South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 5, 2020

DSS

Strong Families - South Dakota's Foundation and Our Future

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DEPARTMENT OF SOCIAL SERVICES
OFFICE OF THE SECRETARY
700 GOVERNORS DRIVE
PIERRE, SD 57501-2291
PHONE: 605-773-3165
FAX: 605-773-4855
WEB: dss.sd.gov

Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

June 5, 2020
1:00 – 3:00 PM

Dial-in number: 866-410-8397
Conference Code: 8176972761

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **CGRP utilization**
- **Orilissa utilization**
- **PA criteria reviews**
  - **Review utilization for Lyrica PA**
  - **Review utilization for Lidoderm PA**
  - **Review utilization for Ketoconazole Topical PA**
  - **Review utilization for Triptan PA**
  - **Review utilization for GLP-1 Receptor Agonist PA**
- **Opioid update**

New business
- **Compound utilization review**
- **Maintenance medication 90-day fill review**
- **Atypical Antipsychotic utilization in children**
- **Ubrelvy**
- **Reyvow**
- **Gvoke & Baqsimi (Glucagon Agents)**

Public comment accepted after individual topic discussion
Next meeting date September 2020 & adjournment

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

Friday, December 13, 2019
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Bill Ladwig, RPh	X
Dana Darger, RPh, Chair	X	Kelley Oehlke, PharmD	
James Engelbrecht, MD	X	Lenny Petrik, PharmD	X
Deidre Van Gilder, PharmD	X	Mike Jockheck, DSS Staff	X
Mikal Holland, MD		Sarah Akers, DSS Staff	X
Richard Holm, MD		Bill Snyder, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:02 PM. The minutes of the June meeting were presented. Ladwig made a motion to approve. Van Gilder seconded the motion. Motion was approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from July 1, 2019 to September 30, 2019. A total of 1,884 PAs were reviewed of which 296 requests (15.71%) were received via telephone and 1,063 requests (56.42%) were received via fax, and 525 (27.87%) were reviewed via electronically.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from July 1, 2019 to September 30, 2019. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, anticonvulsants, amphetamines, and respiratory/CNS stimulants. The top 15 therapeutic classes make up 24.77% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 7.43% of total claims. Darger and Ladwig discussed USP Chapter 800 Standards for Safe Handling of Hazardous Drugs. They requested utilization of compound claims to review at the next meeting.

Old Business

The committee reviewed the calcitonin gene related peptide (CGRP) utilization comparing 2Q19 vs 3Q19. Utilization continues to increase each quarter, including utilization shift from Aimovig to Emgality. Petrik commented seeing similar utilization shifts on the commercial plan side. The committee also reviewed utilization for Orilissa for 3Q19. Committee requested to review utilization for both classes again at the next meeting.

The committee reviewed 3Q19 opioid outcomes compared to previous quarters from the opioid initiatives. Utilization and MME levels indicate decreased trend.

New Business

PA Criteria Review

The committee reviewed all PA criteria currently in effect. Jockheck reminded the committee to also consider removing PAs that are not necessary due to availability of generics, outdated, or now considered out of scope. The following decisions were made, including requesting follow up information for a more in-depth review at the next meeting:

- Lyrica – Committee reviewed utilization for Lyrica and pregabalin for PA removal consideration. Darger requested to review gabapentin utilization at the next meeting before making a decision. It was suggested to also include duloxetine utilization and how other Medicaid states were handling Lyrica, especially surrounding areas.
- Hepatitis C – Snyder provided an update regarding the committee's recommendation from the June meeting. DSS continues to evaluate the recommendation.
- Lidoderm – Darger requested utilization for Lidoderm.
- Ketoconazole Topical – Committee inquired if there were PAs for Extina or Xolegel.
- Head Lice – Committee reviewed utilization and discussed the merits of this PA. Darger commented the PA was developed because of heavy utilization of lindane since providers did not know OTC permethrin was covered. In addition, the potential for Soolantra cream (indications for rosacea) used for head lice treatment was discussed.
- Topical Acne – Committee reviewed utilization for topical acne and rosacea treatment. Baack made a motion to create a rosacea PA. Van Gilder seconded the motion. Motion was approved unanimously.
- Growth Hormones – Baack made a motion to modify PA criteria from "for small gestational age (SGA)" to "for small gestational age plus post-natal growth failure at one year". Ladwig seconded the motion. Motion was approved unanimously.
- Anticoagulants – Van Gilder questioned the need for a PA. Darger commented drugs are used appropriately and suggested monitoring utilization when PA removed. Van Gilder made a motion to remove PA on Eliquis, Pradaxa, Savaysa, and Xarelto. Baack seconded the motion. Motion was approved unanimously.
- Triptans – Ladwig requested to review utilization prior to consideration for PA removal.
- Nasal Steroids – Ladwig requested to review utilization prior to consideration for PA removal.
- Methadone – After discussing previous reasons for the PA on methadone and since it is part of the long-acting-opioid (LAO) PA and MED Limit PA, Ladwig made a motion to remove PA. Baack seconded the motion. Motion was approved unanimously.
- Ophthalmic Antihistamines – Committee reviewed utilization for ophthalmic antihistamines. Ladwig made a motion to remove PA on olopatadine ophthalmic drops. Van Gilder seconded the motion. Motion was approved unanimously.

Engelbrecht made a motion to approve all the PA criteria as amended today. Baack seconded the motion. Motion was approved unanimously.

Ladwig requested reviewing GLP-1 orals at the next meeting.

Review of Sunosi

Sunosi clinical information was presented for review. Committee recommended adding Sunosi to Xyrem PA. Ladwig made a motion to add PA to Sunosi. Engelbrecht seconded the motion. Motion was approved unanimously.

Review of Apadaz
Apadaz clinical information was presented for review. Apadaz is included in the MED Limit PA. Committee recommended adding Apadaz to LAO PA. Engelbrecht made a motion to add PA to Apadaz. Ladwig seconded the motion. Motion was approved unanimously.

Engelbrecht Retirement
Darger read Governor Noem's proclamation designating December 13 as James Engelbrecht Day who devoted his life service to medical practice for the last 45 years. Engelbrecht is retiring after the December 13th meeting. Engelbrecht has been on the committee for the last 16 years. He stated this was the best committee he has served on where experts from pharmacy and medical come together to serve the community of South Dakota.

Adjournment
The next meeting is scheduled for March 13, 2019. Tentative meeting dates for next year are June 5, 2020. Engelbrecht announced as a point of personal preference made a motion to adjourn the meeting and the committee seconded the motion. The motion passed unanimously, and the meeting adjourned at 2:32 PM.

PA Report
1/1/2020 – 3/31/2020

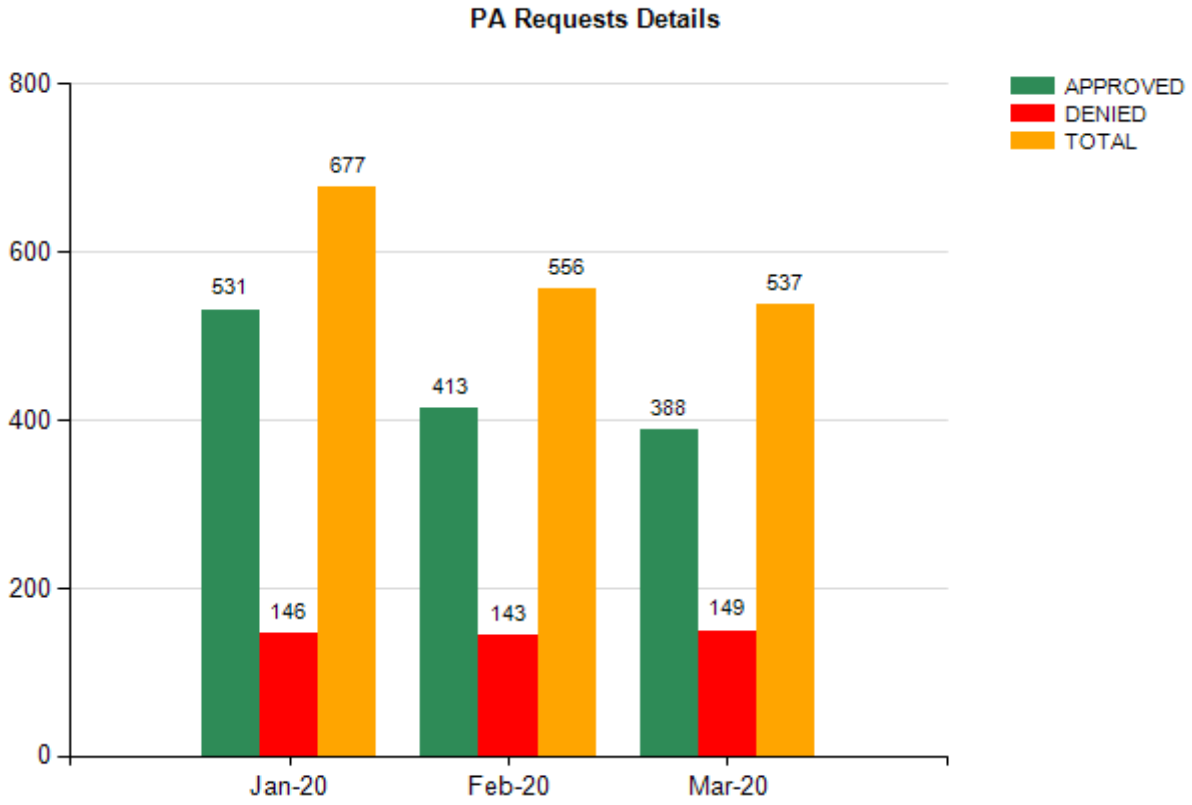
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
STANDARD	1724	1724	0	100%	0%
URGENT	46	46	0	100%	0%
GRAND TOTAL	**1770**	**1770**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
TOTAL	**1,770**	**193**	**11%**	**1,063**	**60%**	**514**	**29%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Jan-20	531	146	677
Feb-20	413	143	556
Mar-20	388	149	537
1Q20	**1,332**	**438**	**1,770**
Percent of Total	**75.25%**	**24.75%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTICS/ANTIMANIC	247	41	288	85.76%	16.27%	, VRAYLAR
58 - ANTIDEPRESSANTS*	230	23	253	90.91%	14.29%	, DULOXETINE HYDROCHLORIDE
65 - ANALGESICS - OPIOID*	130	73	203	64.04%	11.47%	HYDROCODONE/APAP, TRAMADOL
49 - ULCER	152	19	171	88.89%	9.66%	, ESOMEPRAZOLE MAGNESIUM
72 - ANTICONVULSANTS*	97	51	148	65.54%	8.36%	PREGABALIN, CLOBAZAM
Others -	476	231	707	67.33%	39.94%	
1Q20	**1,332**	**438**	**1,770**	**75.25%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	247	41	288	85.76%
58 - ANTIDEPRESSANTS*	230	23	253	90.91%
65 - ANALGESICS - OPIOID*	130	73	203	64.04%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	152	19	171	88.89%
72 - ANTICONVULSANTS*	97	51	148	65.54%
90 - DERMATOLOGICALS*	58	76	134	43.28%
27 - ANTIDIABETICS*	85	6	91	93.41%
52 - GASTROINTESTINAL AGENTS - MISC.*	42	18	60	70.00%
67 - MIGRAINE PRODUCTS*	25	31	56	44.64%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	35	7	42	83.33%
66 - ANALGESICS - ANTI-INFLAMMATORY*	28	11	39	71.79%
12 - ANTIVIRALS*	17	19	36	47.22%
54 - URINARY ANTISPASMODICS	26	10	36	72.22%
83 - ANTICOAGULANTS*	31	2	33	93.94%
16 - ANTI-INFECTIVE AGENTS - MISC.*	23	2	25	92.00%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	18	3	21	85.71%
41 - ANTIHISTAMINES*	17	1	18	94.44%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	8	8	16	50.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	9	5	14	64.29%
75 - MUSCULOSKELETAL THERAPY AGENTS*	9	2	11	81.82%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	6	4	10	60.00%
50 - ANTIEMETICS*	7	3	10	70.00%
86 - OPHTHALMIC AGENTS*	3	7	10	30.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	4	5	9	44.44%
39 - ANTIHYPERLIPIDEMICS*	5	2	7	71.43%
36 - ANTIHYPERTENSIVES*	2	2	4	50.00%
45 - RESPIRATORY AGENTS - MISC.*	3	1	4	75.00%
34 - CALCIUM CHANNEL BLOCKERS*	2	1	3	66.67%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	3	0	3	100.00%
33 - BETA BLOCKERS*	2	0	2	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	1	2	50.00%
02 - CEPHALOSPORINS*	0	1	1	0.00%
04 - TETRACYCLINES*	0	1	1	0.00%
15 - ANTHELMINTICS*	0	1	1	0.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	1	0	1	100.00%
24 - ESTROGENS*	1	0	1	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	1	0	1	100.00%
57 - ANTIANXIETY AGENTS*	1	0	1	100.00%
79 - MINERALS & ELECTROLYTES*	1	0	1	100.00%
82 - HEMATOPOIETIC AGENTS*	1	0	1	100.00%
94 - DIAGNOSTIC PRODUCTS*	1	0	1	100.00%
4Q20	**1,332**	**438**	**1,770**	
Percent of Total	**75.25%**	**24.75%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-20	17	77.27%	5	22.73%	22
Feb-20	15	65.22%	8	34.78%	23
Mar-20	16	66.67%	8	33.33%	24
1Q20	**48**	**69.57%**	**21**	**30.43%**	**69**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
MAVYRET	0	9	9	0.00%
AMITIZA	4	1	5	80.00%
PREGABALIN	4	1	5	80.00%
AJOVY	2	2	4	50.00%
HYDROCODONE/APAP	3	0	3	100.00%
TRAMADOL HCL	3	0	3	100.00%
ARISTADA	2	0	2	100.00%
EPCLUSA	0	2	2	0.00%
ESOMEPRAZOLE MAGNESIUM	2	0	2	100.00%
HUMIRA	2	0	2	100.00%
METHADONE HCL	2	0	2	100.00%
REXULTI	2	0	2	100.00%
CODEINE/APAP	0	1	1	0.00%
AFINITOR	1	0	1	100.00%
AFINITOR DISPERZ	1	0	1	100.00%
AIMOVIG	1	0	1	100.00%
CLINDAMYCIN PHOS/BENZOYL PEROXIDE	1	0	1	100.00%
CLINDAMYCIN/BENZOYL PEROXIDE	1	0	1	100.00%
CLOBAZAM	1	0	1	100.00%
DAPSONE	1	0	1	100.00%
DULOXETINE HYDROCHLORIDE	1	0	1	100.00%
EMGALITY	1	0	1	100.00%
ESCITALOPRAM OXALATE	0	1	1	0.00%
FLUOXETINE HYDROCHLORIDE	1	0	1	100.00%
HYDROCODONE BITARTRATE/APAP	1	0	1	100.00%
HYDROMORPHONE HCL	1	0	1	100.00%
INGREZZA	0	1	1	0.00%
LIDOCAINE	0	1	1	0.00%
MORPHINE SULFATE	1	0	1	100.00%
MYRBETRIQ	1	0	1	100.00%
NUCYNTA	1	0	1	100.00%
OLANZAPINE ODT	1	0	1	100.00%
OTEZLA	1	0	1	100.00%
OXYCODONE HYDROCHLORIDE	1	0	1	100.00%
PALIPERIDONE ER	1	0	1	100.00%
QUETIAPINE FUMARATE	0	1	1	0.00%
SOFOSBUVIR/VELPATASVIR	0	1	1	0.00%
STELARA	1	0	1	100.00%
STRENSIQ	1	0	1	100.00%
TRANSDERM-SCOP	1	0	1	100.00%
1Q20	**48**	**21**	**69**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2020 – 3/31/2020				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	12,338	$164,747.04	$13.35	5.86%
2 MISCELLANEOUS ANTICONVULS	10,947	$1,042,044.37	$95.19	5.20%
3 SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,917	$545,911.52	$61.22	4.23%
4 AMINOPENICILLIN ANTIBIOTICS	8,840	$128,097.99	$14.49	4.20%
5 ATYPICAL ANTIPSYCHOTICS	8,337	$2,250,212.72	$269.91	3.96%
6 SECOND GENERATION ANTIHIS	7,458	$85,303.15	$11.44	3.54%
7 RESPIRATORY AND CNS STIMULANTS	7,014	$859,904.61	$122.60	3.33%
8 AMPHETAMINES	6,308	$1,152,758.56	$182.75	3.00%
9 ADRENALS	6,306	$647,728.20	$102.72	2.99%
10 PROTON-PUMP INHIBITORS	6,155	$216,601.78	$35.19	2.92%
11 OPIATE AGONISTS	5,625	$213,807.11	$38.01	2.67%
12 NEURAMINIDASE INHIBITORS	4,560	$278,438.00	$61.06	2.17%
13 THYROID AGENTS	3,695	$71,401.46	$19.32	1.75%
14 MISC. ANXIOLYTICS, SEDATI	3,510	$124,297.88	$35.41	1.67%
15 SEROTONIN MODULATORS	3,499	$117,052.24	$33.45	1.66%
Total Top 15 Therapeutic Classes	**103,509**	**$ 7,898,306.63**	**$76.31**	**49.15%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2020 – 3/31/2020				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1 ATYPICAL ANTIPSYCHOTICS	8,337	$2,250,212.72	$269.91	3.96%
2 DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	230	$1,167,746.84	$5,077.16	0.11%
3 AMPHETAMINES	6,308	$1,152,758.56	$182.75	3.00%
4 MISCELLANEOUS ANTICONVULS	10,947	$1,042,044.37	$95.19	5.20%
5 RESPIRATORY AND CNS STIMULANTS	7,014	$859,904.61	$122.60	3.33%
6 SKIN AND MUCOUS MEMBRANE	428	$744,701.30	$1,739.96	0.20%
7 ANTINEOPLASTIC AGENTS	290	$724,273.25	$2,497.49	0.14%
8 HEMOSTATICS	44	$658,974.70	$14,976.70	0.02%
9 CYSTIC FIBROSIS (CFTR) CORRECTORS	36	$655,946.57	$18,220.74	0.02%
10 ADRENALS	6,306	$647,728.20	$102.72	2.99%
11 RAPID-ACTING INSULINS	1,351	$647,310.72	$479.13	0.64%
12 LONG-ACTING INSULINS	1,529	$618,636.66	$404.60	0.73%
13 SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,917	$545,911.52	$61.22	4.23%
14 INCRETIN MIMETICS	471	$355,057.78	$753.84	0.22%
15 SOMATOTROPIN AGONISTS	86	$287,683.12	$3,345.15	0.04%
Total Top 15 Therapeutic Classes	**52,294**	**$12,358,890.92**	**$236.33**	**24.83%**

Total Rx Claims from 1/1/2020 – 3/31/2020	**210,610**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2020 – 3/31/2020					
AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1 AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	7,063	$90,932.60	$12.87	3.35%
2 RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE HYDROCHLO	5,021	$568,815.00	$113.29	2.38%
3 NEURAMINIDASE INHIBITORS	OSELTAMIVIR PHOSPHATE	4,499	$273,906.38	$60.88	2.14%
4 SECOND GENERATION ANTIHIS	CETIRIZINE HYDROCHLORIDE	4,072	$42,381.83	$10.41	1.93%
5 PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,677	$42,253.52	$11.49	1.75%
6 SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,500	$157,987.60	$45.14	1.66%
7 AMPHETAMINES	VYVANSE	3,464	$1,004,341.25	$289.94	1.64%
8 LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,399	$46,926.68	$13.81	1.61%
9 MISCELLANEOUS ANTICONVULS	GABAPENTIN	3,261	$56,390.36	$17.29	1.55%
10 SEROTONIN MODULATORS	TRAZODONE HYDROCHLORIDE	3,212	$32,771.23	$10.20	1.53%
11 THYROID AGENTS	LEVOTHYROXINE SODIUM	2,995	$52,535.78	$17.54	1.42%
12 SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	2,948	$60,210.20	$20.42	1.40%
13 AMPHETAMINES	AMPHETAMINE/DEXTROAMPHETA	2,672	$128,266.52	$48.00	1.27%
14 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HYDROCHLORIDE	2,646	$41,662.51	$15.75	1.26%
15 OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	2,472	$43,064.58	$17.42	1.17%
16 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	2,336	$29,661.44	$12.70	1.11%
17 ANGIOTENSIN-CONVERTING EN	LISINOPRIL	2,308	$21,009.42	$9.10	1.10%
18 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HCL	2,058	$23,770.43	$11.55	0.98%
19 ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,022	$43,153.59	$21.34	0.96%
20 OPIATE AGONISTS	HYDROCODONE/ACETAMINOPHEN	1,985	$29,593.15	$14.91	0.94%
21 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,967	$20,594.93	$10.47	0.93%
22 HMG-COA REDUCTASE INHIBIT	ATORVASTATIN CALCIUM	1,903	$22,805.74	$11.98	0.90%
23 SECOND GENERATION ANTIHIS	LORATADINE	1,893	$21,554.85	$11.39	0.90%
24 ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION HYDROCHLORIDE E	1,820	$35,046.05	$19.26	0.86%
25 3RD GENERATION CEPHALOSPORIN ANTIBIOT	CEFDINIR	1,790	$37,706.61	$21.07	0.85%
26 AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANATE P	1,775	$37,135.09	$20.92	0.84%
27 SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HYDROCHLORIDE	1,758	$20,927.74	$11.90	0.83%
28 ADRENALS	PREDNISONE	1,752	$18,397.17	$10.50	0.83%
29 CORTICOSTEROIDS	FLUTICASONE PROPIONATE	1,748	$26,562.39	$15.20	0.83%
30 CENTRAL ALPHA-AGONISTS	CLONIDINE HCL	1,739	$18,120.92	$10.42	0.83%
31 BIGUANIDES	METFORMIN HYDROCHLORIDE	1,608	$13,626.45	$8.47	0.76%
32 COMPOUNDS	COMPOUNDS	1,561	$74,325.97	$47.61	0.74%
33 ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,549	$19,494.50	$12.59	0.74%
34 ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,472	$19,790.90	$13.44	0.70%
35 MISC. CENTRAL NERVOUS SYS	GUANFACINE ER	1,468	$29,836.63	$20.32	0.70%
36 MISCELLANEOUS ANTICONVULS	LAMOTRIGINE	1,450	$21,185.30	$14.61	0.69%
37 5-HT3 RECEPTOR ANTAGONIST	ONDANSETRON ODT	1,430	$21,708.48	$15.18	0.68%
38 1ST GENERATION CEPHALOSPORIN ANTIBIOT	CEPHALEXIN	1,417	$23,450.97	$16.55	0.67%
39 BENZODIAZEPINES (ANTICONV	CLONAZEPAM	1,340	$14,691.26	$10.96	0.64%
40 SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	DULOXETINE HYDROCHLORIDE	1,315	$20,058.23	$15.25	0.62%
41 MISCELLANEOUS ANTICONVULS	LEVETIRACETAM	1,286	$26,947.48	$20.95	0.61%
42 OPIATE AGONISTS	TRAMADOL HCL	1,216	$13,219.17	$10.87	0.58%
43 CORTICOSTEROIDS (SKIN, MUCOUS MEMBR)	TRIAMCINOLONE ACETONIDE	1,212	$17,728.01	$14.63	0.58%
44 CENTRALLY ACTING SKELETAL MUSCLE RELAXT	CYCLOBENZAPRINE HYDROCHLO	1,199	$11,076.47	$9.24	0.57%
45 VITAMIN D	VITAMIN D	1,196	$11,933.88	$9.98	0.57%
46 MISCELLANEOUS ANTICONVULS	TOPIRAMATE	1,187	$16,899.18	$14.24	0.56%
47 OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	IBUPROFEN	1,183	$14,721.08	$12.44	0.56%
48 DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,164	$11,130.18	$9.56	0.55%
49 ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,120	$16,077.00	$14.35	0.53%
50 RESPIRATORY AND CNS STIMULANTS	DEXMETHYLPHENIDATE HCL ER	1,117	$111,791.71	$100.08	0.53%
TOTAL TOP 50 DRUGS		**110,245**	**$3,558,178.41**	**$32.28**	**52.35%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2020 – 3/31/2020					
AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1 AMPHETAMINES	VYVANSE	3,464	$1,004,341.25	$289.94	1.64%
2 RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE HYDROCHLO	5,021	$568,815.00	$113.29	2.38%
3 ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	231	$529,702.52	$2,293.08	0.11%
4 ATYPICAL ANTIPSYCHOTICS	LATUDA	374	$433,880.14	$1,160.11	0.18%
5 CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	18	$360,900.91	$20,050.05	0.01%
6 DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN	54	$354,830.04	$6,570.93	0.03%
7 CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	14	$293,016.22	$20,929.73	0.01%
8 RAPID-ACTING INSULINS	NOVOLOG FLEXPEN	522	$281,667.56	$539.59	0.25%
9 ATYPICAL ANTIPSYCHOTICS	VRAYLAR	252	$279,254.31	$1,108.15	0.12%
10 ATYPICAL ANTIPSYCHOTICS	ARISTADA	117	$276,240.12	$2,361.03	0.06%
11 NEURAMINIDASE INHIBITORS	OSELTAMIVIR PHOSPHATE	4,499	$273,906.38	$60.88	2.14%
12 ADRENALS	FLOVENT HFA	1,021	$238,854.14	$233.94	0.48%
13 MOVEMENT DISORDER	INGREZZA	39	$229,199.58	$5,876.91	0.02%
14 MUCOLYTIC AGENTS	PULMOZYME	66	$227,129.83	$3,441.36	0.03%
15 SKIN AND MUCOUS MEMBRANE	COSENTYX SENSOREADY PEN	34	$214,486.69	$6,308.43	0.02%
16 SKIN AND MUCOUS MEMBRANE	STELARA	12	$210,113.28	$17,509.44	0.01%
17 LONG-ACTING INSULINS	LANTUS SOLOSTAR	616	$208,373.65	$338.27	0.29%
18 NZYMES	STRENSIQ	4	$205,948.80	$51,487.20	0.00%
19 SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	62	$199,255.62	$3,213.80	0.03%
20 MISCELLANEOUS ANTICONVULS	VIMPAT	225	$182,684.84	$811.93	0.11%
21 ANTINEOPLASTIC AGENTS	AFINITOR DISPERZ	6	$179,359.08	$29,893.18	0.00%
22 ATYPICAL ANTIPSYCHOTICS	REXULTI	175	$176,129.15	$1,006.45	0.08%
23 HEMOSTATICS	RECOMBINATE	3	$161,883.04	$53,961.01	0.00%
24 DISEASE-MODIFYING ANTIRHEUMATIC AGNTS	HUMIRA	23	$160,912.96	$6,996.22	0.01%
25 SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,500	$157,987.60	$45.14	1.66%
26 CYSTIC FIBROSIS (CFTR) POTENTIATORS	KALYDECO	6	$143,433.18	$23,905.53	0.00%
27 ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	69	$142,974.25	$2,072.09	0.03%
28 MISCELLANEOUS ANTICONVULS	BANZEL	64	$142,534.26	$2,227.10	0.03%
29 ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	19	$141,172.14	$7,430.11	0.01%
30 LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	311	$138,919.90	$446.69	0.15%
31 MISCELLANEOUS ANTICONVULS	EPIDIOLEX	59	$138,184.77	$2,342.11	0.03%
32 HEMOSTATICS	NOVOSEVEN RT	3	$138,031.50	$46,010.50	0.00%
33 HEMOSTATICS	ADVATE	6	$134,708.68	$22,451.45	0.00%
34 MISCELLANEOUS GI DRUGS	CHOLBAM	6	$132,688.00	$22,114.67	0.00%
35 DISEASE-MODIFYING ANTIRHEUMATIC AGNTS	ENBREL SURECLICK	25	$132,468.00	$5,298.72	0.01%
36 INCRETIN MIMETICS	TRULICITY	174	$130,148.70	$747.98	0.08%
37 AMPHETAMINES	AMPHETAMINE/DEXTROAMPHETA	2,672	$128,266.52	$48.00	1.27%
38 LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	292	$123,337.17	$422.39	0.14%
39 RIFAMYCIN ANTIBIOTICS	XIFAXAN	67	$123,331.08	$1,840.76	0.03%
40 SODIUM-GLU COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	250	$120,291.68	$481.17	0.12%
41 SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	338	$119,060.82	$352.25	0.16%
42 DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	279	$114,625.91	$410.85	0.13%
43 ANTINEOPLASTIC AGENTS	IBRANCE	9	$112,132.23	$12,459.14	0.00%
44 RESPIRATORY AND CNS STIMULANTS	DEXMETHYLPHENIDATE HCL ER	1,117	$111,791.71	$100.08	0.53%
45 HEMOSTATICS	ALPROLIX	8	$106,595.76	$13,324.47	0.00%
46 HIV INTEGRASE INHIBITORS	GENVOYA	34	$106,398.55	$3,129.37	0.02%
47 RAPID-ACTING INSULINS	NOVOLOG	204	$105,792.78	$518.59	0.10%
48 RAPID-ACTING INSULINS	NOVOLOG PENFILL	234	$100,014.27	$427.41	0.11%
49 IMMUNOMODULATORY AGENTS	TECFIDERA	12	$98,917.54	$8,243.13	0.01%
50 SKIN AND MUCOUS MEMBRANE	DUPIXENT	32	$96,321.60	$3,010.05	0.02%
TOTAL TOP 50 DRUGS		**26,642**	**$10,491,013.71**	**$393.78**	**12.65%**

Utilization

Time frame: 7/1/2019 – 1/1/2020
Red font denotes drug is on Prior Authorization

CGRP Inhibitors

	3Q 2019				4Q 2019				1Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Utilizer**
AIMOVIG	49	$27,560.62	$562.46	21	47	$26,441.09	$562.58	18	42	$24,456.28	$582.29	18
AJOVY	7	$3,934.35	$562.05	3	15	$8,422.72	$561.51	6	15	$7,656.56	$510.44	8
EMGALITY	26	$16,251.92	$625.07	10	34	$21,882.09	$634.59	14	38	$24,206.25	$637.01	17
UBRELVY									20	$17,225.74	$861.29	17
Total	**82**	**$47,746.89**		**Female 32 Male 2 Total 34**	**96**	**$56,745.90**		**Female 35 Male 2 Total 37**	**115**	**$73,544.83**		**Female 48 Male 5 Total 53**

Orilissa

	3Q 2019				4Q 2019				1Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
ORILISSA	4	$3,312.86	$828.22	3	1	$828.06	$828.06	1	6	$3,357.62	$559.60	3

*Some states are watching utilization; other states added to PA
*1Q2020 – 2 Rxs at $13.78

Lyrica

	3Q 2019				4Q 2019				1Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
LYRICA	189	$94,348.28	$499.20	130	17	$8,053.06	$473.71	7	17	$10,033.61	$590.21	8
pregabalin	237	$6,638.71	$28.01	142	44	$9,344.68	$21.00	166	371	$7,666.23	$20.66	166
gabapentin	3,157	$54,391.97	$17.23	1,248	3,274	$56,775.72	$17.34	1,249	2,833	$49,105.09	$17.33	1,217

PA Criteria:

- Diagnosis of neuropathic pain associated with postherpetic neuralgia, fibromyalgia, or diabetic peripheral neuropathy, trigeminal neuralgia and trial of tricyclic antidepressant or gabapentin
- Diagnosis of partial onset seizure and Lyrica used as adjunctive therapy
- Diagnosis of neuropathic pain associated with spinal cord injury or radiculopathy
- No concomitant gabapentin therapy

Gabapentin concurrent utilization with opioids and/or BZD

- gabapentin utilization January to December 2019 – 1,970 utilizers
    - gabapentin with opioids – 1,190 utilizers
    - gabapentin with BZD – 570 utilizers
    - gabapentin with opioids and BZD – none

Lidoderm: 4Q 2019 – 1Q 2020

Drug Name	Total Rx	Paid Amount	Paid/ Rx	Utilizing Mbrs	Age Range	SA* PA Request	SA* PA Denied	PA Approve	PA Deny
LIDODERM	0					1,236	1,236	2	220
lidocaine cream 3%	4	$202.09	$50.52	3	34 - 58				
lidocaine gel 2%	39	$3,343.90	$85.74	23	1 - 56				
lidocaine ointment 5%	36	$877.57	$24.38	21	0 - 64				
lidocaine pad 5%	9	$786.37	$87.37	3	51 - 62				
ZTLIDO PAD 1.8%	1	$265.28	$265.28	1	60				

PA Criteria: Diagnosis of postherpetic neuralgia (SilentAuth)

*SA: Silent Auth PAs

Topical Ketoconazole: 4Q 2019 – 1Q 2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
EXTINA foam	0				
XOLEGEL gel	0				
XOLEGEL kit	0				
XOLEGEL DUO/kit	0				
ketoconazole aer 2%	1	$432.49	$439.49	2	19
ketoconazole cream 2%	332	$10,706.30	$32.25	276	0 - 62
ketoconazole shampoo	337	$7,366.75	$21.86	193	0 - 64

PA Criteria: Trial of ketoconazole cream or shampoo

Triptan: 4Q 2019 – 1Q 2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Members	Age Range
eletriptan tab	67	$3,988.51	$59.53	#8.4/27 days	21	24 - 61
frovatriptan tab	1	$288.34	$288.34	#9/30 days	1	38
naratriptan tab	11	$331.72	$30.16	#9/23 days	5	17 - 63
rizatriptan tab	169	$2,993.25	$17.71	#10.7/24 days	83	11 - 53
rizatriptan ODT	24	$465.68	$19.40	#9.5/20 days	13	7 - 44
MAXALT MLT	0					
sumatriptan tab	817	$12,647.02	$15.48	#9.6/24 days	369	6 - 64
sumatriptan inj	30	$6,776.23	$225.87	#2.3/8 days	9	10 - 52
sumatriptan nasal spray	38	$9,054.15	$238.27	#6.6/22 days	21	6 - 57
IMITREX tab	3	$1,735.43	$578.47	#9/30 days	1 (M)	58
zomatriptan tab	26	$1,088.88	$41.88	#9.7/28 days	13	11 - 59
ZOMIG spray	5	$3,005.90	$611.18	#7.2/14 days	3	33 - 51
ZOMIG ZMT	0					
TREXIMET	0					
REYVOW	1	$647.20	$647.20	#8/30 days	1	38
TOTAL	**1,192**	**$43,022.31**			**Female 404: 78% Male 112: 22% Total 516**	

PA Criteria for Tablet: Trial of generic triptan

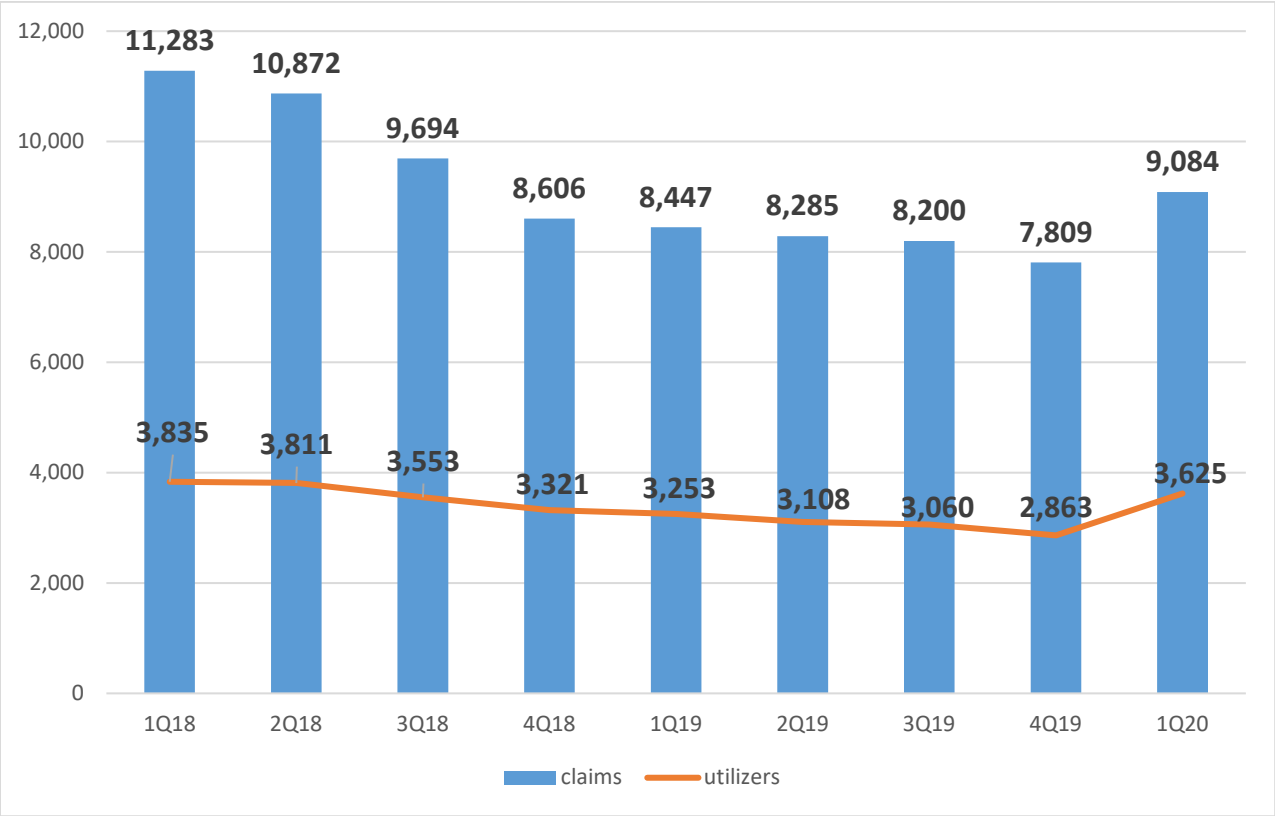
PA Criteria for ODT: Patient is less than 13 years old OR diagnosis of dysphagia

GLP-1 Receptor Agonists: 4Q 2019 -1Q 2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
ADLYXIN (lixisenatide)	0				
BYDUREON PEN (exenatide ER)	63	$42,856.68	$680.26	19	34 - 64
BYDUREON BCise	66	$43,136.43	$653.58	16	19 - 63
BYETTA (exenatide)	8	$5,685.05	$710.63	2	38 - 39
OZEMPIC (semaglutide)	172	$124,879.85	$726.05	47	18 - 64
TRULICIY (dulaglutide)	289	$210,008.99	$726.67	68	22 - 68
VICTOZA (liraglutide)	247	$189,571.21	$767.49	62	13 - 64
RYBELSUS (semaglutide) tablet	1	$779.63	$779.63	1	55
TANZEUM (albiglutide) disc 2018	0				
TOTAL	**846**	**$616,907.84**	**$729.21**	**Female 148 Male 57 Total 205**	

PA Criteria: Diagnosis of Type 2 diabetes mellitus
Rybelsus added to PA April 2020

Opioid Update



-1Q2018 to 4Q2019 excludes IHS
-1Q2020 includes IHS

Opioid Utilization

Utilizers: 3,625

2.8% 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 2.8% of all prescriptions this period, which is 0.7% lower than the benchmark
- 1,114 high opioid utilizers were identified this period, which is -18.9% lower than the benchmark

Opioid claims

PERCENT NON-COMPLIANT
11.3%

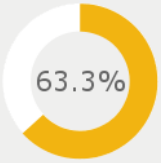
Opioid utilizers

HIGH UTILIZERS
30.7%
1,114 high utilizers

-18.9% under benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

63.3% of all opioid Rxs were filled for short acting opioids. **780** Rxs were for medication assisted therapy (MAT) and **33** 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

79 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,410	136	34	45

MED – view definition

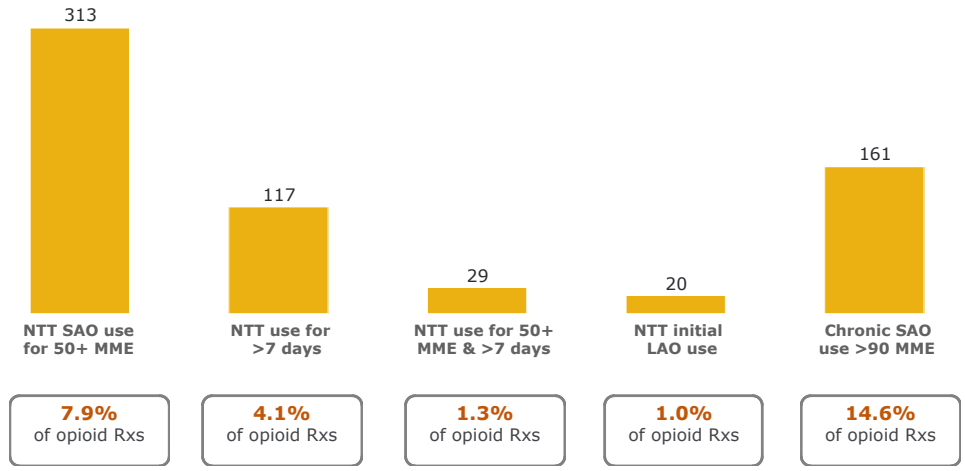
Opioid Opportunity Assessment

SDM iQPR
Viewing: Dec 2019 - Mar 2020
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.3%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



A retrospective review of claims indicates that 411 utilizing members during this timeframe would have hit our opioid UM program, if it had been implemented.

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

DID YOU KNOW?

54 opioid utilizing members use 3 or more pharmacies and 236 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
699	533	727	N/A	124

Anticonvulsants –view definition

Utilization

Compound Summary

Time frame: January 2019 to December 2019

Total # of Ingredients Submitted	Total $ of Ingredients Submitted	Total # of Paid Ingredients	Total $ Submitted of Paid Ingredients	Total $ of Ingredients paid	Dispensing Fees	Total Count of Paid Rxs	Total Paid Amount	Total Member Count
16,417	$1,126,646.44	8,287	$930,512.97	$222,473.34	$62,012.11	5,937	$272,315.98	1,676

Member Age Range	Utilizing Members	Total # of Rx	Total Paid Amount	Plan Cost/Mbr	Plan Cost/Rx	Avg # Rx/Mbr
0 to 1 years old	693	1,585	$32,514.69	$46.92	$20.51	2.29
2 to 5 years old	358	1,155	$27,183.79	$75.93	$23.54	3.23
6 to 12 years old	273	1,466	$107,156.47	$392.51	$73.09	5.37
13 to 17 years old	131	642	$13,915.26	$106.22	$21.67	4.90
18 to 64 years old	272	1,055	$90,282.65	$331.92	$85.58	3.88
65 to 88 years old	4	34	$1,263.12	$315.78	$37.15	8.50

Drug	Utilizing Members	Total # of Rx	Total Paid Amount	Plan Cost/Rx	Age Range
OMEPRAZOLE CAP 40MG, 20MG 10MG	260	874	$24,846.32	$95.56	0 - 64
NYSTATIN TAB-SUS-POW-OINT-CRE, NYSTOP & NYAMYC POW	447	659	$13,174.33	$19.99	0 - 63
LANSOPRAZOLE CAP 30MG 15MG	184	645	$20,709.23	$32.10	0 - 53
BANOPHEN LIQ, BACLOFEN 20MG, 10MG,	136	589	$8,781.71	$14.90	0 - 63
CLONIDINE TAB 0.3MG, 0.2MG, 0.1MG, POW	39	375	$3,993.73	$10.64	0 - 55
LIDOCAINE SOL, POW, OINT, GEL	319	369	$6,898.20	$18.69	0 - 88
TOPIMRATE TAB 100MG, 200MG	15	169	$2,004.98	$29.06	1 - 18
TETRACAINE POW HCL	58	125	$1,215.19	$9.72	1 - 28
CLONAZEPAM TAB 2MG, 1MG	14	107	$1,198.58	$11.20	0 - 35
ZONISAMIDE CAP 100MG	15	97	$1,489.66	$15.36	1 - 19
KETOCONAZOLE CREAM 2%	66	93	$3,666.28	$39.42	0 - 77

Maintenance Medication 90-day Dispensing Fee Estimated Savings

Rx Count	Total # of Rxs after 3 – 30 day fills	Total # Rxs converted to 90 day fills	Dispensing fee amount estimated for 90 day fill	Estimated dispensing fee savings 100% conversion
284,121	152,283	50,761	$504,285	~$1 million

- Based on 2019 utilization
- Generics only
- Maintenance medications only

Atypical Antipsychotic Utilization in Children (17 years old and younger)

	2019		
Identifier	Unique Utilizers	% Per Utilizer	% Per Member <17
One Product Concurrent > 90 Days	793	59.8%	1.62%
One or More Products Concurrent < 90 Days	297	22.4%	0.61%
Two or More Products Concurrent > 90 Days	235	17.7%	0.48%
Grand Total	1,325	100.0%	
Members Age 17 or less - 4/2020	49,057		

- Based on 2019 utilization
- Excludes IHS pharmacy network claims
- Excludes IHS members

Glucagon Utilization: 1Q2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Glucagon kit 1mg	159	$55,232.42	$347.37	116	0 - 64
Glucagen Inj Hypokit	16	$5,376.42	$336.03	11	9 - 60
Baqsimi	29	$14,940.08	$515.17	24	5 - 39
Gvoke	0				

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 4 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms. Ubrogepant is the only oral CGRP inhibitor (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of

olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- Two investigational CGRP inhibitors with near-term anticipated approvals include rimegepant, an oral tablet and oral disintegrating tablet CGRP inhibitor, and eptinezumab, an IV formulation that could be funded under the medical benefit. Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	−
Ajovy (fremanezumab-vfrm)	−
Emgality (galcanezumab-gnlm)	−
Ubrelvy (ubrogepant)	−

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab−aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)	Ubrelvy (ubrogepant)
Acute treatment of migraine with or without aura in adults	-	-	-	✔*
Preventive treatment of migraine in adults	✔	✔	✔	-
Treatment of episodic cluster headache in adults	-	-	✔	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019, Ubrelvy 2019*)

- 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

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 open-label extension (OLE) trial in unpublished formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and

safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).

- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Erenumab-aooe

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD as approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the most bothersome symptom (MBS) freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days

(mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.

- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2019, Ubrelvy prescribing information 2019*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

        - Magnesium IV
        - Isometheptene compounds
        - Combination medications (codeine/APAP, tramadol/APAP)
        - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    - Ubrogepant was reviewed by the AHS prior to FDA-approval for recommendation. The AHS recommend it may have a role in patients with cardiovascular (CV) conditions or in cases of triptan contraindications. Further recommendations include patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
        - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
    - Level A (established efficacy and > 2 Class I trials):
        - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
        - Beta blockers: metoprolol, propranolol, and timolol
        - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
    - Level B (probably effective and 1 Class I or 2 Class II trials):
        - Antidepressants: amitriptyline and venlafaxine
        - Beta blockers: atenolol and nadolol
        - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
    - Level C (possibly effective and 1 Class II trial):
        - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
        - Angiotensin II receptor blockers (ARBs): candesartan
        - Alpha agonists: clonidine and guanfacine
        - Antiepileptic drugs: carbamazepine
        - Beta blockers: nebivolol and pindolol
        - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
    - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
    - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
    - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).

- Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. In cases of serious or severe reactions, treatment should be discontinued.
- Erenumab-aooe has an additional warning and precaution associated with constipation with serious complications noted post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- For the prevention of migraine, erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor prevention studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- For the treatment of episodic cluster headache, galcanezumab−gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- For the treatment of acute migraines, the safety of ubrogepant was evaluated for up to 1 year in an OLE in patients who had ≥ 2 attacks/month. The most common adverse events were nausea (2 to 4%) and somnolence (2 to 3%). The most common adverse reaction resulting in discontinuation in the OLE was nausea.

- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with the 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2019, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Episodic cluster headache: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Max dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Ubrogepant is indicated for acute treatment of migraine with or without aura. Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are indicated for the prevention of migraine. Galcanezumab−gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.

Recent AHS guidelines state that ubrogepant may have a role in patients with CV conditions or in cases of triptan contraindications. It is also noted that other CGRP inhibitors may shortly be FDA-approved for use.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, ubrogepant has a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions in SC formulations and nausea in oral formulations.
- Overall, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and ubrogepant is the only CGRP inhibitor indicated for acute treatment of migraines and also the only oral formulation. The frequency of administration (and route or dose) vary by indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal

	potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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Publication Date: January 2, 2020

INTRODUCTION

- Migraine is a debilitating neurological disorder characterized by recurring, often unilateral, throbbing headaches of moderate to severe intensity that are exacerbated by physical activity and associated with nausea, vomiting, photophobia, and phonophobia. It is a common condition that affects up to 12% of the general population and is more frequent in women than in men *(American Headache Society [AHS] 2019, Cutrer 2019, Rubio-Beltrán et al 2018*).
  - Migraine attacks typically last between 4 and 72 hours in adults, and usually progress through 4 phases: the prodrome, the aura (occurs in approximately 25% of individuals), the headache, and the postdrome.
    - Factors that may trigger a migraine include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame, among others.
- Migraine is currently considered a neurovascular disorder that involves activation of the trigeminovascular system, followed by cranial vasodilation mediated by release of signaling proteins including calcitonin gene-related peptide (CGRP) *(Rubio-Beltrán et al 2018*).
- Prescription drugs for acute migraine treatment include triptans, dihydroergotamine (DHE), and non-steroidal anti-inflammatory drugs (NSAIDs) which can be used alone or in combination with a triptan. All 3 drug classes have restrictions regarding use in patients with cardiovascular disease (CVD) (*Reyvow U.S. Food and Drug Administration [FDA] Summary Review 2019*, *Smith 2019*).
  - First line treatment options include analgesics (eg, NSAIDs, acetaminophen [APAP]) or combination analgesics for mild to moderate attacks not associated with vomiting or nausea. For patients with moderate to severe attacks, oral migraine-specific agents such as triptans are first-line.
- New therapeutic classes for acute treatment of migraine attacks include CGRP antagonists and 5-hydroxytryptamine (5-HT)$_{1F}$ receptor agonists.
  - Reyvow (lasmiditan) was approved in October 2019; it is the first FDA-approved medication in a new class of 5-HT$_{1F}$ receptor agonists, also referred to as “ditans.”
- Lasmiditan binds with high affinity to the 5-HT$_{1F}$ receptor and presumably exerts its therapeutic effects in the treatment of migraine through agonist effects at the 5-HT$_{1F}$ receptor; however, the precise mechanism is unknown (*Reyvow Prescribing Information 2020*).
- Medispan class: Migraine Agents; Serotonin Agonists; Selective Serotonin Agonists (5-HT$_{1F}$)

INDICATION

- Lasmiditan is indicated for the acute treatment of migraine with or without aura in adults.
  - Limitations of use: Lasmiditan is not indicated for the preventive treatment of migraine.
- Information on the indication, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the product, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of lasmiditan in the acute treatment of migraine with or without aura was demonstrated in two Phase 3, double-blind (DB), randomized, placebo-controlled (PC) trials (SAMURAI, *Kuca et al 2018* and SPARTAN, *Goadsby et al 2019*). A total of 3177 adult patients received lasmiditan 50 mg, 100 mg, or 200 mg. Both studies included patients with cardiovascular (CV) risk factors, but only SPARTAN included patients with known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. The efficacy of lasmiditan was evaluated in terms of pain freedom (defined as a reduction of moderate or severe headache pain to no pain) and Most Bothersome Symptom (MBS) freedom (defined as the absence of the self-identified MBS [photophobia, phonophobia, or nausea]) at 2 hours compared to placebo (*Reyvow Prescribing Information 2020*).
  - In both studies, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo (see Table 1) (*Reyvow FDA Summary Review 2019*, *Reyvow Prescribing Information 2020*).

- The treatment effect size for pain freedom at 2 hours post-dose was approximately 7% to 18% greater than placebo across the 3 doses tested.
- The treatment effect size for MBS-freedom at 2 hours was approximately 8% to 16% greater than placebo across the 3 doses tested.

- Pain relief at 2 hours, defined as a reduction in migraine pain from moderate or severe to mild or none, was also evaluated (see Table 1).

Table 1. Results for key migraine efficacy endpoints

	SAMURAI			SPARTAN			
	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Pain free at 2 hours							
N	498	503	515	544	523	521	534
% responders	28.3	31.8	15.3	28.3	31.4	38.8	21.0
Difference from placebo (%)	13	16.5	--	7.3	10.4	17.8	--
p-value	< 0.001	< 0.001	--	0.006	< 0.001	< 0.001	--
MBS free at 2 hours							
N	464	467	480	502	491	478	509
% responders	41.2	40.7	29.6	40.8	44.0	48.7	33.2
Difference from placebo (%)	11.6	11.1	--	7.6	10.8	15.5	--
p-value	< 0.001	< 0.001	--	0.014	< 0.001	< 0.001	--
Pain relief at 2 hours*							
N	498	503	515	544	523	521	534
% responders	54.0	55.3	40.0	55.9	61.4	61.0	45.1
Difference from placebo (%)	14.0	15.3	--	10.8	16.3	15.9	--
*The analysis of pain relief was descriptive and as not controlled for Type I error							

- In both trials, the most common adverse events (AEs) were dizziness, fatigue, lethargy, nausea, paresthesia, and somnolence. No serious treatment-emergent adverse events (TEAEs) related to study drug were reported in SAMURAI, while 2 serious AEs considered to be treatment-related were reported in SPARTAN (100 mg, dystonic reaction; 200 mg, presyncope).
  - The rate of serious AEs with a potential CV etiology was low. The most commonly reported CV TEAEs in the controlled trials were palpitations/heart rate increased/tachycardia occurring in 0.4% of patients on lasmiditan and 0.1% on placebo.

- The open-label (OL) extension trial GLADIATOR (*Brandes et al 2019*) randomized patients from the SAMURAI and SPARTAN trials to receive lasmiditan 100 mg or 200 mg. The goal was to evaluate the safety and efficacy of long-term intermittent use of lasmiditan for the acute treatment of migraine for up to 1 year. Of the 2116 patients who were randomized, 1978 patients received ≥ 1 dose of lasmiditan (safety population) and treated 19,058 migraine attacks. At the time of the data cut-off for the interim analysis, 814 (41.2%) patients in the safety population had completed all 12 months of the study, and 141 (7.1%) patients were continuing treatment. The median duration of time in the study was 288 days.
  - A total of 962 patients (48.6%) reported ≥ 1 TEAE during the study. Frequently reported TEAEs were similar to those in the pivotal trials and included dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%). Dizziness was the most common AE leading to discontinuation.
  - No CV TEAEs potentially due to vasoconstriction were observed. No treatment-emergent serious AE was considered by the investigator to be related to lasmiditan. No deaths were reported during the study.
  - Overall, across all treated attacks at 2 hours post-dose, pain freedom was observed in 29.6% of attacks, MBS freedom in 39.0%, and pain relief in 56.3%, with significantly higher percentages observed in the 200 mg group than in the 100 mg group ($p < 0.001$ for all comparisons).
- Analyses evaluating the safety and efficacy of a second lasmiditan dose when taken for rescue or recurrence found some evidence of efficacy when taken for headache recurrence, but there was no clear benefit of a second dose for rescue treatment (*Loo et al 2019*). However, due to shortcomings with the analyses, the FDA did not consider the data

to be informative and did not consider efficacy of the second dose to be established. Thus, the lasmiditan label only recommends that a single dose of lasmiditan be taken in a 24-hour period (*Reyvow FDA Summary Review 2019).*

- An Institute for Clinical and Economic Review (ICER) network meta-analysis (*Atlas et al 2020*) of 33 randomized controlled trials (RCTs) was conducted to compare the safety and efficacy of lasmiditan and the oral CGRP antagonists, rimegepant and ubrogepant, for acute treatment of migraine to each other, placebo, and triptans.
  - Lasmiditan, rimegepant, and ubrogepant all had higher odds of achieving pain freedom and pain relief at 2 hours vs placebo. Compared to each other, none of these interventions showed statistically significant differences, although lasmiditan showed statistically nonsignificant higher odds of achieving pain freedom. All interventions showed lower odds of achieving pain freedom compared to eletriptan and sumatriptan, but statistical significance was not reached for lasmiditan vs sumatriptan. Similar trends were observed for pain relief at 2 hours.
  - Lasmiditan and the CGRP antagonists all had higher odds of achieving freedom from MBS at 2 hours post-dose compared to placebo. Compared to each other, none of the interventions showed a statistically significant difference. None of the triptan studies assessed this outcome.
  - The ICER ratings on the net comparative health benefit of lasmiditan vs comparators for various populations are as follows:
    - For adults who have failed non-prescription drugs and who have failed or are contraindicated to triptans, the evidence for lasmiditan compared to placebo was considered to be “B+”, meaning there’s a moderate certainty of a small or substantial health benefit, with a high certainty of at least a small net health benefit.
    - For patients who have failed non-prescription drugs and are eligible for triptans, lasmiditan was rated a “C-“ vs triptans, meaning that there is moderate certainty that the comparative net health benefit is either comparable or inferior. Results of the meta-analysis suggest that lasmiditan is less efficacious than triptans, although they do not exclude comparable efficacy compared to sumatriptan. However, there is a higher incidence of AEs with lasmiditan compared to triptans.
    - Results of the analysis suggest that lasmiditan may be slightly more efficacious than rimegepant and ubrogepant, but they do not exclude comparable efficacy. However, any possible greater efficacy is at best balanced by the higher incidence of adverse events and may be outweighed by them; thus, lasmiditan received a “C-“ compared to the oral CGRP antagonists.

CLINICAL GUIDELINES

- The American Headache Society (AHS) guidelines recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate migraine attacks. Migraine-specific agents such as triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to NSAIDs or caffeinated combinations (*AHS 2019*).
  - The guidelines state that emerging acute treatments for migraine headache such as the CGRP antagonists, ubrogepant and rimegepant, and the selective 5-HT_{1F} receptor agonist, lasmiditan, do not have vasoconstrictive effects; therefore, they may play a role in patients with CV contraindications to triptans. It is recommended that patients be eligible for these newer agents if they have contraindications to the use of triptans or have failed to respond to or tolerate ≥ 2 oral triptans.
- Similar to the AHS guidelines, a number of other guidelines recommend non-opioid analgesics for mild to moderate migraine, and migraine specific-agents (eg, triptans) for moderate to severe migraine (*Mayans and Walling 2018*, *Silberstein 2000*, *Steiner et al 2019*).

SAFETY SUMMARY

- Lasmiditan carries warnings and precautions for the following:
  - Driving impairment: Patients are advised not to drive or operate machinery for at least 8 hours after taking lasmiditan, even if they feel well enough to do so. Patients who cannot follow this advice should not take the drug. Patients may not be able to assess their own driving competence and degree of impairment caused by lasmiditan.
  - Central nervous system (CNS) depression: Lasmiditan causes CNS depression, including dizziness and sedation. It should be used with caution if taken in combination with alcohol or other CNS depressants.
  - Serotonin syndrome: Reactions consistent with serotonin syndrome have been reported in patients taking lasmiditan. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (eg, hyperreflexia, incoordination), and/or

gastrointestinal AEs (eg, nausea, vomiting, diarrhea). The drug should be discontinued if serotonin syndrome is suspected.
  - Medication overuse headache (MOH): Overuse of acute migraine drugs (eg, ergotamines, triptans, opioids, or a combination of these drugs for ≥ 10 days per month) may lead to exacerbation of headache. Detoxification of patients may be necessary.
- The most common AEs reported by patients in the clinical trials were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness.
  - Lasmiditan was associated with decreases in heart rate and small transient increases in blood pressure. Although the clinical trials enrolled many patients with CV risk factors, only a small percentage of patients (1%) had ischemic heart disease, thus limiting the assessment of lasmiditan's safety in these patients. According to the FDA, the data do not support the need for CV restrictions with the use of lasmiditan; however, they are too limited to definitively establish the CV safety of the drug (*Reyvow FDA Summary Review 2019*).
- Concomitant use of lasmiditan and P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrates should be avoided. Caution is advised when patients are taking lasmiditan in combination with alcohol or other CNS depressants, serotonergic drugs, and heart-rate lowering drugs.
- Lasmiditan is a Schedule V controlled substance (C-V).
  - In a human abuse potential study in recreational poly-drug users, subjects taking lasmiditan reported statistically significantly higher "drug liking" scores vs placebo and statistically significantly lower "drug liking" scores vs alprazolam (C-IV).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Reyvow (lasmiditan)	Tablets	Oral	The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. No more than one dose should be taken in 24 hours, and lasmiditan should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery	A second dose of lasmiditan has not been shown to be effective for the same migraine attack. The safety of treating an average of more than 4 migraine attacks in a 30-day period has not been established. Lasmiditan may be taken with or without food.

See the current prescribing information for full details

CONCLUSION

- Lasmiditan, the first FDA-approved medication in a new class of 5-HT_{1F} receptor agonists, is indicated for the acute treatment of migraine with or without aura in adults.
  - In 2 DB, PC, RCTs, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo.
  - Lasmiditan has not been compared to other acute migraine treatments such as triptans or oral CGRP antagonists in head-to-head trials.
  - Results of a network meta-analysis evaluating lasmiditan, triptans (sumatriptan and eletriptan), and oral CGRP antagonists (rimegepant, ubrogepant) suggest that lasmiditan is less efficacious than triptans but do not exclude comparable efficacy compared to sumatriptan; however, there is a higher incidence of AEs with lasmiditan compared to triptans. Results also suggest that lasmiditan may be slightly more efficacious than rimegepant and ubrogepant, but they do not exclude comparable efficacy; however, any possible greater efficacy of lasmiditan is at best balanced by the higher incidence of AEs and may be outweighed by them.
- Various clinical guidelines recommend non-opioid analgesics for mild to moderate migraine attacks and migraine specific-agents (eg, triptans) for moderate to severe attacks. According to guidelines from the AHS, newer acute

treatments for migraine such as lasmiditan may play a role in patients who have failed, have contraindications to, or who cannot tolerate triptans.

- Lasmiditan has warnings for CNS depression, serotonin syndrome, MOH, and driving impairment. Patients should not engage in potentially hazardous activities such as driving for at least 8 hours after each dose of the drug. Common AEs reported in the clinical trials included dizziness, fatigue, paresthesia, and sedation. Lasmiditan is a Schedule V controlled substance.
- Lasmiditan, which has high affinity and selectivity for 5-HT_{1F} receptors and lacks the vasoconstrictor activity associated with triptans and ergotamines, may offer an alternative treatment option to some patients. Factors to consider include the abuse potential, the risk of driving impairment for at least 8 hours after each dose, and the restriction to a single dose per 24 hours.

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Publication Date: February 20, 2020

Therapeutic Class Overview
Glucagon agents

INTRODUCTION

- Hypoglycemia in patients with diabetes can be defined as episodes of abnormally low plasma glucose concentration that expose the individual to potential harm. An alert value for hypoglycemia is defined as blood glucose < 70 mg/dL. Clinically important hypoglycemia is defined as blood glucose < 54 mg/dL, but the physiologic response to low blood glucose can be variable (*American Diabetes Association [ADA] 2020*, *Cryer 2019*).
- Hypoglycemia frequently affects patients with type 1 diabetes (T1DM), in whom the risk of severe hypoglycemia (episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) increases with intensive therapy. Patients with T1DM report an average of up to 3 episodes of severe hypoglycemia per year. Severe hypoglycemia affects patients with type 2 diabetes (T2DM) less commonly; those who are treated with a sulfonylurea, a meglitinide, or insulin are generally at higher risk (*Cryer 2019, Seaquist et al 2013*).
  - In 2014, the Centers for Disease Control and Prevention (CDC) reported 245,000 episodes of hypoglycemia resulted in emergency department visits (incidence ratio of 11.2 per 1000 patients with diabetes).
- Hypoglycemia causes symptoms such as tremor, anxiety, tachycardia, sweating, hunger, dizziness, weakness, drowsiness, confusion, and possibly, seizure and coma at lower plasma glucose concentrations. Although extreme, prolonged hypoglycemia can cause brain death, the majority of episodes are reversed after the glucose level is raised. Rare fatal episodes are generally thought to be due to other mechanisms such as ventricular arrhythmia (*Cryer 2019, Seaquist et al 2013*).
- The goal of treatment of hypoglycemia is to normalize the plasma glucose concentration by administering carbohydrates (dietary or parenteral according to the level of consciousness), or in cases of severe hypoglycemia, by administering glucagon (*Cryer 2019*).
  - Patients with symptomatic hypoglycemia should ingest glucose in the form of tablets, juice, milk, other snacks, or a meal.
  - Patients with severe hypoglycemia can usually be treated quickly by giving intravenous (IV) dextrose.
  - In a person with impaired consciousness and no established IV access, administration of glucagon (subcutaneously [SC], intramuscularly [IM], or intranasally [IN]) by a second party will usually lead to recovery of consciousness within approximately 15 minutes, although it may be followed by marked nausea or even vomiting.
    - The response to IV glucose and glucagon is transient; therefore, treatment of hypoglycemia often needs to be followed by a continuous infusion of glucose or by intake of food if the patient is able to eat.
- Injectable glucagon has been approved for use in the U.S. for several decades (*Baqsimi FDA News Release 2019*). A few injectable products (ie, GlucaGen and Glucagon Emergency Kits [GEKs] by Lilly [GEK-L] and Fresenius Kabi [GEK-F]) have been approved for SC or IM administration that require the caregiver to reconstitute the glucagon powder with the diluent prior to injection. A recently approved product, Gvoke (glucagon injection), is available as an auto-injector or prefilled syringe for SC administration and does not require reconstitution. Baqsimi (glucagon nasal powder) is the first IN administered glucagon to be approved; it can be delivered by placing the tip of the device in one nostril and depressing a small plunger that discharges the powder into the nostril without need for inhalation from the patient (*Cryer 2019*).
- Medispan Class: Glucagon

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Baqsimi (glucagon)	-
GlucaGen HypoKit (glucagon)	-
Glucagon Emergency Kit (glucagon)*	-
Gvoke (glucagon)†	-

* Products from Lilly and Fresenius Kabi

†The prefilled syringe formulation is currently available; the auto-injector formulation will be launched at a later date.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Baqsimi (glucagon)	GEK-F/GEK-L	GlucaGen HypoKit (glucagon)	Gvoke (glucagon)
Severe hypoglycemia in patients with diabetes	✔ (≥ 4 years of age)	✔ (all ages)	✔ (all ages)	✔ (≥ 2 years of age)

Note: GlucaGen and the GEKs are indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. This indication is not addressed in this review

(*Prescribing information: Baqsimi 2019, GlucaGen HypoKit 2018, GEK-F 2019, GEK-L 2019, Gvoke 2019*)

- 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

- Two randomized, open-label (OL), 2-period, crossover (XO), noninferiority studies compared the efficacy of a single 3 mg dose of Baqsimi to a single 1 mg dose of IM glucagon injection (GlucaGen) for treatment of insulin-induced hypoglycemia in adults with diabetes. One of the studies included 70 adult patients with T1DM, while the other study included 83 adult patients with T1DM or T2DM. The primary outcome measure was the proportion of patients achieving treatment success, defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon (*Baqsimi prescribing information 2019*, *Data on file [Eli Lilly and Company] 2019*, *Rickels et al 2016*).
  - In both studies, Baqsimi demonstrated noninferiority to IM glucagon in reversing insulin-induced hypoglycemia (98.8 to 100% for Baqsimi vs 100% for IM glucagon). In one study, the mean time to treatment success was 11.6 minutes for the Baqsimi group vs 9.9 minutes for the IM glucagon group while in the other study, the mean time to treatment success was 15.9 minutes for Baqsimi group vs 12.1 minutes for the IM glucagon group.
- In a pediatric study of 48 patients aged ≥ 4 years with T1DM, similar results for Baqsimi 3 mg vs weight-based (0.5 mg or 1 mg) IM glucagon were observed. The primary endpoint was the percentage of patients with a glucose increase of ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon administration (*Baqsimi prescribing information 2019*, *Data on file [Eli Lilly and Company] 2019, Sherr et al 2016*).
  - Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥ 20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase ≥ 20 mg/dL ranged from 10.8 to 14.2 minutes for Baqsimi and 10.8 to 12.5 minutes for IM glucagon.
- In a comparative usability study (N = 31) evaluating the use of Baqsimi and IM glucagon by individuals in a simulated emergency event, participants were significantly more likely to successfully administer a full dose with Baqsimi (94% of attempts) than with injectable glucagon (13% of attempts) (*Yale et al 2017*).
- In 2 OL, real-world usability studies involving caregivers of adults with T1DM (N = 69) and caregivers of children with T1DM (N = 15), Baqsimi was successful in treating episodes of moderate and severe hypoglycemia in 95.7% of adults and 100% of children. Of note, the trials had serious quality limitations and additional data are needed to validate the results (*Deeb et al 2018, Seaquist et al 2018)*.
- Two randomized, 2-way, XO, noninferiority studies (N = 181) compared the efficacy of Gvoke 1 mg SC to GEK-L 1 mg SC for treatment of insulin-induced hypoglycemia in adults with T1DM. The primary efficacy endpoint was the proportion of patients achieving treatment success, defined as either an increase in plasma glucose from a mean value at the time of glucagon administration to an absolute value ≥ 70 mg/dL or a relative increase of ≥ 20 mg/dL at 30 minutes after receiving study glucagon (*Gvoke prescribing information 2019, Christensen et al 2019 [poster]*).
  - In a pooled analysis of both studies, the proportion of patients who achieved treatment success was 99% in the Gvoke group and 100% in the GEK-L group, and the comparison between groups met the prespecified non-inferiority

margin. The mean time to treatment success was 13.8 minutes in the Gvoke group and 10 minutes in the GEK-L group.

- An OL study of 31 patients aged ≥ 2 years with T1DM evaluated 2 doses of Gvoke for treatment of insulin-induced hypoglycemia. Patients aged 2 to < 6 years and 6 to < 12 years received Gvoke 0.5 mg SC while patients aged ≥ 12 years received either Gvoke 0.5 mg or 1 mg SC (*Gvoke prescribing information 2019*, *Buckingham et al 2018 [poster]*).
  - All evaluable patients achieved a target dose of at least 25 mg/dL.
- Two human factors studies evaluated whether the Gvoke prefilled syringe could be effectively administered (*Newswanger et al 2019*). In a formative study (N = 11), there was a 100% success rate while in the validation study (N = 75), 99% of patients successfully administered the full dose. Similarly, 2 human factors studies evaluated whether the Gvoke auto-injector could be effectively administered (*Valentine et al 2019*). In the simulated-use comparative usability study (N = 16), 88% of participants were able to successfully administer a rescue injection using Gvoke compared with 31% with the GEKs. In the validation study (N = 75), 98.7% of patients successfully administered the rescue injection using the Gvoke auto-injector.

CLINICAL GUIDELINES

- ADA guidelines recommend that all patients at increased risk of hypoglycemia with blood glucose < 54 mg/dL be prescribed glucagon so that it would be available if needed. Caregivers, school personnel, or family members should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals, particularly with the availability of IN and stable soluble glucagon available in auto-injector pens (*ADA 2020*).
- The American Association of Clinical Endocrinologists/American College of Endocrinology guidelines recommend that SC or IM glucagon or IV glucose be given by a trained family member or medical personnel to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*Handelsman et al 2015*).

SAFETY SUMMARY

- All glucagon products are contraindicated in patients with known hypersensitivity to any of the constituents of the formulation, and they all carry a warning for lack of efficacy in patients with decreased hepatic glycogen. They are also contraindicated or have a warning for patients with pheochromocytoma and insulinoma. The injectable products also have a warning for necrolytic migratory erythema due to postmarketing reports following continuous glucagon infusion.
- The most common adverse events (AEs) with Baqsimi were nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, and itchy nose, throat and eyes. Common AEs with the injectable products included nausea, vomiting, and injection site reactions.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Baqsimi (glucagon)	Nasal powder	IN	One actuation of the IN device into 1 nostril; if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance	The dose should be administered by inserting the tip into 1 nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
GEK-F (glucagon)	Injection (kit requiring reconstitution)	IM, IV, SC	One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new kit may be administered	The product should be reconstituted according to instructions before administration.
GEK-L (glucagon)				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
GlucaGen HypoKit (glucagon)			while waiting for emergency assistance	Common SC/IM injection sites are the upper arms, thighs or buttocks.
Gvoke (glucagon)	Injection (auto-injector, prefilled syringe)	SC	One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance	The injection may be given in the lower abdomen, outer thigh, or outer upper arm.

See the current prescribing information for full details

CONCLUSION

- Severe hypoglycemia is generally defined as a hypoglycemic event that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action. Immediate treatment is necessary to increase blood sugar and prevent serious complications, such as loss of consciousness, seizure, coma, or death.
- Treatment guidelines recommend that glucagon be given by a trained caregiver to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*ADA 2020*, *Handelsman et al 2015).*
- Injectable glucagon in the form of kits containing a prefilled syringe of diluent and a vial of glucagon powder for reconstitution has been approved for use in the U.S. for many years. Two new glucagon formulations have been approved that provide additional options for the treatment of severe hypoglycemia in patients with diabetes that may simplify the process of glucagon administration. Gvoke is available in the form of an auto-injector or prefilled syringe that does not require reconstitution, while Baqsimi is the first IN formulation of glucagon.

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Publication Date: January 13, 2020