufacturer's prescribing information
    4.2. Higher dose or quantity is supported by one of the following compendia:
        - American Hospital Formulary Service Drug Information
        - Thomson Micromedex DrugDex
        - Clinical pharmacology
        - United States Pharmacopoeia-National Formulary (USP-NF)
    4.3. Physician provides evidence from published biomedical literature to support safety and additional efficacy at doses/quantities greater than those approved by the FDA (Food and Drug Administration) for the diagnosis indicated
5. Physician acknowledges that the potential benefit outweighs the risk associated with the higher dose or quantity

State B

1. Clinically valid reason as to why the patient cannot use a preferred NSAID and 5-HT receptor agonist as separate agents (NOTE: Patient convenience is NOT an approval reason)

Commercial

1. Requested drug is being used for a Food and Drug Administration (FDA)-approved indication
2. Trial and failure (of a minimum 30-day supply) or intolerance to two of the following generics:
    - almotriptan tablet
    - eletriptan tablet
    - frovatriptan tablet
    - naratriptan tablet
    - rizatriptan tablet/rizatriptan orally dissolving tablet (ODT)
    - sumatriptan tablet/nasal spray
    - zolmitriptan tablet/zolmitriptan ODT

Optum Rx®

Therapeutic Class Overview

Ophthalmic agents, miscellaneous

Introduction

- The focus of this overview is ophthalmic solutions used for the treatment of cystinosis and neurotrophic keratitis (NK).
- Cystinosis is a very rare, multisystem autosomal recessive disease that causes an accumulation of cystine throughout all of the cells in the body. This can lead to damage and dysfunction in various organs and tissues, including the eyes. Cystinosis is caused by mutations in the cystinosin, lysosomal cystine transporter (*CTNS*) *gene.* Three forms have been described based on age and severity: infantile, late-onset (juvenile), and adult (*Elmonem et al 2016, Liang et al 2017, Niaudet 2024*).
  - Infantile (nephropathic) cystinosis is the most severe form, becoming evident within the first year of life. Infants experience poor growth and development, metabolic imbalances, early end-stage renal disease (if left untreated), thyroid failure, and multiorgan dysfunction.
    - Infantile cystinosis is the most severe and most common (95%) form of cystinosis, affecting 1 in every 100,000 to 200,000 children.
  - Juvenile cystinosis is less severe than the infantile form. While children may experience some of the same symptoms, the progression of kidney dysfunction is slower.
  - Adult (benign or ocular) cystinosis is the mildest form, and results in symptoms such as photophobia. Systemic symptoms are generally not present.
- Management for infantile and juvenile cystinosis includes symptomatic therapy (eg, fluid and electrolyte supplementation, vitamin D repletion) and the use of oral cysteamine starting soon after diagnosis to preserve renal function, prevent hypothyroidism, and improve growth. Oral administration of cysteamine directly treats the disease by reducing the intracellular cystine content. Topical cysteamine is available in ophthalmic solution formulations to target corneal cystine crystal deposits and reduce photophobia; systemic cysteamine does not prevent corneal crystal accumulation due to lack of vascularization of the cornea (*Niaudet 2024*).
  - Cystaran (cysteamine hydrochloride ophthalmic solution) received Priority Review from the Food and Drug Administration (FDA) for the treatment of corneal cystine accumulation in patients with cystinosis in 2012 (*FDA Web site 2025*).
  - Cystadrops (cysteamine hydrochloride ophthalmic solution) received standard FDA approval in 2020 (*FDA Web site 2025*). It is a viscous ophthalmic formulation with several differences from Cystaran, including a lower concentration of cysteamine, less frequent dosing, and no frozen storage requirement.
- NK is a rare, degenerative eye disease caused by dysfunction of corneal trigeminal innervation that plays a key role in maintaining anatomical and functional integrity of the ocular surface (eg, reflex tears). This leads to corneal epithelial breakdown, impaired healing, and the development of corneal ulcerations. The hallmark of NK is the decrease or absence of corneal sensation. Other symptoms can include photophobia, blurred vision, red or dry eyes, and decreased acuity (*National Organization for Rare Disease [NORD] 2023, Sacchetti and Lambiase 2014*).
  - NK is not common in children. The estimated prevalence is < 5 per 10,000 individuals (*NORD 2023*).
  - The standard of care for early NK is the administration of topical lubricants. For persistent epithelial defects and corneal ulceration, treatment options may include therapeutic contact lenses, patching, topical autologous serum application, amniotic membrane grafting, corneal neurotization, tarsorrhaphy, and nerve growth factor eyedrops (*Oxervate FDA medical review 2018, Mukamal et al 2023*).
    - Oxervate (cenegermin) is a novel recombinant human nerve growth factor which demonstrated complete corneal healing in clinical trials for many patients with NK (*FDA web site 2025*).
- Medispan classes: Ophthalmic Agents; Ophthalmics - Cystinosis Agents; Ophthalmic Nerve Growth Factors

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Cystadrops (cysteamine) ophthalmic solution 0.37%	-
Cystaran (cysteamine) ophthalmic solution 0.44%	-
Oxervate (cenegermin) ophthalmic solution 0.002%	-

*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Cystadrops (cysteamine)	Cystaran (cysteamine)	Oxervate (cenegermin)
Treatment of corneal cystine crystal deposits in adults and children with cystinosis	✔		
Treatment of corneal cystine crystal accumulation in patients with cystinosis[a]		✔	
Treatment of neurotrophic keratitis[b]			✔

[a]Although children are not specifically listed in the indication, the Pediatric Use section of the prescribing information does note that safety and effectiveness of Cystaran have been established.
[b]Pediatric Use: The safety and effectiveness of Oxervate have been established in the pediatric population. Use in this population is supported by evidence from adequate and well-controlled trials in adults with additional safety data in pediatric patients from 2 years of age and older.

(*Prescribing information: Cystadrops 2020, Cystaran 2025, Oxervate 2018*)

- 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 efficacy of Cystaran was evaluated in 3 clinical trials (Study 1 [CAPTOC], Study 2 [98-EI-0109S], and Study 3 [98-EI-1090E0]) in approximately 300 patients. The primary efficacy endpoint in the trials was the decrease from baseline of ≥ 1 unit in the photo rated corneal cystine crystal score (CCCS) at some time point during the study when baseline CCCS ≥ 1, or a lack of an increase of > 1 unit in CCCS throughout the study when baseline CCCS < 1 (*Cystaran prescribing information 2022, Cystaran FDA medical review 2012*).
  - Response rates ranged from 32% to 67% in patients with a baseline CCCS ≥ 1 who received Cystaran. In Study 1, 2, and 3, respectively, in eyes with a baseline CCCS of ≥ 1, response was achieved in 32% (n = 94/291; 95% confidence interval [CI], 27 to 38), 67% (n = 10/15; 95% CI, 38 to 88), and 33% (n = 3/9; 95% CI, 8 to 70), respectively. In Study 1 for patients with baseline CCCS < 1, the response rate was 13% (n = 4/30; 95% CI, 4 to 32).
  - The FDA review states the importance of strict adherence to administration requirements (1 drop in each eye, every waking hour); In the CAPTOC study, among patients who were considered excellent compliers, 42.1% (77/183) of eyes had a response compared to 15.2% (21/138) of non-compliers (difference, 26.9%) (*Cystaran FDA statistical review 2010*).
- Cystadrops was evaluated in the CHOC study, a 90-day, Phase 3, open-label, active-controlled, multicenter trial that randomized cystinosis patients to receive Cystadrops (n = 15) or cysteamine hydrochloride 0.10% (n = 16) 4 times daily (*Liang et al 2017*).
  - For the primary outcome, the reduction in in-vivo confocal microscopy (IVCM) total score at Day 90 was superior with Cystadrops (4.6 ± 3.1; n = 22 eyes) vs cysteamine hydrochloride 0.10% (0.46 ± 3.38; n = 20 eyes; treatment difference, 3.8; 95% CI, 2.1 to 5.6; p < 0.0001).
    - The relative change in IVCM total score from baseline to Day 90 was -40% with Cystadrops vs -0.7% with cysteamine hydrochloride 0.10%.
    - In patients treated with Cystadrops, the mean IVCM total score decreased from 10.6 at baseline to 6.0 at day 90 (p = 0.001).
  - For the secondary outcomes, photophobia, CCCS, and corneal crystal depth were significantly improved with Cystadrops vs cysteamine hydrochloride 0.10% (p = 0.0048, p = 0.0015, and p = 0.0031, respectively).
- A systematic review and meta-analysis of 7 studies compared the efficacy of various topical cysteamine products in patients with cystinosis. The authors concluded that both Cystaran (vs cystamine [not available in the United States]), and Cystadrops (vs standard formulation 0.1% [no longer available]) were efficacious at decreasing corneal cystine density (*Kaur et al 2021*).
- The safety and efficacy of cenegermin in 48 patients with NK were evaluated in an 8-week, multicenter, randomized, double-masked, vehicle-controlled trial (NGF0214); follow up was 24 weeks. The primary endpoint was healing of the neurotrophic lesion (ie, persistent epithelial defect or corneal ulcer) after 8 weeks of masked treatment by conventional

(< 0.5 mm of fluorescein staining in the greatest dimension of the lesion) and conservative assessment (0-mm lesion staining and no other residual staining). The key secondary endpoint was corneal healing at 4 weeks after masked treatment (*Pflugfelder et al 2020*).
  - At 8 weeks, conventional assessment showed 16/23 (69.6%) cenegermin-treated patients and 7/24 (29.2%) vehicle-treated patients achieved < 0.5 mm of lesion staining (difference, 40.4%; 95% CI, 14.2 to 66.6; p < 0.006). Conservative assessment also showed a statistically significant difference at 8 weeks; 15 of 23 cenegermin-treated patients (65.2%) and 4/24 vehicle treated patients (16.7%) achieved 0 mm of lesion staining with no other residual staining (difference, 48.6%; 95% CI, 24 to 73.1; p < 0.001).
  - Corneal healing after 4 weeks was statistically significant with conservative definition at both 4- and 8-week timepoints (p = 0.006 at 4 weeks and p = 0.001 at 8 weeks), while the conventional definition of corneal healing was statistically significant only at 8 weeks (p = 0.004), and not 4 weeks (p = 0.091).
- Long term
- A systematic review and meta-analysis of 20 studies (N = 571) evaluated the percentage of eyes with corneal healing after patients were treated with various agents for NK. Overall, there was no significant difference found in the percentage of patients with corneal healing between specific treatments including nerve growth factor eyedrops (ie, cenegermin; 75%), autologous serum (92%), neurotization (99%), or amniotic membrane transplantation (86%). The specific treatments had better percentage of complete healing compared to nonspecific treatments such as lubricants (p < 0.001). Time to complete healing was 24.2 days with nerve growth factor eyedrops, 27.6 days with autologous serum, 117 days with neurotization, and 16.4 days with amniotic membrane transplantation. Only nerve growth factor eyedrops and amniotic membrane transplantation improved visual acuity (*Roumeau et al 2022*).

Clinical Guidelines

Nephropathic cystinosis: an international consensus document (*Emma et al 2014*)
- An international consensus document was created to summarize shared opinions among experts to increase disease awareness and to guide diagnosis and treatment of infantile cystinosis.
- Specific cystine-depleting treatment with cysteamine currently represents the mainstay of therapy, allowing depletion of lysosomal cystine in most tissues. It should be initiated as early as possible and continued lifelong. Although cysteamine does not cure the disease, it dramatically improves the overall prognosis.
  - Strong evidence indicates that oral cysteamine lowers cystine content in muscle and other tissues, and prevents or delays late, nonrenal complications of cystinosis.
- The pathognomonic and most frequently described ocular manifestation of cystinosis is deposition of cystine crystals in the conjunctiva and cornea.
- Oral cysteamine has no effect on corneal cystine deposits. Cystinosis patients need to be treated topically with cysteamine hydrochloride eye drops that dissolve crystals and alleviate symptoms.
  - Results have been obtained with a 0.55% collyrium (eye wash) taken 6 to 10 times per day. However, most patients apply cysteamine eye drops less frequently (4 to 6 times per day).
  - A commercial 0.44% cysteamine ophthalmic solution (Cystaran) has been approved for clinical use in the United States, and a 0.55% gel formulation (Cystadrops) has also been developed. (Cystadrops contains 0.37% cysteamine, equivalent to 0.55% cysteamine hydrochloride.)

Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy (*Dana et al 2021*)
- A consensus document was created by a panel of experts from the United States to summarize shared recommendations regarding the screening, diagnosis, and treatment of NK.
- Once diagnosed, NK can be classified into 3 stages using the Mackie classification, from the relatively mild Stage 1 (corneal epithelial changes) and moderate Stage 2 (corneal epithelial defect) to the more severe Stage 3 (corneal ulcer, perforation, melting).
- Management of NK is based on clinical severity, and treatment aims to stop the progression of corneal damage and promote epithelial healing.
- Multiple treatments may be used concurrently, particularly in more advanced disease. Treatments include medical management, nonsurgical interventions, and surgical interventions.
  - For all stages of NK, optimal care includes discontinuing preservative-containing topical medications to the extent possible. For topical medications that do not have preservative-free alternatives, working to decrease the dose is recommended.

- For all patients with NK (regardless of stage), optimal treatments may include preservative-free tear substitution or lubricants (including gels and ointments), punctal occlusion, and autologous serum tears/umbilical cord serum drops/platelet-rich plasma drops.
- For patients with Stage 2 disease, additional optimal treatments include cenegermin, prophylactic topical preservative-free antibiotics, matrix metalloproteinases inhibitors such as oral tetracyclines (eg, doxycycline), corneal therapeutic contact lenses, and fresh-frozen self-retained amniotic membrane.
  - Cenegermin is currently the only FDA-approved treatment for NK.
- For Stage 3 disease, in addition to the treatments recommended in Stage 2, optimal treatments include synthetic tissue adhesive, tarsorrhaphy, amniotic membrane transplant, and corneal neurotization.

Safety Summary

- Warnings and Precautions:
  - Cysteamine:
    - To minimize contamination of tip and solution, avoid direct contact of the tip with eyelids, surrounding areas, or any surfaces.
    - The ophthalmic solutions contain benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed before application and can be reinserted 15 minutes after administration.
  - Cenegermin:
    - Contact lenses should be removed prior to administration of cenegermin solution as they can limit the distribution onto the affected areas of corneal lesion. Lenses can be reinserted 15 minutes after administration.
    - Cenegermin may cause mild to moderate eye pain during treatment. If a more serious eye reaction occurs, the patient should be advised to contact their physician.
- Adverse Effects (AEs)
  - Cysteamine (Cystaran):
    - The most common AEs (≥ 10%) include sensitivity to light, redness, eye pain/irritation, headache, and visual field defects.
  - Cysteamine (Cystadrops):
    - The most common AEs (≥ 10%) include eye pain, blurred vision, eye irritation, ocular hyperemia, instillation site discomfort, eye pruritus, increased lacrimation, and ocular deposits.
  - Cenegermin:
    - The most common AEs (> 5%) include eye pain, ocular hyperemia, eye inflammation, and increased lacrimation.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cystadrops (cysteamine hydrochloride ophthalmic solution)	Viscous ophthalmic solution 0.37%	Topical ophthalmic	One drop in each eye 4 times per day during waking hours	Storage prior to opening: Refrigerator (2°C to 8°C) Storage after opening: Room temperature (20°C to 25°C); Discard after 7 days
Cystaran (cysteamine hydrochloride ophthalmic solution)	Ophthalmic solution 0.44%	Topical ophthalmic	One drop in each eye every waking hour	Storage prior to opening: Freezer (-25°C to -15°C), thaw for 24 hours before use Storage after opening: Refrigerator or room temperature (2°C to 25°C); Discard after 7 days

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Oxervate (cenegermin)	Ophthalmic solution 0.002%	Topical ophthalmic	One drop in affected eye 6 times daily at 2-hour intervals for 8 weeks.	Pharmacy storage: Freezer at or below -20°C Patient storage: Refrigerator at 2°C to 8°C. A vial opened for daily use may be stored under refrigeration or at room temperature up to 25°C; Discard opened vial after 12 hours.

See the current prescribing information for full details.

Conclusion

- Cystinosis is a rare, multisystem autosomal recessive disease that causes an accumulation of cystine throughout cells in the body that can lead to damage and dysfunction in various organs and tissues, including the eyes. Topical cysteamine is available in ophthalmic solution formulations to target corneal cystine crystal deposits; systemic cysteamine does not prevent corneal crystal accumulation due to lack of vascularization of the cornea.
  - Cysteamine is available as a Cystadrops (cysteamine 0.37%; a viscous solution), and Cystaran (cysteamine 0.44%; a standard solution). Both agents are indicated and the standard of care for the treatment of corneal cystine crystal deposits in adults and children with cystinosis.
  - Cystadrops requires less frequent dosing (4 times per day) compared to Cystaran (every waking hour) and does not require frozen storage.
  - Though there are no direct comparisons, both cysteamine products demonstrated reductions in corneal cystine crystal density in their respective clinical trials. The safety profiles were consistent, and reported AEs were typical of ophthalmic medications including blurred vision and eye discomfort or irritation.
  - An international consensus document indicates that patients with ocular cystinosis need to be treated topically with cysteamine hydrochloride eye drops that dissolve crystals and alleviate symptoms; oral cysteamine has no effect on corneal deposits.
- NK is a rare, degenerative eye disease caused by dysfunction of corneal nerves that play a key role in maintaining anatomical and functional integrity of the ocular surface.
  - Oxervate (cenegermin) is a novel recombinant human nerve growth factor and the only FDA-approved treatment for NK, a rare degenerative eye disease. The management of NK is based on clinical severity, and treatment aims to stop the progression of corneal damage and promote epithelial healing.
  - An expert consensus statement recommends the use of cenegermin in patients with stage 2 disease, where corneal defect has occurred. In a clinical trial, cenegermin demonstrated complete corneal healing for many patients. The most common AE is mild to moderate eye pain.
- For all 3 agents, contact lenses should be removed before application and can be reinserted 15 minutes after administration.

References

- Cystadrops. Package insert. Recordati Rare Diseases Inc.; August 2020.
- Cystaran. Package insert. Leadiant Biosciences, Inc.; February 2022.
- Dana R, Farid M, Gupta PK, et al. Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. *BMC Ophthalmology*. 2021;21:327. doi:10.1186/s12886-021-02092-1.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed July 15, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Elmonem MA, Veys KR, Soliman NA, et al. Cystinosis: a review. *Orphanet J Rare Dis*. 2016;11:47. doi: 10.1186/s13023-016-0426-y.
- Emma F, Nesterova G, Langman C, et al. Nephropathic cystinosis: an international consensus document. *Nephrol Dial Transplant*. 2014;29(Suppl 4): iv87-iv94. doi:10.1093/ndt/gfu090.
- Food and Drug Administration. Cystaran medical review. September 28, 2012. Accessed July 15, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/200740Orig1s000MedR.pdf.
- Food and Drug Administration. Cystaran statistical review. September 28, 2012. Accessed August 7, 2025. 200740Orig1s000StatR.pdf

- Food and Drug Administration. Oxervate medical review. July 23, 2018. Accessed July 14, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000MedR.pdf
- Francesco E, Galina N, Craig L, et al. Nephropathic cystinosis: an international consensus document. *Nephrol Dial Transplant*. 2014;29(Suppl 4): iv87–iv94. doi: 10.1093/ndt/gfu090.
- Kaur S, Sarma P, Kaur H, et al. Efficacy and safety of topical cysteamine in corneal cystinosis: A systematic review and meta-analysis. *Am J Ophthalmol*. 2021:223:275-285. doi: 10.1016/j.ajo.2020.07.052.
- Liang H, Labbé A, Le Mouhaër J, Plisson C, Baudouin C. A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: An open-label randomized comparative Phase III pivotal study. *IOVS*. 2017;58(4):2275-2283.
- National Organization for Rare Diseases (NORD). Neurotrophic keratitis. Updated November 16, 2023. Accessed July 11, 2025. https://rarediseases.org/rare-diseases/neurotrophic-keratitis/.
- Niaudet P. Cystinosis. UpToDate Web site. Updated March 26, 2024. Accessed July 11, 2025. www.uptodate.com.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. Accessed June 26, 2023. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
- Oxervate. Package insert. Dompé U.S. Inc.;October 2019.
- Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: A multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology*. 2020;127(1):14-26.
- Roumeau S, Dutheil F, Sapin V, et al. Efficacy of treatments for neurotrophic keratopathy: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(8):2623-2637. doi: 10.1007/s00417-022-05602-z.
- Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.

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Optum Rx®

Therapeutic Class Overview

Triptans

Introduction

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype associated with a higher average attack frequency) and with aura. According to the International Headache Society (IHS) International Classification of Headache Disorder, migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of migraine include a unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by routine physical activity. Migraine without aura is also associated with at least 1 of the following: nausea, vomiting, or both and photophobia/phonophobia. Migraine with aura includes ≥ 1 of the following reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, or retinal. When attacks occur ≥ 15 days/month for > 3 months, patients are considered to have chronic migraines (*Cutrer et al 2024, Snow et al 2002, IHS 2018*).
- Migraine or severe headache affected approximately 15.9% of Americans in 2018, and has a higher prevalence in women (21%) than men (10.7%), according to data from the National Hospital Interview survey (*Burch et al 2021*).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (*FDA Industry Guidance [migraine] 2018, Tfelt-Hansen et al 2012*).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (*Clinical Pharmacology 2025*). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Schwedt and Garza 2025*).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (*Schwedt and Garza 2025*).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan (with the exception of Zembrace SymTouch) is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥ 12 years of age), and rizatriptan (for ≥ 6 years of age) (*Drugs@FDA 2025*).
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (ODT; rizatriptan, zolmitriptan), oral film (rizatriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (*Drugs@FDA 2025*).
- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
almotriptan malate tablet	✔
naratriptan hydrochloride tablet	✔ ‡
Frova (frovatriptan succinate) tablet	✔
Imitrex (sumatriptan) tablet, injection	✔ ‡
Imitrex, Tosymra (sumatriptan) nasal spray	✔ §
Imitrex Statdose (sumatriptan) autoinjector, cartridge refill	✔
Maxalt, Maxalt MLT (rizatriptan benzoate) tablet, ODT	✔
Migranow (sumatriptan and camphor/menthol) tablet and gel kit	-†
Onzetra Xsail (sumatriptan) nasal powder	-
Relpax (eletriptan hydrobromide) tablet	✔

Drug	Alternative Available (same molecular entity)*
Sumansetron (sumatriptan/ondansetron) tablet kit	-†
Symbravo (rizatriptan/meloxicam) tablet	-
Treximet (sumatriptan/naproxen sodium) tablet	✔
Zembrace SymTouch (sumatriptan) injection	-
zolmitriptan ODT	✔ ‡
Zomig (zolmitriptan) nasal spray, tablet	✔

*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
† FDA unapproved product.
‡ As of 2025, branded Amerge, Zomig-ZMT, and Imitrex injection have been discontinued; however, generics are still available.
§ Generics are available for Imitrex 5 and 20 mg nasal spray; however, no generic is available in the same dose strength as Tosymra (10 mg).

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	almotriptan	Frova (frovatriptan)	Imitrex (sumatriptan)	Imitrex Statdose (sumatriptan)	Maxalt (rizatriptan)	Maxalt MLT (rizatriptan)	Migranow (sumatriptan/camphor/menthol)	naratriptan	Onzetra Xsail (sumatriptan)	Relpax (eletriptan)	Sumansetron (sumatriptan/ondansetron)	Symbravo (rizatriptan/meloxicam)	Tosymra (sumatriptan)	Treximet (sumatriptan/naproxen)	Zembrace SymTouch (sumatriptan)	zolmitriptan ODT	Zomig (zolmitriptan)
Acute treatment of migraine with or without aura in adults	✔	✔	✔	✔	✔	✔	✔ ‖	✔	✔	✔	✔ △	✔	✔	✔	✔	✔	✔ ‡
Acute treatment of cluster headache in adults			✔ *	✔													
Acute treatment of migraine with or without aura (aged ≥ 6 years)					✔	✔											
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)	✔																

Indication	almotriptan	Frova (frovatriptan)	Imitrex (sumatriptan)	Imitrex Statdose (sumatriptan)	Maxalt (rizatriptan)	Maxalt MLT (rizatriptan)	Migranow (sumatriptan/camphor/menthol)	naratriptan	Onzetra Xsail (sumatriptan)	Relpax (eletriptan)	Sumansetron (sumatriptan/ondansetron)	Symbravo (rizatriptan/meloxicam)	Tosymra (sumatriptan)	Treximet (sumatriptan/naproxen)	Zembrace SymTouch (sumatriptan)	zolmitriptan ODT	Zomig (zolmitriptan)
Acute treatment of migraine with or without aura (aged ≥ 12 years)														✔			✔ †‡

Abbreviation: ODT = orally disintegrating tablet
Class Limitations of Use: No agents in this class are intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established
‖ Indication applies only to the sumatriptan component
¶ Indicated for those weighing 40 kg or more
ΔOndansetron tablets are indicated for the prevention of: (1) nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2; (2) nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy; (3) nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen; (4) postoperative nausea and/or vomiting. Sumatriptan tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of sumatriptan tablets have not been established for cluster headache, which is present in an older, predominantly male population.

(*Prescribing information: almotriptan 2017, Frova 2018, Imitrex injection 2023, Imitrex nasal spray 2024, Imitrex tablets 2024, Maxalt and Maxalt MLT 2022, Migranow 2024, naratriptan 2023, Onzetra Xsail 2024, Relpax 2020, Sumansetron 2023, Symbravo 2025, Tosymra 2024, Treximet 2024, Zembrace SymTouch 2024, Zomig nasal spray 2019, Zomig tablets 2022, zolmitriptan ODT 2024*)

- 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

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours, sustained pain-free response, reducing rescue medication use, and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (*Bird et al 2014, Brandes et al 2007, Cady et al 2015, Derry et al 2012[a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Law et al 2016, Oldman et al 2002, Pascual et al 2007, Poolsup et al 2005, Halker Singh et al 2020, Zembrace SymTouch prescribing information 2023, Richer et al 2016*).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. Triptans have been evaluated in numerous meta-analyses and comparative trials, with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All triptans are effective at treating migraines and are well tolerated; however, there are some notable differences between the different agents and formulations. Based

on older evidence and reviews, the following conclusions were drawn (*Derry et al 2012[a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Oldman et al 2002, Pascual et al 2007*):
  - Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-freedom and headache relief at 2 hours post-dose for oral agents (*Oldman et al 2002*); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (*Ferrari et al 2002, Pascual et al 2007*). Naratriptan 2.5 mg has lower efficacy rates of pain-freedom and headache relief at 2 hours (*Pascual et al 2007*) while eletriptan has a lower rate of recurrence (*Ferrari et al 2002*).
  - Subcutaneous sumatriptan is the most effective for acute migraine treatment but is associated with more adverse events (AEs) relative to the other triptan formulations (*Oldman et al 2002, Derry et al 2012[c]*).
  - Frovatriptan has the least number of head-to-head trials with active comparators. A pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group ($p < 0.001$) (*Cortelli et al 2011*).
  - Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (*Brandes et al 2007*).
  - Most triptans are well tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (*Ferrari et al 2002*).
- Recent evidence is summarized below:
  - Novel sumatriptan nasal formulations have been studied in placebo-controlled (PC) clinical trials. Onzetra Xsail was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines (ie, TARGET and COMPASS). The TARGET study (N = 230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs 45%, respectively; $p = 0.002$). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs 27%; $p = 0.03$) (*Cady et al 2015*). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (N = 275; 1531 migraines assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores ($p < 0.001$). At 2 hours, the rates of pain relief (freedom) were comparable (*Tepper et al 2015*).
  - A phase 2 trial of Tosymra in 107 patients with 2 to 8 migraines/month found improved response (freedom from headache pain at 2 hours post-dose) compared with placebo (43.8% vs 22.5%; $p = 0.044$). Tosymra was also significantly better than placebo at alleviating bothersome symptoms such as nausea, photophobia, and phonophobia 2 hours post-dose (70.7% vs 39.5%; $p = 0.004$) (*Lipton et al 2018*).
  - Data to support the approval of Zembrace SymTouch were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (*Zembrace SymTouch prescribing information 2023, Imitrex injection prescribing information 2023*).
  - In a randomized, DB, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (Zembrace SymTouch) and 6 mg subcutaneous sumatriptan (Sumavel DosePro – now discontinued) were compared in 20 patients with rapidly escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs 52.6%, respectively; $p = 0.87$). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the 6 mg dose (1 patient vs 4 patients) (*Cady et al 2017*).
  - The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. This DB, 4-arm, parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours (29.7% vs 16.6%, respectively; $p < 0.001$). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% of patients) (*Winner et al 2016*).
- The FDA approval of Symbravo (rizatriptan/meloxicam) was based on the results of two Phase 3, randomized, DB, PC trials, MOMEMTUM and INTERCEPT. The co-primary endpoints in both studies were the proportion of patients with

pain freedom (defined as the absence of migraine pain at 2 hours following the treatment) at 2 hours post-dose and most bothersome symptom (MBS; nausea, phonophobia, or photophobia) freedom at 2 hours post-dose, compared to placebo. The endpoint was assessed using a 0 to 3 scale where 0 represents no pain, 1 represents mild pain, 2 represents moderate pain, and 3 represents severe pain.
    - In MOMENTUM, 1594 patients with a history of migraine with our without aura we randomized to Symbravo (n = 456), rizatriptan 10 mg (n = 456), meloxicam 20 mg (n= 455), or placebo (n = 227) for the treatment of a migraine of moderate to severe pain intensity with a single dose of medication. Rescue medication (triptans or NSAID) was allowed 2 hours after the initial treatment. Overall, the percentage of patients achieving headache pain freedom at 2 hours and MBS freedom after a single dose of Symbravo was statistically significantly greater than with placebo (pain freedom, 19.9% vs 6.7%; MBS freedom (36.9% vs 24.4%; $p < 0.01$ for both endpoints).
    - In INTERCEPT, 302 patients with a history of migraine with our without aura we randomized to Symbravo (n = 152) or placebo (n = 150). for the treatment of a migraine of moderate to severe pain intensity with a single dose of medication. Rescue medication was allowed 2 hours after the initial treatment. Overall, the percentage of patients achieving headache pain freedom at 2 hours and MBS freedom after a single dose of Symbravo was statistically significantly greater than with placebo (pain freedom, 32.6% vs 16.3%, $p = 0.002$; MBS freedom, 43.9% vs 26.7%, $p = 0.003$).

- Meta-analysis and systematic reviews
    - A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-freedom after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs sumatriptan 25 mg), rizatriptan 10 mg (vs sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence of AEs were found (*Derry et al 2014*).
    - A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (*Bird et al 2014*).
    - In pediatric patients, a Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing freedom from pain in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (*Richer et al 2016*).
    - A recent comparative effectiveness systematic review for episodic migraine treatment by the Agency for Healthcare Research and Quality (AHRQ) reported that triptans demonstrated pain relief at 2 hours and had sustained pain relief at 1 day compared to placebo; however, they had increased risk of mild and transient AEs (*Halker Singh et al 2020*).
    - A systematic review of 25 studies (17 RCTs, 8 non-randomized) evaluated the effectiveness of various triptans for acute headache in pediatric migraine and concluded that rizatriptan (5 mg) and sumatriptan (nasal spray, 10 mg, and 20 mg) had higher efficacy compared to other triptans (*Chanchlani et al 2023*).
    - A 2024 systematic review and network meta-analysis that included 137 randomized trials with more than 89,000 patients compared 17 interventions for the acute treatment of migraine episodes in adults. All treatments were superior to placebo for freedom from pain at 2 hours, with eletriptan being the most effective followed by rizatriptan, sumatriptan, and zolmitriptan (*Karlsson et al 2024*).
    - An American College of Physicians (ACP) 2025 systematic review and meta-analysis of 21 comparative and 165 placebo-controlled trials evaluated the efficacy, safety, and cost-effectiveness of treatments for acute episodic migraine in adults (*Gartlehner et al 2025*). For pain outcomes at 2 hours and pain freedom up to 48 hours the analysis demonstrated the following:
        - Efficacy
            - High certainty of evidence: triptans > NSAIDs; triptans + NSAIDs > NSAIDs alone
            - Moderate certainty of evidence: triptans + acetaminophen > acetaminophen alone; triptans + NSAIDs > triptans alone
            - Low certainty of evidence: triptans > acetaminophen; triptans + acetaminophen > triptans alone; triptans + NSAIDs > triptans + acetaminophen
        - Safety

- Higher risk of adverse events with triptans compared to other treatments

Clinical Guidelines

Acute treatment of migraine

- The 2025 ACP clinical guideline provides recommendations for treatment of acute episodic migraine in outpatient settings (*Qaseem et al 2025*).
  - Treatments recommended based on comparative efficacy and safety, patient preference, and cost considerations include combination treatment with:
    - Triptans plus NSAIDs
    - Triptans plus acetaminophen
- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2021, which were reaffirmed in 2022 (*Ailani et al 2021*). The Society recommends the use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans, dihydroergotamine (DHE), small molecule CGRP receptor antagonists ("gepants"), and selective serotonin (5-HT_{1F}) receptor antagonists (lasmiditan) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate between the triptans but recommend that non-oral routes are used when severe nausea or vomiting is present.
- The IHS published practice recommendations in 2024 based on existing global treatment guidelines and expert consensus. Triptans are recommended for those not responding to appropriate doses of analgesics or NSAIDs. For patients who achieve a partial response with a triptan, increasing the dose, switching to a different route of administration, or adding an NSAID is recommended. Non-response to a triptan can be managed by switching to a different agent within the class however, after 3 different agents are tried, use of agents from another class is suggested (ie, gepants or lasmiditan). Gepants and lasmiditan are also recommended for patients who cannot tolerate or have contraindications to triptan therapy. Ergot derivatives are recommended if treatment options with better safety profiles have been exhausted (*Puledda et al 2024).*
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2021 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein et al 2012 [guideline reaffirmed in 2022; guideline update in progress as of 2024]).*
- In 2019, the American Academy of Neurology (AAN) and AHS published a guideline on the acute treatment of migraine in children and adolescents (*Oskoui et al 2019 [reaffirmed 2022]*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.

Cluster Headache

- Updated guidelines for the treatment of cluster headache from the European Academy of Neurology make a strong recommendation for the use of subcutaneous sumatriptan with oxygen for the acute treatment of cluster headache (*May et al 2023).* Older guidelines from AHS published in 2016 recommended that either subcutaneous sumatriptan or zolmitriptan nasal spray are established as effective in the acute therapy of cluster headache (*Robbins et al 2016*).

Safety Summary

- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan, and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of a MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.

- Sumatriptan/naproxen and rizatriptan/meloxicam are contraindicated in the setting of coronary artery bypass graft (CABG) surgery; in those patients with a history of asthma, urticaria, rhinitis, nasal polyps syndrome, or allergic-type reactions after taking aspirin (ASA) or NSAIDs; use during the third trimester of pregnancy (sumatriptan/naproxen only); severe hepatic impairment (sumatriptan/naproxen only); and in patients with moderate to severe renal insufficiency at risk for renal failure due to volume depletion or who are on dialysis (rizatriptan/meloxicam only)

- Sumatriptan/naproxen and rizatriptan/meloxicam have a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events. Serious skin reactions including fixed drug eruption and a life-threatening variant called generalized bullous fixed drug eruption have been reported with NSAID use.
- The following warnings and precautions are associated with medications in the class:
  - Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, rizatriptan/meloxicam, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vasospasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides.
  - Almotriptan, rizatriptan, and zolmitriptan have reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures following administration. Sumatriptan/naproxen and rizatriptan/meloxicam also have warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema that may worsen heart failure; hyperkalemia; renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); drug reaction with eosinophilia and systemic symptoms (DRESS); the potential to mask inflammation and fever; elevated liver enzymes; fetal toxicity (including premature closure of fetal ductus arteriosis and oligohydramnios/neonatal renal impairment); and hematologic toxicity (eg, anemia).
  - Naratriptan, frovatriptan, sumatriptan, sumatriptan/naproxen, rizatriptan/meloxicam ,eletriptan, and zolmitriptan nasal spray have a warning for hypersensitivity reactions, including anaphylaxis and angioedema. In addition, the needle shield of the prefilled syringe of injectable sumatriptan (Imitrex and Imitrex Statdose) contains a latex derivative that has the potential to cause allergic reactions in patients sensitive to latex.
  - Zolmitriptan ODT contains phenylalanine; the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - Generally, the most common AEs associated with 5-HT1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other cardiac events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR, 0.86; 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR, 2.23; 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund et al 2017*).

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
almotriptan	Tablets	Oral	Adults and adolescents (≥ 12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 25 mg	Safety of treating > 4 migraines in 1 month has not been established In adults, 12.5 mg dose is more effective Hepatic impairment and severe renal impairment: recommended starting dose is 6.25 mg not to exceed 12.5 mg in any 24-hour period
Frova (frovatriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 7.5 mg	Safety of treating > 4 migraines in 1 month has not been established
Imitrex, Imitrex Statdose (sumatriptan)	Tablets, nasal spray, autoinjector, single dose vial, cartridges for refill	Oral, intranasal, SC	Tablets (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Intranasal (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 40 mg Maximum single dose: 20 mg SC injection (adults): Given as a single dose; may repeat administration in 1 hour Maximum daily dose: 12 mg Maximum single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine	Tablets and nasal spray: safety of treating > 4 migraines in 1 month has not been established Contraindicated for use in severe hepatic impairment (all formulations) Mild or moderate hepatic impairment (tablets): maximum single dose should not exceed 50 mg Administer the needle only to the skin; IM or IV delivery should be avoided
Maxalt, Maxalt MLT (rizatriptan)	Tablets, ODT	Oral	Adults: Given as a single dose; may repeat administration in 2 hours	Safety of treating > 4 migraines in 1 month in adults and > 1 dose within 24 hours in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Maximum daily dose: 30 mg Pediatric (≥ 6 years): Weight based dosing: 5 mg for < 40 kg and 10 mg for ≥ 40 kg	patients 6 to 17 years of age have not been established For ODT, administration with liquid is not necessary Dosage adjustments for patients on concurrent propranolol is required
Migranow (sumatriptan + camphor/ menthol)	Tablet (sumatriptan) + gel (4% camphor/10% menthol)	Oral + topical	Adults: Sumatriptan: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Camphor/menthol: Apply to affected area up to 3 or 4 times daily	Safety of treating > 4 migraines in 1 month has not been established Gels should not be applied to wounds, damaged skin, mucous membranes, or eyes Hepatic impairment: maximum single dose of sumatriptan should in general not exceed 50 mg; contraindicated for use in severe hepatic impairment
naratriptan	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 4 hours Maximum daily dose: 5 mg	Safety of treating > 4 migraines in 1 month has not been established Mild or moderate renal or hepatic impairment: recommended starting dose is 1 mg not to exceed 2.5 mg in any 24-hour period Contraindicated for use in severe renal and hepatic impairment
Onzetra Xsail (sumatriptan)	Capsule in disposable nosepiece for use with breath-powered delivery device only	Intranasal	Adults: 2 nosepieces (1 nosepiece in each nostril) administered using the breath-powered delivery device; may repeat administration in 2 hours Maximum daily dose: 2 doses (44 mg/4 nosepieces) or 1 dose (22	Safety of treating > 4 migraines in 1 month has not been established Breath-powered powder delivery requires a forceful blow through

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			mg/2 nosepieces) of Onzetra Xsail and 1 dose of another sumatriptan product, separated by at least 2 hours	the mouthpiece to deliver the powder into each nostril Contraindicated for use in severe hepatic impairment
Relpax (eletriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 80 mg Maximum single dose: 40 mg	Safety of treating > 3 migraines in 1 month has not been established
Sumansetron (sumatriptan/ ondansetron)	Tablets	Oral	Tablets: Sumatriptan may be given as a single dose; may repeat administration in 2 hours. Maximum daily dose: 200 mg Ondansetron administrations vary: (1) Give within 30 minutes before HEC or; (2) give twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy.	Safety of treating > 4 migraines in 1 month has not been established There is evidence that doses of sumatriptan 50 and 100 mg may provide a greater effect than a 25 mg dose, but the 100 mg may not provide a greater effect than 50 mg Hepatic impairment: maximum single dose of sumatriptan should in general not exceed 50 mg; contraindicated for use in severe hepatic impairment. For ondansetron, do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥ 10). There is no experience beyond first-day administration in these patients.
Symbravo (rizatriptan/meloxicam	Tablets	Oral	Adults: Given as a single dose Maximum daily dose is 1 tablet (10 mg rizatriptan/20 mg meloxicam)	May be administered with or without food; tablets should not be divided, crushed, or chewed

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Equivalent systemic exposures with use of the separate agents compared to the combination tablet has not been demonstrated. Use of the agents separately is not a substitute for the combination product. Safety of treating > 7 headaches in a 30-day period has not been established
Tosymra (sumatriptan)	Nasal spray	Intranasal	Adults: Given as a single dose; may repeat after 1 hour Maximum daily dose: 30 mg	Administered as a single spray to 1 nostril May be administered 1 hour after another sumatriptan product
Treximet (sumatriptan/ naproxen)	Tablets	Oral	Adults: Given as a single dose (85/500 mg tablet) Pediatric (≥ 12 years): Given as a single dose (10/60 mg tablet) Maximum daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet (85/500 mg) in a 24-hour period for adolescents	May be administered with or without food; tablets should not be split, crushed, or chewed Safety of treating > 5 migraines in adults and > 2 migraines in pediatric patients over the span of 1 month has not been established Mild or moderate hepatic impairment: recommended dose is 1 tablet (10/60 mg) in a 24-hour period Contraindicated for use in severe hepatic impairment
Zembrace SymTouch (sumatriptan)	Autoinjector	SC	Adults: Injected as a single dose; each dose should be separated by at least 1 hour Maximum daily dose: 12 mg Maximum single dose: 3 mg	The needle penetrates ¼ inch of skin; IM or IV delivery should be avoided Administer dose to the upper arm or thigh

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				May be administered 1 hour after another sumatriptan product Contraindicated for use in severe hepatic impairment
zolmitriptan	ODT	Oral	Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 10 mg Maximum single daily dose: 5 mg	Safety of treating > 3 migraines (oral) in 1 month has not been established For ODT, administration with liquid is not necessary Do not break ODT because they are not functionally scored. ODTs are not recommended in moderate or severe hepatic impairment as these tablets should not be broken in half Dosage adjustments for patients on concurrent cimetidine is required
Zomig (zolmitriptan)	Tablets, nasal spray	Oral; intranasal	Tablets (adults): Given as a single dose; may repeat administration in 2 hours Nasal spray (adults and adolescents ≥ 12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 10 mg Maximum single dose: 5 mg	Safety of treating > 3 migraines (oral) or > 4 migraines (intranasal) in 1 month has not been established Moderate to severe hepatic impairment: recommended dose is 1.25 mg (one-half of one 2.5 mg tablet); limit the total daily dose in severe hepatic impairment to no more than 5 mg/day Nasal spray is not recommended in moderate to severe hepatic impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Dosage adjustments for patients on concurrent cimetidine is required

Abbreviation: IM = intramuscular; HEC = highly emetogenic cancer chemotherapy; IV = intravenous; MEC = moderately emetogenic cancer chemotherapy; ODT = orally disintegrating tablet; SC = subcutaneous.
See the current prescribing information for full details

Conclusion

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Schwedt and Garza 2025, Clinical Pharmacology 2025*).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 2 fixed-dose triptan/NSAIDs (sumatriptan/naproxen and rizatriptan/meloxicam) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet), rizatriptan (ODT and tablet), and zolmitriptan (nasal spray, ODT, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (*Francis et al 2010*). Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan are available generically in at least 1 dosage form or strength (*Drugs@FDA 2025*).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of Zembrace SymTouch) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and pharmacodynamic data, subcutaneous and intranasal formulations generally have a quicker onset of action and subcutaneous formulations generally have a lower NNT, but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (OR, 1.11; 95% CI, 0.84 to 1.43) and treatment-related AE (OR, 0.86; 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR, 2.23; 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund et al 2017*).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- The AHS published updated treatment guidelines for migraine in 2021 (*Ailani et al 2021*). They recommend the triptans or DHE for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These

guidelines do not differentiate between the triptans but recommend that non-oral routes be used when severe nausea or vomiting is present. There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2021 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein et al 2012 [guideline reaffirmed in 2022; guideline being updated as of 2024*].

- The IHS 2024 guidelines recommend triptans for those not responding to appropriate doses of analgesics or NSAIDs (*Puledda et al 2024)*.
- The 2025 American College of Physicians (ACP) clinical guideline for treatment of acute episodic migraine in outpatient settings recommend a combination of either triptans plus NSAIDs or triptans plus acetaminophen. (*Qaseem et al 2025*).
- For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (*Francis et al 2010, Robbins et al 2016*). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (*Robbins et al 2016*).
- In 2019, the AAN and AHS published a guideline on the acute treatment of migraine in children and adolescents, which was reaffirmed in October 2022 (*Oskoui et al 2019*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.
- All triptans are generally effective for the acute treatment of migraine attacks and are well tolerated with a similar safety profile. Although some triptans have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injectable treatments have been associated with the fastest onset of action; therefore, they are amenable for quick relief. However, injectable triptans are associated with more AEs compared to oral or nasal dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient need, response, preference, migraine severity, and tolerability.

References

- Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache*. 2021[a];61(7):1021-1039. doi:10.1111/head.14153.
- Almotriptan. Package insert. Mylan Pharmaceuticals, Inc., May 2017.
- Bird S, Derry S, Moore RA. Zolmitriptan for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2014 May 21;5:CD008616.
- Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007;297(13):1443-54.
- Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: Updated age, sex, and socioeconomic-specific estimates from government health surveys. *Headache*. 2021;61(1):60-68. doi: 10.1111/head.14024.
- Cady RK, McAllister PJ, Spierings EL, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). *Headache*. 2015 Jan;55(1):88-100.
- Cady RK, Munjal S, Cady RJ, Manley HR, Brand-Schieber E. Randomized, double-blind, crossover study comparing DFN-11 injection (3 mg subcutaneous sumatriptan) with 6 mg subcutaneous sumatriptan for the treatment of rapidly-escalating attacks of episodic migraine. J Headache Pain. 2017; 18(1):17.
- Chanchlani R, Agrawal A, Janjua D, Hafsa AN. The efficacy of different triptans for the treatment of acute headache in pediatric migraine: a systematic review. *Indian Pediatr*. 2023;60(8):663-671.
- Clinical Pharmacology Web site. Accessed May 5, 2025. https://www.clinicalkey.com/pharmacology/.
- ClinicalTrials.gov. Initiating Early Control of Migraine Pain and Associated Symptoms (INTERCEPT). ClinicalTrials.gov identifier: NCTNCT04163185. Updated April 30, 2021. Accessed August 7, 2025. https://clinicaltrials.gov/study/NCT04163185?term=NCT04163185&rank=1
- ClinicalTrials.gov. Maximizing Outcomes in Treating Acute Migraine (MOMENTUM). ClinicalTrials.gov identifier: NCT03896009. Updated August 24, 2023. Accessed August 7, 2025. https://clinicaltrials.gov/study/NCT03896009?term=NCT03896009&rank=1
- Cortelli P, Allais G, Tullo V, et al. Frovatriptan versus other triptans in the acute treatment of migraine: pooled analysis of three double-blind, randomized, cross-over, multicenter, Italian studies. *Neurol Sci*. 2011;32 Suppl 1:S95-8.
- Cutrer FM. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. UpToDate website. Updated November 6, 2024. Accessed May 5, 2025. http://www.uptodate.com/.
- Derry CJ, Derry S, Moore RA. Sumatriptan (all routes of administration) for acute migraine attacks in adults – overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2014 May 28;5:CD009108.
- Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012[a];2:CD009663.
- Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012[b];2:CD008615.
- Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012[c];2:CD009665.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed April 29, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.

- Evers S, Aphra J, Freese A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. *Eur J Neurol*. 2009 Sep;16(9):968-81.
- Ferrari MD, Goldsby PJ, Roan KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*. 2002;22(8):633-58.
- FDA Guidance for Industry. Migraine: developing drugs for acute treatment. February 2018. Accessed May 5, 2025. https://www.fda.gov/media/89829/download.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventative pharmacologic treatment of cluster headache. *Neurology*. 2010;75:463-73.
- Frova. Package insert. Endo Pharmaceuticals Inc.; August 2018.
- Gartlehner G, Dobrescu A, Wagner G, et al. Pharmacologic Treatment of Acute Attacks of Episodic Migraine: A Systematic Review and Network Meta-analysis for the American College of Physicians. *Ann Intern Med*. 2025;178(4):507-524. doi: 10.7326/ANNALS-24-02034
- Halker Singh RB, VanderPluym JH, Morrow AS, et al. Acute treatments for episodic migraine. Rockville (MD): Agency for Healthcare Research and Quality (US); December 2020. https://effectivehealthcare.ahrq.gov/sites/default/files/cer-239-acute-migraine-evidence-summary.pdf. Accessed October 15, 2024.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
- Imitrex nasal spray. Package insert. GlaxoSmithKline; March 2024.
- Imitrex injection Package insert. GlaxoSmithKline; February 2023.
- Imitrex tablets. Package insert. GlaxoSmithKline; February 2024.
- International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202
- Karlsson WK, Ostinelli EG, Zhuang ZA, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: systematic review and network meta-analysis. *BMJ*. 2024 Sep 18;386:e080107. doi: 10.1136/bmj-2024-080107.
- Law S, Derry S, Moore RA. Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2016 Apr 20;4:CD008541.
- Lipton RB, Munjal S, Brand-Schieber E Rapoport AM. DFN-02 (sumatriptan 10 mg with a permeation enhancer) nasal spray vs placebo in the acute treatment of migraine: a double-blind, placebo-controlled study. *Headache*. 2018;58(5):676-687. doi: 10.1111/head.13309.
- Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- Maxalt and Maxalt-MLT. [Package insert. Organon & Co; June 2022.
- May A, Evers S, Goadsby PJ, et al. European Academy of Neurology guidelines on the treatment of cluster headache. *Eur J Neurol*. 2023;30(10):2955-2979. doi:10.1111/ene.15956
- Migranow. Package insert. PureTek Corporation; December 2024.
- Naratriptan. Package insert. Bionpharma, Inc; December 2023.
- Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain*. 2002;97(3):247-57.
- Onzetra Xsail. Package insert. Currax Pharmaceuticals LLC.; April 2024.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. Accessed May 5, 2025..https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019;93(11):487-499. doi: 10.1212/WNL.0000000000008095.
- Pascual J, Mateos V, Roig C, Sanchez-Del-Rio M, Jiménez D. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache*. 2007;47(8):1152-68.
- Poolsup N, Leelasangaluk V, Jittangtrong J, et al. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther*. 2005;30(6):521-32.
- Puledda F, Sacco S, Diener HC, et al. International Headache Society global practice recommendations for the acute pharmacological treatment of migraine. *Cephalalgia*. 2024 Aug;44(8):3331024241252666. doi: 10.1177/03331024241252666.
- Qaseem A, Tice JA, Etxeandia-Ikobaltzeta I, et al. Pharmacologic Treatments of Acute Episodic Migraine Headache in Outpatient Settings: A Clinical Guideline From the American College of Physicians. *Ann Intern Med*. 2025 Apr;178(4):571-578. doi: 10.7326/ANNALS-24-03095.
- Relpax. Package insert. Pfizer; March 2020.
- Richer L, Billinghurst L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev*. 2016 Apr 19;4: CD005220.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016 Jul;56(7):1093-106. doi: 10.1111/head.12866.
- Schwedt TJ, Garza I. Acute treatment of migraine in adults. UpToDate website. Updated May 2, 2025. Accessed May 5, 2025. https://www.uptodate.com/.
- Silberstein SD, Holland S, Freitaq F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012 Apr 24;78(17):1337-45 (reaffirmed on October 22, 2022; guideline update in progress as of 2024).
- Snow V, Weiss K, Wall EM, Mottur-Pilson C, for the American Academy of Family Physicians and American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med*. 2002;137(10):840-9.
- Sumansetron. Package insert. PureTek Corporation; January 2023.
- Symbravo. Package insert. Axsome Therapeutics; February 2025.

- Tepper SJ, Cady RK, Silberstein S, et al. AVP-825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. *Headache*. 2015 May;55(5):621-35.
- Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia*. Jan 2012;32(1):6-38.
- Tosymra. Package insert. Upsher-Smith Laboratories LLC.; November 2024.
- Treximet. Package insert. Currax Pharmaceuticals, LLC.;December 2024.
- Thorlund K, Toor K, Wu P, et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. Cephalalgia. 2017;37(10):965-978.
- Winner P, Farkas V, Stillova H, et al. Efficacy and tolerability of zolmitriptan nasal spray for the treatment of acute migraine in adolescents: Results of a randomized, double-blind, multi-center, parallel-group study (TEENZ). *Headache.* 2016 Jul;56(7):1107-1119.
- Zembrace SymTouch. Package insert. Upsher-Smith Laboratories LLC.; November 2024.
- Zolmitriptan orally disintegrating tablet. Package insert. Alembic Pharmaceuticals, Inc.: February 2024.
- Zomig nasal spray. Package insert. Amneal Pharmaceuticals; May 2019.
- Zomig tablets/ Package insert. Amneal Pharmaceuticals; March 2022.

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