South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

December 10, 2021

South Dakota
Department of
Social Services

Table of Contents

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

December 10, 2021
1:00 – 3:00 PM

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_ZmJlMmIzN2EtMWZmZS00ZWI1LThiNDItOWFmNmM1N2E5OTcx%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
425899727@t.plcm.vc
Video Conference ID: 118 999 524 3

Join by phone
+1 952-222-7450
Phone Conference ID: 352 995 833#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Pancreatic enzyme utilization**
- **Review of PA forms and criteria**
- **Hepatitis C update**
- **Opioid update**

New business
- **Antineoplastic oral drugs**
- **Anticonvulsants**
- **Gastrointestinal drugs**
- **Insulin quantity**
- **JAK inhibitor criteria**
- **Trudhesa**

Public input accepted after individual topic discussion
Next meeting date March 4, 2022 & adjournment

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

Friday, September 24, 2021
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Heather Preuss, MD	
Dana Darger, RPh, Chair	X	Matthew Stanley, DO	
Mikel Holland, MD	X	Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	X	Mike Jockheck, DSS Staff	X
Kelley Oehlke, PharmD	X	Matthew Ballard	
Lenny Petrik, PharmD	X	Bill Snyder, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:05 pm. The minutes of the June meeting were presented. Jockheck noted to make a change under Administrative Business to reflect minutes from March meeting instead of December. Ladwig made a motion to approve. Baack seconded the motion. The motion was unanimously approved via roll call vote.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from April 1, 2021 to June 30, 2021. A total of 1,455 PAs were reviewed of which 141 requests (9.7%) were received via telephone and 847 requests (58.2%) were received via fax, and 467 (32.1%) were reviewed via electronically. There was a 15% decrease of PAs received from the previous quarter. Antidiabetics made its debut on the Top Therapeutic Classes reviewed for PA.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from April 1, 2021 to June 30, 2021. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, skin and mucous membrane agents, cystic fibrosis correctors, and anticonvulsants. These top 15 therapeutic classes make up 25.59 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 8.89 % of total claims. Dupixent was noted twice on the top 50 drugs by paid amount. Dupxient 300 mg strength is linked to skin and mucous membrane agents and Dupxient 200 mg strength is linked to interleukin antagonist class. With the strengths combined, Dupixent rose to number 10 on the list. Baack commented combining the utilization of these strengths together to provide the actual information on cost per prescription and number of people on it. Darger brought to attention Creon utilization.

Old Business

90-Day Fill

Jockheck provided an update on the 90-day fill which was implemented on 10/1/2020. A 90-day supply of generic maintenance medication is allowed after member establishes three monthly fills. Utilization had continued to creep up each month and eventual leveling off. Ladwig commented as long as there is no brand utilization abuse, there is not a need for continual monitoring at each meeting.

Atypical antipsychotic utilization in children
Committee continued the conversation on the proposed PA criteria for prescribers wanting to add a 3 or more atypical antipsychotics. The areas of the criteria that were of interest for in-depth were the age at which the specialist is involved in care and criteria allowing more than 3 atypical antipsychotics. Committee reviewed members 6 to 12 years old taking more than 2 atypical antipsychotics. After review, committee decided to table the discussion for Dr. Stanley's input.

ADHD utilization
Committee reviewed ADHD comparison of PMPM and PUPM of other state Medicaid programs and State B's PA criteria. Ladwig commented South Dakota's PMPM was in the ballpark of other states' PMPM. Committee also reviewed utilization of Vyvanse chewable tablets.

Gabapentin high-dose utilization
Committee reviewed eleven members taking over 4,800 mg per day of gabapentin. Baack was concerned about the children taking over 4,800 mg per day. Van Gilder surmised these were probably children on gabapentin 250 mg liquid. In addition, one member identified during 1Q2021 utilization had switched to pregabalin during 2Q2021. This left four members taking over 4,800 mg per day of gabapentin. Committee discussed placing quantity limits of greater than 3.6 g per day.

Darger inquired if there was any public comment. There were none.

Opioid update
The committee reviewed 2Q2021 opioid outcomes compared to previous quarters from the opioid initiatives. There was an increase in opioid utilization and opioid utilizers during second quarter which corresponds to the increase in total eligible members.

Review PA forms and criteria
The committee reviewed utilization of drugs on PA that are available as generics now. After review, the committee decided on the following:

- Nuvigil and Provigil – keep PA on all brands and generics
- Onfi – remove PA on generics only but keep PA on brands
- Oracea – keep step therapy on all brands and generics
- Proton Pump Inhibitors (Nexium granules and Protonix PAK) – keep PA on all brands and generics
- Qualaquin – keep PA on all brands and generics
- Soma 250 – keep step therapy on all brands and generics
- Ultram ER – keep step therapy on all brands and generics

Ladwig made the motion on the Onfi PA to retain the PA on brands but remove generics from PA. Van Gilder seconded the motion. Darger inquired if there was any public comment on prior authorizations. There were none. The motion was unanimously approved via roll call vote.

Juxtapid
The committee reviewed the proposed Juxtapid PA criteria. Darger inquired if there was any public comment. There were none. Van Gilder motioned to approve the PA criteria as presented. Baack seconded the PA criteria. The motion was unanimously approved via roll call vote.

Imcivree
The committee reviewed the proposed Imcivree PA criteria. Cody Gerber from Rhythm Pharmaceuticals provided public comment on Imcivree. Baack requested changing the term "weight loss" to "weight management". Baack made a motion to approve the PA criteria as presented with the "weight management" term change. Ladwig seconded the motion. The motion was unanimously approved via roll call vote.

New Business

Dermatological PA approval review
Committee reviewed the PA approval rate for topical acne, rosacea, headlice and topical onychomycosis. Based on current trend, no changes were needed.

Antiviral PA approval review
Committee reviewed the PA approval rate for antiviral drugs. Petrik made a motion to review Hepatitis C PA criteria at the next meeting. Baack seconded the motion. The motion was unanimously approved via roll call vote. Porscha Showers from Gilead Sciences was available for questions. Holly Budlong from AbbVie provided public comment. Jennifer Davies from Gilead Sciences provided public comment.

Cholbam utilization
Committee reviewed the utilization of Cholbam. Baack reviewed the utilization and since the diagnosis supported it, no changes were needed.

Pancreatic enzyme utilization
Committee reviewed the utilization for pancreatic enzymes. Stacy Peters, clinical pharmacist, from Sanford's Children's Specialty Clinic provided public comment. Holly Budlong from AbbVie provided public comment. Committee requested to review this class again at the next meeting and for utilization to include average quantity information.

Hemophilia factor product utilization
Committee reviewed the utilization for hemophilia factor products. Brandon Yip from Sanofi provided public comment. Brianna Murphy, a pediatric hematologist, from Sanford's Children's Specialty Clinic provided public comment. Sammy Samuelson from Genentech provided public comment.

Cystic fibrosis mediation compliance
Committee reviewed the cystic fibrosis medication compliance. Darger inquired if there was any public comment. There were none.

Brexafemme
Brexafemme clinical information was presented for review. Darger inquired if there was any public comment. There were none. Baack made a motion to add step therapy or PA to Brexafemme. Ladwig seconded the motion. The motion was unanimously approved via roll call vote.

Adjournment

The next meeting is scheduled on December 10, 2021. The March meeting is tentatively scheduled on March 4, 2022. The Committee made a motion to adjourn the meeting and everyone seconded the motion. The motion passed unanimously, and the meeting adjourned at 3:03 pm.

PA Report
7/1/2021 – 9/30/2021

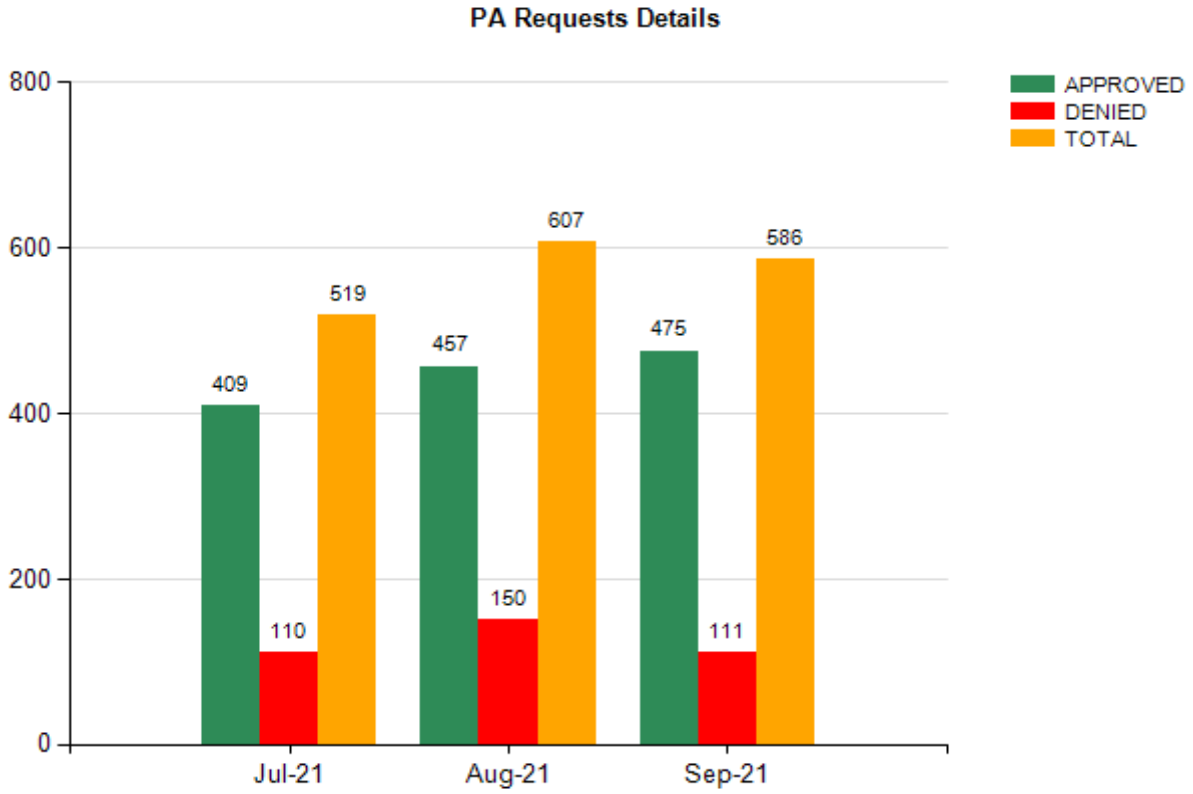
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 hrs Urgent - 24 hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	1,664	1,664	0	100.00%	0.00%
Urgent	48	48	0	100.00%	0.00%
Grand Total	**1,712**	**1,712**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
Total	**1,712**	**141**	**8.2%**	**914**	**53.4%**	**657**	**38.4%**

PA Initial Requests Summary

Month	Approved	Denied	Total
July-21	409	110	519
August-21	457	150	607
Septebmer-21	475	111	586
3Q21	1,341	371	1,712
Percent of Total	78.33%	21.67%	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTIC/ANTIMANIC	269	24	293	91.81%	17.11%	, INVEGA SUSTENNA
27 - ANTIDIABETICS*	165	18	183	90.16%	10.69%	, OZEMPIC
90 - DERMATOLOGICALS*	97	78	175	55.43%	10.22%	IVERMECTIN, CLINDAMYCIN/BENZ
65 - ANALGESICS - OPIOID*	106	59	165	64.24%	9.64%	TRAMADOL, HYDROCODONE
58 - ANTIDEPRESSANTS*	131	21	152	86.18%	8.88%	, SERTRALINE
OTHERS -	573	171	744	77.02%	43.46%	
3Q21	**1,341**	**371**	**1,712**	**78.33%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	269	24	293	91.81%
27 - ANTIDIABETICS*	165	18	183	90.16%
58 - ANTIDEPRESSANTS*	131	21	152	86.18%
65 - ANALGESICS - OPIOID*	106	59	165	64.24%
90 - DERMATOLOGICALS*	97	78	175	55.43%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	83	14	97	85.57%
52 - GASTROINTESTINAL AGENTS - MISC.*	74	15	89	83.15%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	58	14	72	80.56%
67 - MIGRAINE PRODUCTS*	57	29	86	66.28%
72 - ANTICONVULSANTS*	57	6	63	90.48%
66 - ANALGESICS - ANTI-INFLAMMATORY*	47	6	53	88.68%
41 - ANTIHISTAMINES*	36	4	40	90.00%
16 - ANTI-INFECTIVE AGENTS - MISC.*	30	6	36	83.33%
54 - URINARY ANTISPASMODICS*	20	6	26	76.92%
75 - MUSCULOSKELETAL THERAPY AGENTS*	17	5	22	77.27%
50 - ANTIEMETICS*	14	3	17	82.35%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	9	0	9	100.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	9	4	13	69.23%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	9	3	12	75.00%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	9	5	14	64.29%
33 - BETA BLOCKERS*	8	0	8	100.00%
39 - ANTIHYPERLIPIDEMICS*	6	6	12	50.00%
36 - ANTIHYPERTENSIVES*	5	3	8	62.50%
83 - ANTICOAGULANTS*	5	2	7	71.43%
34 - CALCIUM CHANNEL BLOCKERS*	3	3	6	50.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	3	3	6	50.00%
12 - ANTIVIRALS*	2	18	20	10.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	2	0	2	100.00%
02 - CEPHALOSPORINS*	1	0	1	100.00%
03 - MACROLIDES*	1	0	1	100.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	0	1	100.00%
32 - ANTIANGINAL AGENTS*	1	0	1	100.00%
37 - DIURETICS*	1	0	1	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	1	0	1	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	4	5	20.00%
45 - RESPIRATORY AGENTS - MISC.*	1	1	2	50.00%
74 - NEUROMUSCULAR AGENTS*	1	3	4	25.00%
82 - HEMATOPOIETIC AGENTS*	1	0	1	100.00%
25 - CONTRACEPTIVES*	0	2	2	0.00%
43 - COUGH/COLD/ALLERGY*	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	0	2	2	0.00%
86 - OPHTHALMIC AGENTS*	0	3	3	0.00%
3Q21	**1,341**	**371**	**1,712**	
Percent of Total	**78.33%**	**21.67%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jul-21	13	68.42%	6	31.58%	19
Aug-21	21	84.00%	4	16.00%	25
Sep-21	12	66.67%	6	33.33%	18
3Q21	**46**	**74.19%**	**16**	**25.81%**	**62**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
MAVYRET	0	7	7	0.00%
AMITIZA	3	0	3	100.00%
TRAMADOL HCL	3	0	3	100.00%
AIMOVIG	1	1	2	50.00%
DEXILANT	2	0	2	100.00%
EPCLUSA	1	1	2	50.00%
INVEGA SUSTENNA	2	0	2	100.00%
MALATHION	2	0	2	100.00%
MOVANTIK	2	0	2	100.00%
NORDITROPIN FLEXPRO	2	0	2	100.00%
OTEZLA	1	1	2	50.00%
STELARA	2	0	2	100.00%
XELJANZ	2	0	2	100.00%
ACETAMINOPHEN/CODEINE	1	0	1	100.00%
ADAPALENE	0	1	1	0.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
BANZEL	1	0	1	100.00%
CEPHALEXIN	1	0	1	100.00%
CLINDAMYCIN/BENZOYL PEROXIDE	0	1	1	0.00%
EMGALITY	1	0	1	100.00%
EPIDIOLEX	1	0	1	100.00%
EPIDUO FORTE	1	0	1	100.00%
HEMLIBRA	1	0	1	100.00%
HUMIRA PEN	1	0	1	100.00%
HYDROCODONE/ACETAMINOPHEN	1	0	1	100.00%
HYSINGLA ER	1	0	1	100.00%
LEDIPASVIR/SOFOSBUVIR	0	1	1	0.00%
LINZESS	1	0	1	100.00%
LUBIPROSTONE	0	1	1	0.00%
MEDROXYPROGESTERONE ACETATE	0	1	1	0.00%
METHADONE HCL	1	0	1	100.00%
MODAFINIL	1	0	1	100.00%
MORPHINE SULFATE	1	0	1	100.00%
MYRBETRIQ	1	0	1	100.00%
NUCYNTA ER	1	0	1	100.00%
NURTEC	1	0	1	100.00%
OLANZAPINE ODT	1	0	1	100.00%
OZEMPIC	0	1	1	0.00%
PULMOZYME	1	0	1	100.00%
SOFOSBUVIR/VELPATASVIR	1	0	1	100.00%
ZIPRASIDONE HCL	1	0	1	100.00%
ZOLMITRIPTAN ODT	1	0	1	100.00%
3Q21	**46**	**16**	**62**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 7/1/2021 – 9/30/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	14,142	$180,691.99	$12.78	6.52%
2	ANTICONVULSANTS, MISCELLANEOUS	11,642	$1,117,903.77	$96.02	5.37%
3	ATYPICAL ANTIPSYCHOTICS	8,883	$2,639,144.62	$297.10	4.10%
4	SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,828	$558,850.73	$63.30	4.07%
5	SECOND GENERATION ANTIHISTAMINES	8,104	$92,336.64	$11.39	3.74%
6	AMINOPENICILLIN ANTIBIOTICS	6,678	$100,899.07	$15.11	3.08%
7	ADRENALS	6,598	$694,702.81	$105.29	3.04%
8	RESPIRATORY AND CNS STIMULANTS	6,547	$495,600.01	$75.70	3.02%
9	AMPHETAMINES	6,527	$1,101,716.78	$168.79	3.01%
10	PROTON-PUMP INHIBITORS	6,240	$192,931.31	$30.92	2.88%
11	OPIATE AGONISTS	5,739	$173,342.81	$30.20	2.65%
12	ANXIOLYTICS, SEDATIVES, & HYPNOTICS, MISC	4,525	$152,142.22	$33.62	2.09%
13	CONTRACEPTIVES	4,224	$129,629.25	$30.69	1.95%
14	THYROID AGENTS	3,659	$72,863.19	$19.91	1.69%
15	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,629	$202,240.71	$55.73	1.67%
Total		**101,491**	**$7,912,259.55**	**$77.96**	**48.60%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 7/1/2021 – 9/30/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	ATYPICAL ANTIPSYCHOTICS	8,883	$2,639,144.62	$297.10	4.10%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	295	$1,735,698.69	$5,883.72	0.14%
3	CYSTIC FIBROSIS (CFTR) CORRECTORS	67	$1,430,796.39	$21,355.17	0.03%
4	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	574	$1,372,162.10	$2,390.53	0.26%
5	ANTICONVULSANTS, MISCELLANEOUS	11,642	$1,117,903.77	$96.02	5.37%
6	AMPHETAMINES	6,527	$1,101,716.78	$168.79	3.01%
7	HEMOSTATICS	46	$1,025,516.73	$22,293.84	0.02%
8	ANTINEOPLASTIC AGENTS	302	$795,951.03	$2,635.60	0.14%
9	ADRENALS	6,598	$694,702.81	$105.29	3.04%
10	LONG-ACTING INSULINS	1,327	$660,458.83	$497.71	0.61%
11	INCRETIN MIMETICS	814	$654,228.64	$803.72	0.38%
12	SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,828	$558,850.73	$63.30	4.07%
13	RAPID-ACTING INSULINS	1,313	$553,746.21	$421.74	0.61%
14	RESPIRATORY AND CNS STIMULANTS	6,547	$495,600.01	$75.70	3.02%
15	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	156	$452,349.55	$2,899.68	0.07%
Total		**51,348**	**$14,594,229.44**	**$284.22**	**24.59%**

Total Rx Claims from 7/1/2021 – 9/30/2021	**216,877**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 7/1/2021 – 9/30/2021						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	5,025	$67,859.16	$13.50	2.32%
2	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	4,675	$197,340.74	$42.21	2.16%
3	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,647	$253,544.37	$54.56	2.14%
4	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE	4,593	$48,968.02	$10.66	2.12%
5	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,674	$43,541.10	$11.85	1.69%
6	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,483	$48,243.15	$13.85	1.61%
7	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE	3,395	$42,326.36	$12.47	1.57%
8	ANTICONVULSANTS, MISCELLANEOUS	GABAPENTIN	3,276	$56,990.63	$17.40	1.51%
9	AMPHETAMINES	VYVANSE	3,253	$986,895.91	$303.38	1.50%
10	SEROTONIN MODULATORS	TRAZODONE	3,214	$33,301.24	$10.36	1.48%
11	AMPHETAMINES	AMPHETAMINE/DEXTROA	3,111	$91,441.99	$29.39	1.43%
12	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	3,101	$39,954.18	$12.88	1.43%
13	THYROID AGENTS	LEVOTHYROXINE SODIUM	2,937	$49,942.62	$17.00	1.35%
14	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HCL	2,493	$29,478.93	$11.82	1.15%
15	CENTRAL ALPHA-AGONISTS	CLONIDINE	2,319	$22,740.54	$9.81	1.07%
16	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION	2,277	$44,907.70	$19.72	1.05%
17	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	2,238	$46,777.07	$20.90	1.03%
18	ANGIOTENSIN-CONVERTING ENZYME INHIBIT	LISINOPRIL	2,171	$20,335.81	$9.37	1.00%
19	VACCINES	PFIZER-BIONTECH COVID-19	2,079	$82,116.90	$39.50	0.96%
20	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,052	$33,470.72	$16.31	0.95%
21	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	2,021	$23,983.88	$11.87	0.93%
22	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	2,006	$24,412.59	$12.17	0.92%
23	SECOND GENERATION ANTIHISTAMINES	LORATADINE	1,964	$21,431.56	$10.91	0.91%
24	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	1,856	$30,798.43	$16.59	0.86%
25	ADRENALS	PREDNISONE	1,852	$18,416.33	$9.94	0.85%
26	1ST GENERATION CEPHALOSPORIN ANTIBIOTIC	CEPHALEXIN	1,835	$29,939.98	$16.32	0.85%
27	ANTICONVULSANTS, MISCELLANEOUS	LAMOTRIGINE	1,819	$26,403.80	$14.52	0.84%
28	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,780	$22,606.18	$12.70	0.82%
29	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONAT	1,744	$26,095.74	$14.96	0.80%
30	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANA	1,642	$32,183.03	$19.60	0.76%
31	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,613	$19,081.39	$11.83	0.74%
32	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,590	$20,786.95	$13.07	0.73%
33	BIGUANIDES	METFORMIN	1,571	$14,732.41	$9.38	0.72%
34	OPIATE AGONISTS	HYDROCODONE	1,562	$24,285.58	$15.55	0.72%
35	COMPOUNDS	-	1,544	$97,894.23	$63.40	0.71%
36	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,518	$16,755.74	$11.04	0.70%
37	SEL. SEROTONIN, NOREPI REUPTAKE INHIBITOR	DULOXETINE	1,481	$23,227.95	$15.68	0.68%
38	5-HT3 RECEPTOR ANTAGONISTS	ONDANSETRON ODT	1,432	$20,799.25	$14.52	0.66%
39	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRAN)	TRIAMCINOLONE ACETONID	1,403	$20,587.81	$14.67	0.65%
40	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE	1,372	$24,429.31	$17.81	0.63%
41	3RD GENERATION CEPHALOSPORIN ANTIBIOTIC	CEFDINIR	1,368	$29,126.78	$21.29	0.63%
42	ANTICONVULSANTS, MISCELLANEOUS	LEVETIRACETAM	1,319	$29,509.72	$22.37	0.61%
43	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPRINE	1,235	$13,025.16	$10.55	0.57%
44	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE ER	1,220	$21,949.75	$17.99	0.56%
45	DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,212	$12,065.56	$9.96	0.56%
46	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,211	$16,981.91	$14.02	0.56%
47	ANXIOLYTICS, SEDATIVES, & HYPNOTICS, MISC	HYDROXYZINE	1,205	$14,417.11	$11.96	0.56%
48	ANTICONVULSANTS, MISCELLANEOUS	TOPIRAMATE	1,185	$16,946.30	$14.30	0.55%
49	ANTIBACTERIALS (SKIN, MUCOUS MEMBRANE)	MUPIROCIN	1,171	$20,797.73	$17.76	0.54%
50	OPIATE AGONISTS	TRAMADOL HCL	1,164	$12,305.64	$10.57	0.54%
	Total Top 50 Drugs		**109,908**	**$2,966,154.94**	**$26.99**	**50.68%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 7/1/2021 – 9/30/2021						
	AHFS Description	Drug Label Name	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	44	$1,051,874.12	$23,906.23	0.02%
2	AMPHETAMINES	VYVANSE	3,253	$986,895.91	$303.38	1.50%
3	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN	126	$981,774.86	$7,791.86	0.06%
4	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	318	$752,813.29	$2,367.34	0.15%
5	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	STELARA	28	$528,492.95	$18,874.75	0.01%
6	ATYPICAL ANTIPSYCHOTICS	LATUDA	386	$482,937.83	$1,251.13	0.18%
7	ATYPICAL ANTIPSYCHOTICS	ARISTADA	163	$416,233.55	$2,553.58	0.08%
8	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	23	$378,922.27	$16,474.88	0.01%
9	HEMOSTATICS	ADVATE	7	$373,784.09	$53,397.73	0.00%
10	SKIN/MUCUS MEMBRN & INTERLEUKIN ANTAG	DUPIXENT	105	$322,658.83	$3,072.94	0.05%
11	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	263	$304,649.70	$1,158.36	0.12%
12	INCRETIN MIMETICS	OZEMPIC	357	$284,183.80	$796.03	0.16%
13	MUCOLYTIC AGENTS	PULMOZYME	62	$271,326.20	$4,376.23	0.03%
14	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,647	$253,544.37	$54.56	2.14%
15	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	75	$238,070.96	$3,174.28	0.03%
16	VESICULAR MONOAMINE TRANSPORT2 INHIBIT	INGREZZA	40	$230,983.13	$5,774.58	0.02%
17	ADRENALS	FLOVENT HFA	957	$228,922.56	$239.21	0.44%
18	ANTICONVULSANTS, MISCELLANEOUS	VIMPAT	249	$217,078.44	$871.80	0.11%
19	LONG-ACTING INSULINS	LANTUS SOLOSTAR	494	$215,183.45	$435.59	0.23%
20	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	50	$214,987.66	$4,299.75	0.02%
21	ATYPICAL ANTIPSYCHOTICS	REXULTI	194	$212,244.01	$1,094.04	0.09%
22	INCRETIN MIMETICS	TRULICITY	260	$209,780.38	$806.85	0.12%
23	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	4,675	$197,340.74	$42.21	2.16%
24	ANTICONVULSANTS, MISCELLANEOUS	EPIDIOLEX	79	$188,861.07	$2,390.65	0.04%
25	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	372	$187,180.82	$503.17	0.17%
26	HEMOSTATICS	HEMLIBRA	3	$184,880.43	$61,626.81	0.00%
27	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	275	$172,956.21	$628.93	0.13%
28	VASODILATING AGENTS (RESPIRATORY TRACT)	UPTRAVI	11	$169,530.47	$15,411.86	0.01%
29	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	COSENTYX SENSORDY PEN	31	$166,748.16	$5,378.97	0.01%
30	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SURECLICK	31	$157,178.18	$5,070.26	0.01%
31	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	TREMFYA	13	$155,299.66	$11,946.13	0.01%
32	GI DRUGS, MISCELLANEOUS	CHOLBAM	7	$149,323.85	$21,331.98	0.00%
33	HEMOSTATICS	RECOMBINATE	3	$145,659.75	$48,553.25	0.00%
34	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA	20	$139,779.02	$6,988.95	0.01%
35	RAPID-ACTING INSULINS	INSULIN ASPART FLEXPEN	366	$138,617.01	$378.74	0.17%
36	DIGESTANTS	CREON	84	$136,123.43	$1,620.52	0.04%
37	OTHER MISCELLANEOUS THERAPEUTIC AGENTS	EVRYSDI	7	$134,108.46	$19,158.35	0.00%
38	RIFAMYCIN ANTIBIOTICS	XIFAXAN	61	$133,428.18	$2,187.35	0.03%
39	HEMOSTATICS	XYNTHA SOLOFUSE	3	$133,413.57	$44,471.19	0.00%
40	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	290	$131,085.69	$452.02	0.13%
41	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	39	$128,983.83	$3,307.28	0.02%
42	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	60	$128,844.64	$2,147.41	0.03%
43	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	328	$121,109.88	$369.24	0.15%
44	DIRECT FACTOR XA INHIBITORS	ELIQUIS	269	$118,658.55	$441.11	0.12%
45	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	TALTZ	18	$113,663.90	$6,314.66	0.01%
46	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	233	$113,528.88	$487.25	0.11%
47	ALPHA- AND BETA-ADRENERGIC AGONISTS	EPINEPHRINE	382	$112,953.60	$295.69	0.18%
48	ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	14	$110,539.24	$7,895.66	0.01%
49	ANTINEOPLASTIC AGENTS	JAKAFI	5	$103,320.85	$20,664.17	0.00%
50	RAPID-ACTING INSULINS	NOVOLOG FLEXPEN	174	$101,063.47	$580.82	0.08%
	Total Top 50 Drugs		**19,924**	**$13,037,750.84**	**$654.37**	**9.19%**

Old Business

Pancreatic Enzyme Utilization

Time frame: 9/1/2021 to 9/31/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/Rx	Utilizers	Age Range
Creon 3,000 u	7	$2,841.51	$405.93	#278 per 27 days	3	1 – 59
Creon 6,000 u	23	$16,135.76	*$701.55	#410 per 18 days	10	1 – 54
Creon 12,000 u	6	$8,538.56	$1,423.09	#417 per 29 days	3	6 – 59
Creon 24,000 u	39	$84,018.94	$2,154.33	#319 per 26 days	18	6 – 63
Creon 36,000 u	9	$24,588.66	$3,073.58	#304 per 27 days	3	18 – 63
CREON	**84**	**$136,123.43**	**$1,620.52**	**#270 per 27 days**	**37**	**1 – 63**
Pancreaze	0					
Pertzye 16,000 u	5	$11,766.05	$2,353.21	#466 per 30 days	3	2 -23
Viokace 10,440 u	3	$987.15	$329.05	#100 per 34 days	1	45
Zenpep 5,000 u	5	$1,217.74	$243.55	#261 per 23 days	3	14 – 60
Zenpep 10,000 u	9	$17,571.41	$1,952.38	#539 per 30 days	4	33 – 55
Zenpep 15,000 u	2	$2,508.84	$1,254.42	#240 per 30 days	1	64
Zenpep 20,000 u	3	$2,575.95	$858.65	#120 per 30 days	1	41
Zenpep 25,000 u	1	$2,110.62	$2110.62	#240 per 30 days	1	51
Zenpep 40,000 u	3	$37,822.81	$12,604.92	#900 per 30 days	1	42
ZENPEP	**23**	**$63,807.37**	**$2,774.23**	**#432 per 28.5 days**	**11**	**3 – 64**

*3 claims paid with primary insurance

Review PA Forms and Criteria

Time frame: 7/1/2021 to 9/30/2021

Uloric

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Uloric	0					
febuxostat 40 mg	7	$293.72	$41.96	#29 per 29 days	4	32 – 59
febuxostat 80 mg	6	323.11	$53.85	#30 per 30 days	2	35 – 42
allopurinol 100 mg	127	$1,563.67	$12.31	#43 per 32 days	55	18 – 64
allopurinol 300 mg	100	$1,366.95	$13.67	#37 per 34 days	43	25 – 64
colchicine 0.6 mg	28	$949.53	$33.91	#30.2 per 25 days	16	19 – 63
Colcrys 0.6 mg	1	$52.48	$52.48	#60 per 30 days	1	44

*Red font denotes drug is on PA

Uloric PA Criteria

1. Diagnosis of chronic gout **AND**
2. One of the following:
   - **2.1.** Patient has received an adequate trial of at least 1 month of allopurinol **OR**
   - **2.2.** Patient has renal or hepatic dysfunction

Warnings

- FDA added boxed warning for increased risk of death with gout medicine Uloric (febuxostat) 2/21/19

Antihistamines

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
cetirizine sol 1mg/ml	1,134	$14,547.47	$12.83	#151 per 28 days	742	0 – 59
cetirizine sol 5mg/5ml	300	$4,072.55	$13.58	#132 per 26 days	259	0 – 26
cetirizine 5mg	176	$1,695.23	$9.63	#29 per 29 days	92	4 – 101
cetirizine 10mg	3,515	$35,151.31	$10.00	#28 per 28 days	1,595	0 – 102
cetirizine 5mg chew	2	$145.88	$72.94	#30 per 30 days	2	4 – 7
cetirizine ODT	0					
cetirizine-D 5-120mg	51	$1,621.40	$31.79	#39 per 22 days	24	13 – 88
desloratadine 5mg tab	2	$50.36	$25.18	#30 per 30 days	1	25
desloratadine ODT	0					
Clarinex syrup	0					
fexofenadine 60mg	24	$439.46	$18.31	#33 per 26 days	12	4 – 68
fexofenadine 180mg	305	$4,280.34	$14.03	#27 per 27 days	119	9 – 97
fexofenadine-D 60mg/120mg	2	$68.00	$34.00	#45 per 22.5 days	2	15 – 16
fexofenadine suspension	0					
fexofenadine ODT	0					
levocetirizine sol 2.5mg/5ml	8	$427.43	$53.43	#145 per 30 days	4	5 – 34
levocetirizine 5mg	95	$1,160.03	$12.21	#30 per 29 days	44	7 – 62
loratadine sol 5mg/5ml	228	$3,538.16	$15.52	#159 per 23 days	146	0 – 70
loratadine 10mg	2,200	$23,866.22	10.85	#27 per #27 days	866	5 – 101
Claritin 5mg Chew	1	$32.35	$35.35	#30 per 30 days	1	10
loratadine RDT (Reditab)	0					
loratadine-D	52	$1,091.53	$20.99	#26 per 24 days	28	11 – 89

*Red font denotes drug is on PA

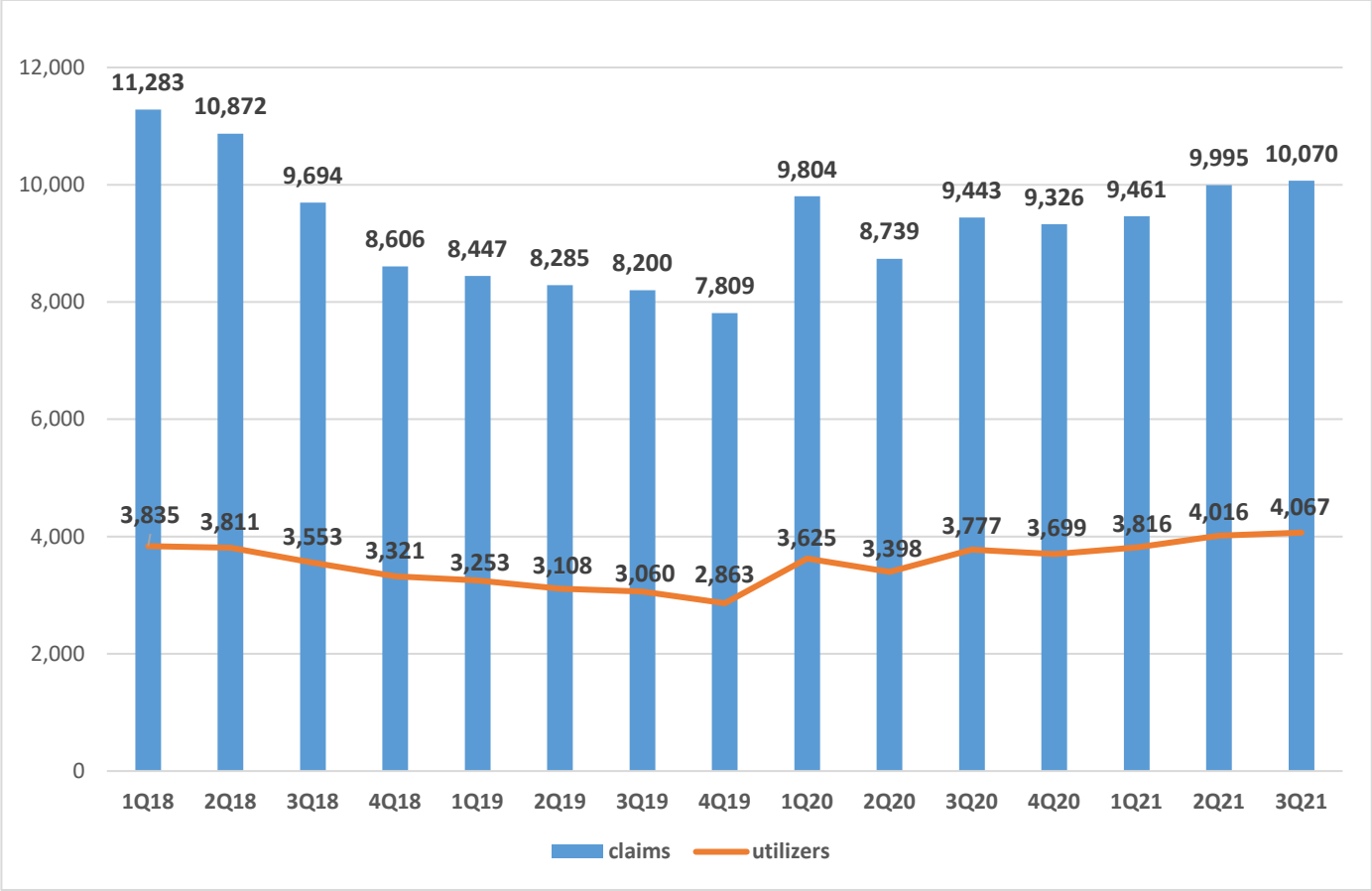
Antihistamines PA Criteria

1. One of the following:

- Patient is younger than 13 years of age **OR**
- Has documented difficulty in swallowing diagnosis

Hepatitis C Update

Opioid Summary



- 1Q2018 to 4Q2019 excludes IHS
- 1Q2020 to current includes IHS
- 2Q2020 pandemic closure

Total Eligibility and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,089	21.9%
2Q2020	126,777	20,747	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,488	17.2%
1Q2021	139,748	24,405	17.5%
2Q2021	142,872	26,162	18.3%
3Q2021	146,023	27,847	19.1%

Opioid Utilization Snapshot

SDM 2Q2021

Mar 21 to Jun 21

Opioid Claims **9,995**

3.2% prescription claims filled for an opioid

0.4% higher than Medicaid FFS benchmark

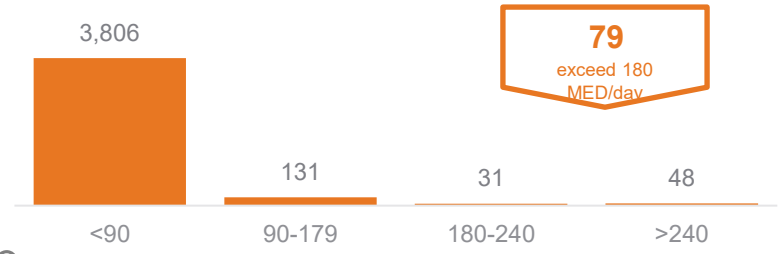
Utilizers **4,016**

30.4% are high utilizers [1]

-3.6% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

55 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

240 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

3Q2021

Jun 21 to Sep 21

Opioid Claims **10,070**

3.1% prescription claims filled for an opioid

0.5% higher than Medicaid FFS benchmark

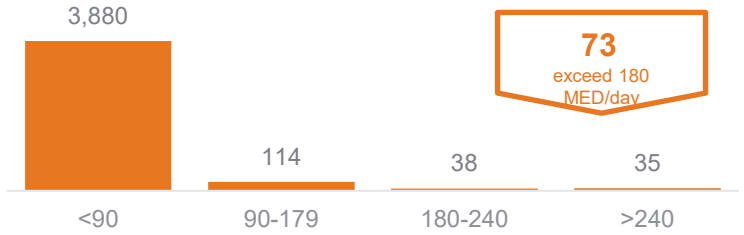
Utilizers **4,067**

29.8% are high utilizers [1]

-4.5% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

50 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

262 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUMRx®

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

Opioid Utilization

Opportunities date range: Jun - Sep 2021
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 4,067

3.1% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.1% of all prescriptions this period, which is 0.5% higher than the benchmark
- 1,213 high opioid utilizers were identified this period, which is -4.5% lower than the benchmark

Opioid claims

10,070
TOTAL RXS

PERCENT OPIOID CLAIMS
3.1%

Opioid utilizers

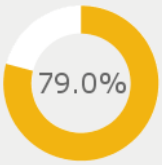
4,067
TOTAL UTILIZERS

HIGH UTILIZERS
29.8%
1,213 high utilizers

-4.5% under benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

79.0% of all opioid Rxs were filled for short acting opioids. **1,435** Rxs were for medication assisted therapy (MAT) and **113** 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 *– Medication Assisted Therapy (buprenorphine, etc)*
Overdose rescue therapy – *opioid overdose reversal w/naloxone*
MME *– relative potency of an opioid to a morphine dose*

Utilizers by cumulative MED

73 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,880	114	38	35

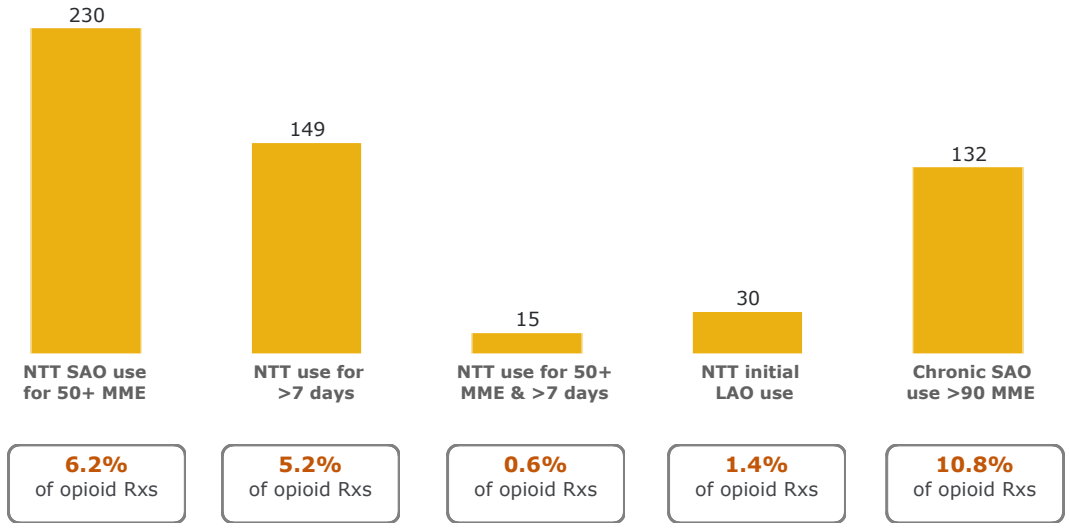
MED *– Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period*

Opioid Opportunity Assessment

Opportunities date range: Jun - Sep 2021
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



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

50 opioid utilizing members use 3 or more pharmacies and 262 opioid utilizing members use 3 or more prescribers

NNT - New to Therapy
SAO - Short Acting Opioid
LAO - Long Acting Opioid
MME - Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
702	540	688	N/A	137

Anticonvulsants –view definition

New Business

Antineoplastic oral drugs

Time frame: 7/1/2021 to 9/30/2021

Cancer Indication	Drug Name	Total Rx	Amount Paid	Paid/Rx	Utilizer
ANTINEOPLASTIC AGENTS	HYDROXYUREA CAP 500MG	10	$371.41	$37.14	5
ANTINEOPLASTIC AGENTS	DROXIA CAP 300MG (hydroxyurea)	3	$90.47	$30.16	1
Breast cancer - CDKIs	IBRANCE CAP 100MG (palbociclib)	2	$26,158.18	$13,079.09	1
Breast cancer - CDKIs	IBRANCE CAP 75MG (palbociclib)	4	$52,329.56	$13,082.39	1
Breast cancer - CDKIs	IBRANCE TAB 125MG (palbociclib)	1	$13,079.09	$13,079.09	1
Breast Cancer - CDKIs	VERZENIO TAB 100MG (abemaciclib)	2	$26,137.26	$13,068.63	1
Breast Cancer - HER2 Targeted Therapies	TUKYSA TAB 150MG (tucatinib)	1	$19,805.55	$19,805.55	1
Breast cancer - mTOR inhibitors	AFINITOR DIS TAB 2MG (everolimus)	3	$89,679.69	$29,893.23	1
Breast cancer - mTOR inhibitors	EVEROLIMUS TAB 7.5MG	3	$0.00	$0.00	1
Chronic Myeloid Leukemia (CML)	SPRYCEL TAB 100MG (dasatinib)	3	$43,855.59	$14,618.53	1
Chronic Myeloid Leukemia (CML)	SPRYCEL TAB 20MG (dasatinib)	3	$37,884.84	$12,628.28	1
Chronic Myeloid Leukemia (CML)	SPRYCEL TAB 70MG (dasatinib)	2	$16,844.70	$8,422.35	1
Chronic Myeloid Leukemia (CML)	IMATINIB MES TAB 100MG	1	$27.00	$27.00	1
Chronic Myeloid Leukemia (CML)	IMATINIB MES TAB 400MG	1	$20.70	$20.70	1
GIST, Renal, Hepatic, Colorectal, Thyroid, Bladder	LONSURF TAB 15-6.14 (trifluridine-tipiracil)	1	$7,179.45	$7,179.45	1
GIST, Renal, Hepatic, Colorectal, Thyroid, Bladder	LONSURF TAB 20-8.19 (trifluridine-tipiracil)	1	$9,569.11	$9,569.11	1
Leukemias	PURIXAN SUS 20MG/ML (mercaptopurine)	11	$17,011.76	$1,546.52	5
Leukemias	TABLOID TAB 40MG (thioguanine)	2	$2,447.71	$1,223.86	2
Lymphomas	CALQUENCE CAP 100MG (acalabrutinib)	1	$14,071.25	$14,071.25	1
Lymphomas	IMBRUVICA TAB 420MG (ibrutinib)	3	$41,798.52	$13,932.84	1
Misc agents/Rare cancers	KOSELUGO CAP 10MG (selumetinib)	4	$36,334.04	$9,083.51	1
Misc agents/Rare cancers	TEMOZOLOMIDE CAP 100MG	7	$2,976.75	$425.25	3
Misc agents/Rare cancers	TEMOZOLOMIDE CAP 140MG	8	$970.18	$121.27	3
Misc agents/Rare cancers	TEMOZOLOMIDE CAP 20MG	1	$126.02	$126.02	1
Multiple Myeloma oral TNF	POMALYST CAP 3MG (pomalidomide)	2	$38,140.68	$19,070.34	1
Multiple Myeloma oral TNF	POMALYST CAP 4MG (pomalidomide)	1	$19,070.34	$19,070.34	1
Myelofibrosis	JAKAFI TAB 20MG (ruxolitinib)	3	$44,283.75	$14,761.25	1
Myelofibrosis	JAKAFI TAB 25MG (ruxolitinib)	2	$59,037.10	$29,518.55	1
No TCO - Old drugs, no new data (Xeloda)	CAPECITABINE TAB 500MG	13	$890.01	$68.46	6
No TCO - Old drugs, no new data (Xeloda)	CAPECITABINE TAB 150MG	5	$309.48	$61.90	2
Non-Small Cell Lung Cancer	LUMAKRAS TAB 120MG (sotorasib)	3	$53,721.75	$17,907.25	1
NTRK Fusion inhibitors	VITRAKVI CAP 100MG (larotrectinib)	2	$65,614.50	$32,807.25	1
Old drugs, no new data	MERCAPTOPURINE TAB 50MG	29	$1,482.96	$51.14	13
Old drugs, no new data	METHOTREXATE TAB 2.5MG	120	$2,140.49	$17.84	58
Old drugs, no new data	XATMEP SOL 2.5MG/ML (methotrexate)	7	$7,255.85	$1,036.55	6
Prostate cancer - androgen synthesis inhibitor	ABIRATERONE TAB 250MG	10	$2,827.70	$282.77	5
Skin cancer - BRAF	BRAFTOVI CAP 75MG (encorafenib)	2	$25,367.50	$12,683.75	1
Skin cancers	MEKTOVI TAB 15MG (binimetinib)	2	$16,597.60	$8,298.80	1
	TOTAL			**$795,508.54**	

Anticonvulsants

Time Frame: 7/1/2021 to 9/30/2021 – 3,933 members taking anticonvulsant

Generic Name	Drug Name	Total Rxs	Paid Amount	Paid/Rx	Utilizers
brivaracetam	**BRIVIACT SOL 10MG/ML**	7	$8,184.29	**$1,169.18**	1
	BRIVIACT TAB	23	**$30,603.96**	**$1,330.61**	8
9 members with seizure diagnosis		NP Family Health – 4, NP Pediatric Care Neurology –2, Student, Ophthalmology			
cannabidiol Lennox-Gastaut. Dravet, tuberous sclerosis	**EPIDIOLEX SOL 100MG/ML**	79	**$188,861.07**	**$2,390.65**	26
carbamazepine bipolar disorder, mania	carbamazepine SUSP 100mg/5ml	31	$2,697.58	$87.02	9
	carbamazepine CHW 100mg	46	$2,789.19	$60.63	16
	carbamazepine TAB 200mg	97	$3,310.40	$34.13	35
	carbamazepine TAB ER	51	$4,534.02	$88.90	21
	carbamazepine CAP ER	86	$9,674.39	$112.49	86
	TEGRETOL-XR TAB 100mg	3	$223.47	$74.49	1
	EPITOL TAB 200MG	8	$272.46	$34.06	3
clobazam Lennox-Gastaut Off label: Dravet	clobazam susp 2.5mg/ml	119	$11,881.15	$99.84	34
	ONFI SUSP 2.6MG/ML	3	$3,668.70	**$1,222.90**	1
	clobazam TAB	152	$5,631.77	$37.05	56
	ONFI TAB	5	$8,438.30	**$1,687.66**	2
	SYMPAZAN MIS	12	$17,002.20	**$1,416.85**	4
clonazepam panic disorder	clonazepam ODT	203	$4,221.48	$20.80	140
	clonazepam TAB	1,517	$16,743.96	$11.04	574
	KLONOPIN TAB	8	$1,593.28	$199.16	3
diazepam	DIASTAT ACDL GEL 5-10	6	$2,094.15	$349.03	6
	DIASTAT PED GEL 2.5mg	1	$306.23	$306.23	1
	diazepam gel	59	$17,997.41	$305.04	49
	VALTOCO NASAL SPRAY	8	$5,170.57	**$646.32**	3
divalproex bipolar disorder, mania	DEPAKOTE TAB DR	5	$2,700.37	**$540.07**	3
	DEPAKOTE ER TAB 500MG	6	$2,481.19	**$413.53**	2
	DEPAKOTE SPRIKLE CAP 125MG	19	$4,822.63	**$253.82**	6
	divalproex CAP 125mg	153	$10,579.25	$69.15	57
	divalproex TAB ER	**1,047**	$21,915.51	$20.93	317
eslicarbazepine	**APTIOM TAB 400MG**	3	$3,091.50	**$1,030.50**	1
1 member with seizure diagnosis		Student			
ethosuximide	ethosuximide SOL 250mg/5ml	22	$1,257.68	$57.17	11
	ethosuximide CAP 250mg	62	$4,120.28	$66.46	25
felbamate	felbamate SUSP 600mg/5ml	32	$15,737.76	**$491.81**	9
	FELBATOL TAB 400MG	3	$8,041.15	**$2,680.38**	1
	felbamate TAB	37	$6,799.83	**$183.78**	12
fenfluramine	**FINTEPLA SOL 2.2MG/ML**	4	**$68,337.80**	**$17,084.45**	1
1 member with seizure diagnosis		Neurology			
gabapentin	gabapentin SOL 250mg/5ml	98	$3,582.78	$36.56	30
	gabapentin CAP	**2,279**	$34,649.16	$15.20	969
	gabapentin TAB	893	$18,680.19	$20.92	354
	HORIZANT TAB 600MG ER	2	$856.82	**$428.41**	1
lacosamide	**VIMPAT SOL 10MG/ML**	56	**$42,885.46**	**$765.81**	14
	VIMPAT TAB	192	**$173,041.17**	**$901.26**	60
4 members without partial or tonic-clonic seizures > 2 members with mental health disorder				Neurology – 3, Family 2	

Generic Name	Drug Name	Total Rxs	Paid Amount	Paid/Rx	Utilizers
lamotrigine bipolar disorder	LAMICTAL TAB	17	**$31,594.39**	**$1,858.49**	7
	lamotrigine TAB	**1,767**	**$23,855.05**	$13.51	627
	LAMICTAL ODT KIT	1	$591.48	**$591.48**	1
	lamotrigine TAB ODT	15	$9,755.01	**$650.33**	6
	lamotrigine CHW 5MG	48	$2,823.79	$58.83	18
	LAMICTAL XR TAB	2	$1,282.90	**$641.45**	1
	lamotrigine TAB ER	86	$9,342.70	$108.64	41
levetiracetam	KEPPRA SOL 100MG/ML	6	$10,804.78	**$1,800.80**	2
	levetiracetam SOL 100mg/ml	453	$10,260.23	$22.65	163
	KEPPRA TAB	10	$5,935.94	**$593.59**	3
	levetiracetam TAB	866	$19,249.49	$22.23	330
	KEPPRA XR TAB	6	$7,915.28	**$1,319.21**	2
	levetiracetam TAB ER	32	$1,110.78	$34.71	11
	SPRITAM TAB 250MG	1	$1,123.49	**$1,123.49**	1
midazolam	**NAYZILAM 5MG NASAL SPRAY**	26	$12,145.18	**$467.12**	14
oxcarbazepine Off-label: bipolar Off-label not rec: mania	TRILEPTAL SUSP 300MG/5ML	3	$1,670.31	**$556.77**	1
	oxcarbazepine SUS 300mg/5ml	161	**$22,978.95**	**$142.73**	56
	oxcarbazepine TAB	444	$11,683.24	$26.31	155
	OXTELLAR XR TAB	11	$13,134.18	**$1,194.02**	4
perampanel	**FYCOMPA TAB**	9	$10,004.64	**$1,111.63**	4
4 members with seizure diagnosis		Neurophysiology, Student, Neurology, Pediatrics			
phenytoin	phenytoin CHW 50mg	26	$722.41	$27.79	7
	DILANTIN CHW 50MG	5	$888.41	**$177.68**	2
	phenytoin susp 125/5ml	16	$528.36	$33.02	4
	phenytoin EX cap 30mg	109	$3,201.19	$29.37	39
	DILANTIN CAP 30MG	6	$581.20	$96.87	3
pregabalin Off-label: GAD, social phobia	pregabalin SOL 20mg/ml	3	$118.23	$39.41	1
	LYRICA CAP	11	$6,347.56	**$577.05**	5
	pregabalin CAP	716	$11,488.62	$16.05	321
primidone	primidone tab	26	$457.48	$17.60	12
rufinamide Lennox-Gastaut Off-label: partial seizure	BANZEL SUSPENSION 40MG/ML	4	**$10,650.60**	**$2,662.65**	2
	rufinamide SUSP 40mg/ml	34	**$40,829.35**	**$1,200.86**	8
	BANZEL TAB	16	**$46,946.83**	**$2,934.18**	7
	rufinamide TAB	9	$9,323.09	**$1,035.90**	3
All members with either Lennox-Gastaut or seizure diagnosis					
tiagabine	tiagabine TAB 12mg	3	$1,285.23	**$428.41**	1
1 member with seizure diagnosis		Neurology			
topiramate Off label: bipolar, binge-eating, bulimia	TOPAMAX SPR CAP 25MG	3	$4,568.91	**$1,522.97**	1
	topiramate CAP	21	$2,098.89	$99.95	9
	TOPAMAX TAB	10	$11,911.22	**$1,191.12**	3
	topiramate TAB	**1,159**	**$14,788.59**	$12.76	492
	topiramate CAP ER	12	$4,087.01	**$340.58**	6
	TROKENDI XR CAP	20	**$16,204.82**	**$810.24**	20
valproic acid bipolar disorder, mania	valproic acid CAP 250mg	44	$1,661.04	$37.75	21
	valproic acid SOL 250mg/5ml	221	$4,411.88	$19.96	59
vigabatrin	vigabatrin TAB 500mg	3	**$62,063.07**	**$20,687.69**	1
1 member with seizure diagnosis		Neurology			
zonisamide	zonisamide CAP	130	$3,064.65	$23.57	45

Red font denotes drug is on PA

Gastrointestinal Drug, Misc Review

Time frame: 7/1/2021 to 9/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty
AMITIZA CAP 24MCG	32	$10,026.99	$313.34	15	#52 per 26 days
lubiprostone cap 24 mcg	40	$11,652.14	$291.30	18	#57 per 29 days
AMITIZA CAP 8MCG	18	$5,495.40	$305.30	7	#50 per 30 days
lubiprostone cap 8mcg	22	$6,588.63	$299.48	11	#58 per 29 days
LINZESS CAP 145MCG	83	$37,398.41	$450.58	43	#31 per 29 days
LINZESS CAP 290MCG	55	$24,731.60	$449.67	25	#29 per 29 days
LINZESS CAP 72MCG	59	$25,037.50	$424.36	24	#28 per 28 days
MOTEGRITY TAB 1MG	5	$2,268.60	$453.72	2	#30 per 30 days
MOTEGRITY TAB 2MG	8	$2,761.16	$345.15	3	#30 per 30 days
MOVANTIK TAB 12.5MG	3	$1,421.89	$473.96	3	#40 per 40 days
MOVANTIK TAB 25MG	20	$7,088.08	$354.40	11	#29 per 29 days
SYMPROIC TAB 0.2MG	1	$390.44	$390.44	1	#30 per 30 days
TRULANCE TAB 3MG	20	$7,395.55	$369.78	9	#24 per 25 days
VIBERZI TAB 75MG	2	$2,667.12	$1,333.56	2	#60 per 30 days
CHOLBAM CAP 250MG	4	$99,642.20	$24,910.55	1	#30 per 30 days
CHOLBAM CAP 50MG	3	$49,681.65	$16,560.55	1	#60 per 30 days
GATTEX KIT 5MG (short bowel syndrome)	2	$83,348.18	$41,674.09	1	#1 per 30 days
OCALIVA TAB 10MG (biliary cirrhosis)	2	$15,213.76	$7,606.88	1	#30 per 30 days
TOTAL					

Red font denotes drug is on PA

AMITIZA (lubiprostone) PA criteria:

- Chronic idiopathic constipation
- Diagnosis of irritable bowel syndrome with constipation (IBS-C) AND patient is female
- Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain including chronic pain related to prior cancer or its treatment who do not require frequent (i.e., weekly) opioid dosage escalation

LINZESS (linaclotide) PA criteria:

- Diagnosis of chronic idiopathic constipation OR irritable bowel syndrome with constipation (IBS-C)

MOVANTIK (naloxegol oxalate) PA criteria:

- Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain including OR chronic pain related to prior cancer or its treatment who do not require frequent (i.e., weekly) opioid dosage escalation

MOTEGRITY (prucalopride) PA criteria:

- Diagnosis of chronic idiopathic constipation

SYMPROIC (naldemedine) PA criteria:

- Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain including chronic pain related to prior cancer or its treatment who do not require frequent (i.e., weekly) opioid dosage escalation

TRULANCE (plecanatide) PA criteria:

- Diagnosis of chronic idiopathic constipation OR irritable bowel syndrome with constipation (IBS-C)

VIBERZI (eluxadoline) PA criteria:

- Diagnosis of irritable bowel syndrome with diarrhea (IBS-D)

Insulin quantity review
Time frame: 7/1/2021 to 9/30/2021

Rapid Acting	Total Rx	Paid Amount	Paid/Rx	Utilizers	Qty Limit	Avg Qty
insulin lispro						
Admelog Inj 100u/ml	3	$409.02	$136.34	1		#10 per 20 days
Humalog Inj 100u/ml	34	$18,493.07	$543.92	17	45ml/30 days	#30 per 28 days
Insulin Lisp 100u/ml	88	$27,493.39	$312.43	38		#19.8 per 29.7 days
Admelog Solo Inj 100u/ml	4	$1,008.02	$252.01	3	45ml/30 days	#15 per 37.5 days
Humalog Kwik 100u/ml*	33	$16,574.75	$502.27	23		#15.4 per 28 days
Humalog Jr 100u/ml	11	$7,429.49	$675.41	5	45ml/30 days	#22.6 per 28.3 days
Insulin Lispro Junior	27	$8,027.93	$297.33	16		#16.2 per 32.7 days
Humalog Kwik 200u/ml*	22	$22,174.63	$1,007.94	5	45ml/30 days	#14.5 per #10.6 days
insulin glulisine						
Apidra Inj U-100	3	$3,285.81	$1,094.51	1	45ml/30 days	#40 per 33 days
Apidra Inj Solostar*	7	$3,341.53	$477.36	3		#9-15 per 20-30 days
insulin aspart with niacinamide						
Fiasp Inj 100u/ml	5	$3,132.07	$626.41	2	45ml/30 days	#26 per 22.8 days
Fiasp Flex Touch*	11	$8,015.25	$728.66	6	45ml/30 days	#20 per 28.7 days 1 Rx- 90/30 days (PA)
Fiasp Penfil U-100*	5	$1,777.26	$592.42	3	45ml/30 days	#15 per 40.6 days
insulin aspart protamine & aspart (human)						
Ins Asp Prot Inj Flexpen*	6	$2,295.28	$382.55	5		#30 per 40 days
Novolog Mix Flex Relion*	2	$171.76	$85.88	1	45ml/30 days	#15 per 46 days
Novolog Mix Flexpen*	5	$2,223.82	$444.76	3		#13.2 per 29.4 days
Insulin Aspart 70/30	3	$1,382.19	$460.73	1	50ml/30 days	#30 per 28 days
insulin aspart						
Insulin Aspart Inj 100u/ml	132	$37,487.52	$283.99	56		#21.9 per 24.8 days
Novolog 100u/ml	84	$47,405.56	$564.35	32	50ml/30 days	#21.2 per 22.7 days
Novolog Relion	10	$1,243.34	$124.33	6		#23 per 26.4 days
Insulin Aspart Flexpen*	364	$137,760.98	$378.47	212	45ml/30 days	#20.2 per 30.9 days 6 Rxs- 60 to 90 ml (PA)
Novolog Flexpen*	197	$102,085.55	$518.20	110		#17 per 30.7 days
Insulin Aspart PenFill*	154	$49,521.51	$321.57	69	45ml/30 days	#18.5 per 31.7 days
Novolog PenFill*	99	$48,230.21	$487.17	43		#16 per 29.7 days
Total	**1,309**	**$550,969.94**	**$420.91**	**610**		

Short Acting	Total Rx	Paid Amount	Paid/Rx	Utilizers	Qty Limit	Avg Qty
insulin regular						
Humulin R U-100	11	$1,670.14	$151.83	5	60ml/30 days	#10 per 22.7 days
Humulin R U-500	14	$11,573.26	$826.66	4	20ml/30 days	#9.8 per 23.4 days
Novolin R 100 unit	13	$3,383.47	$260.27	7	60ml/30 days	#15 per 26.7 days 1 Rx- 90 per 30 (PA) 7 Rxs #15 q 10 days
Novolin R Relion	2	$46.46	$23.23	2	60ml/30 days	#10 per 23.5 days
Novolin R U-100	15	$4,093.95	$272.93	7	60ml/30 days	#20 per 23.7 days 4 Rxs #20 q 21 days 5 Rx q #30 q 17 days
Total	**55**	**$20,767.28**	**$377.59**	**25**		

Intermediate Acting	Total Rx	Paid Amount	Paid/Rx	Utilizers	Qty Limit	Avg Qty
insulin NPH (human) Isophane						
Humulin N	17	$4,308.20	$253.42	9		#17 per 27.8 days
Novolin N U-100	25	$5,333.94	$213.36	9	60ml/30 days	#17.2 per 26.5 days
Novolin N Relion	10	$318.62	$31.86	4		#14 per 21 days
insulin NPH (human) isophane						
Humulin N U-100 KWP	35	$14,258.22	$407.38	26	45ml/30 days	#13.2 per 37 days
Novolin N 100 unit	18	$3,833.40	$212.97	10		#16.5 per 26.7 days
insulin NPH isophane & reg (human)						
Humulin 70/30 KWP	5	$2,303.63	$460.73	4	45ml/30 days	#15 per 27 days
Novolin 70/30 FP	7	$2,318.90	$331.27	3		#19 per 31 days
Novolin 70/30 Relion	1	$24.88	$24.88	1	60ml/30 days	#10 per 30 days
Total	**118**	**$32,699.79**	**$277.12**	**62**		

Long Acting	Total Rx	Paid Amount	Paid/Rx	Utilizers	Qty Limit	Avg Qty
insulin degludec						
Tresiba Flex 100 unit	160	$75,349.76	$470.94	89		#14.6 per 34.9 days 1 Rx- 84 per 30 days
Tresiba Flex 200 unit	115	$97,606.45	$848.75	59		#13.2 per 31.5 days
insulin degludec-liraglutide						
Xultophy 100/3.6	3	$3,316.02	$1,105.34	1		#15 per 34 days
insulin detemir						
Levemir	33	$17,148.44	$519.65	16		#18.8 per 32 days
Levemir FlexTouch*	233	$113,528.88	$487.25	131		#16.5 per 35 days
insulin glargine						
Basaglar 100 unit	70	$22,673.81	$323.91	35		#17 per 32.8 days
Lantus 100/ml	95	$38,143.89	$401.52	41	50ml/30 days	#14.4 per 22.7 days
Lantus Solostar 100/ml*	493	$214,767.65	$435.64	282	45ml/30 days	#15.8 per 35.5 days
Semglee 100u/ml*	7	$1,111.17	$158.74	4	45ml/30 days	#15.8 per 33.4 days
Semglee SOL 100u/ml*	10	$1,053.51	$105.35	1	50ml/30 days	#10 per 8 days
Toujeo Max 300 IU/ml*	43	$34,168.34	$794.61	15		#9.4 per 22 days
Toujeo Solo 300 IU/ml*	35	$22,579.78	$645.14	18		#7.7 per 29.6 days
insulin glargine-lixisenatide						
Soliqua Inj 100/33	28	$18,043.62	$644.42	15		#12.8 per 29 days
Total	**1,325**	**$659,491.32**	**$497.73**	**676**		

	Total Rx	Paid Amount	Paid/Rx	Utilizers
Grand Total	**2,807**	**$1,263,928.33**	**$450.12**	**911**

JAK Inhibitor Criteria Review

On September 1, 2021, the FDA announced that after review of a large randomized safety clinical trial, there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with Xeljanz, Xeljanz XR (tofacitinib). The FDA believes the other Janus kinase (JAK) inhibitors, Olumiant (baricitinib) and Rinvoq (upadacitinib), have similar risks because they share the same mechanism of action as Xeljanz. Xeljanz, Xeljanz XR, Olumiant, and Rinvoq currently carry a boxed warning for serious infections, mortality, malignancy and thrombosis.

- *Prescriber attests that the benefits of using this agent outweigh the risks of heart-related events (heart attack, stroke, blood clots, etc.),* ***<u>if patient has one of the following:</u>***
    - *history of smoking/is currently smoking*
    - *cardiovascular risk factors*
    - *developed a malignancy other than a successfully treated nonmelanoma skin cancer*

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers
OLUMIANT (baricitinib)	0			
RINVOQ (upadacitinib)	3	$15,436.49	$5,145.50	1
XELJANZ sol 1mg/ml (tofacitinib)	2	$7,121	$3,560.50	2
XELJANZ tab 5mg (tofacitinib)	7	$33,649.25	$4,807.04	3
XELJANZ XR tab 11mg (tofacitinib)	13	$62,422.08	$4,801.70	5
JAKAFI tabs (ruxolitinib)	5	$103,320.85		2
OPZELURA cream (ruxolitinib)	0			

Red font denotes drug is on PA

OLUMIANT PA criteria:

1. Diagnosis of rheumatoid arthritis
2. Patient is ≥ 18 years of age
3. Prescribed by or in consultation with a rheumatologist
4. The medication will not be used in combination with another biologic agent
5. Patient has had an inadequate response to, intolerance to, or contraindication to one or more non-biologic DMARDs

RINVOQ PA criteria:

1. Diagnosis of rheumatoid arthritis
2. Patient is ≥ 18 years of age
3. Prescribed by or in consultation with a rheumatologist
4. The medication will not be used in combination with another biologic agent
5. Patient has had an inadequate response to, intolerance to, or contraindication to one or more non-biologic DMARDs

XELJANZ/XR PA criteria:

1. Diagnosis of rheumatoid arthritis, psoriatic arthritis, or polyarticular juvenile idiopathic arthritis AND Patient has had an inadequate response to, intolerance to, or contraindication to DMARDs (i.e., azathioprine, methotrexate, mercaptopurine)
2. Diagnosis of ulcerative colitis AND Patient has had an inadequate response to, intolerance to, or contraindication to conventional therapy with one or more of the following: corticosteroids (i.e., prednisone, methylprednisolone), 5-ASAs (i.e., mesalamine, sulfasalazine, balsalazide, olsalazine), non-biologic DMARDs
3. Patient is ≥ 2 years of age for polyarticular juvenile idiopathic arthritis or 18 years of age for other diagnosis
4. Prescribed by or in consultation with a rheumatologist
5. The medication will not be used in combination with another biologic agent

Trudhesa comparison for acute treatment of migraine headaches with or without aura
Time frame: 7/1/2021 to 9/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
TRUDHESA (dihydroergotamine mesylate) nasal	0				
Cafergot (ergotamine/caffeine) tabs	0				
Migergot (ergotamine/caffeine) rectal supp	0				
Ergomar (ergotamine) sublingual tabs	0				
butalbital/APAP tabs/caps	0				
butalbital/caffeine/APAP caps/tabs [Fioricet]	153	$4,694.43	$30.68	82	12 – 63
butalbital/caffeine/ASA tabs [Fiorinal]	1	$20.33	$20.33	1	22
REYVOW (lasmiditan) tabs	2	$980.29	$490.15	2	26, 63
NURTEC (rimegepant) ODT tabs	33	$28,820.45	$873.35	22	21 – 59
UBRELVY (ubrogepant) tabs	45	$33,884.16	$864.09	29	18 – 60

Red font denotes drug is on PA

REYVOW and NURTEC ODT PA Criteria:

1. Patient has had a trial and failure of a triptan in the last 120 days OR
2. Patient has had an inadequate response to, intolerance to, or contraindication to triptans OR

UBRELVY PA Criteria:

3. Patient has had a trial and failure of a triptan in the last 120 days OR
4. Patient has had an inadequate response to, intolerance to, or contraindication to triptans OR
5. Patient has cardiovascular disease (Ubrelvy only)

INTRODUCTION

- Migraine is a disabling, episodic, primary headache disorder. Worldwide, it affects over 1 billon people and is considered the leading cause of disability in people younger than 50 years old. Individuals with a family history of migraine are more susceptible to developing them, and female sex is a risk factor of migraines that can persist into adulthood; in general migraine headaches are more common in adult women than men (17% vs 6%) *(Ashina et al 2021*, *Cutrer et al 2020, International Headache Society [IHS] 2018, Oskoui et al 2019).*
- Migraines are categorized into 2 types: with aura or without aura. Migraines without aura are more common and account for approximately 75% of cases (*Cutrer et al 2020, IHS 2018).*
  - Migraine attacks typically last between 4 and 72 hours in adults, and usually progress through 4 phases: the prodrome, the aura (occurring in approximately 25% of individuals), the headache, and the postdrome.
  - Factors that may trigger a migraine can include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame.
- Tension-type headaches (TTH) is the most prevalent type of headache, affecting 30 to 78% of the general population, and is one of the most common reasons why individuals purchase over the counter analgesics. TTH can be further categorized into episodic (frequent or infrequent) and chronic types; common features include mild to moderate intensity, bilateral pressing or tightening (non-pulsating), and usually does not cause nausea, vomiting, photophobia, phonophobia that is commonly seen with migraines (*IHS 2018, Taylor 2020[a], Taylor 2020[b]*).
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen [APAP]), and moderate to severe attacks are treated more migraine specific agents including triptans, calcitonin gene-related peptide (CGRP) antagonist or other agents. The use of ergot alkaloids has been largely displaced with the advent of triptans for acute treatment (*Schwedt 2021*, *Tfelt-Hansen 2013*).
- The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, aspirin [ASA]) followed by combination analgesics containing caffeine plus a simple analgesic. The efficacy of the simple analgesics tends to decrease with increasing frequency of the headaches (*Taylor 2020[b], Bentsen et al 2010*).
- Avoiding medication overuse headache (MOH) is an important goal of acute therapy and can occur when primary headache disorders (eg, migraine, tension-type) have been treated with excessive amounts of acute symptomatic medications. The risk of developing MOH appears to be highest with opioids, butalbital-containing combination analgesics, and analgesic-caffeine combinations; thus guidelines recommend against their use due to this (*Bendtsen et al 2010, Garza 2019, Silberstein and McCrory et al 2001, Schwedt 2021*).
  - In order to prevent the development of MOH, most acute medications should be limited to less than 10 days per month (or less than 15 days per month for ASA, APAP, and NSAIDs), and preventive therapies should be used as the mainstay in patients with frequent headaches.
- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies, which may be in part due to insufficient outcomes reporting in early trials and inconsistencies in demonstrating statistically significant differences in headache relief, and the lack of more recent clinical trials (*Tfelt-Hansen 2000, Silberstein and McCrory 2003)*. Additionally, ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism, and caffeine enhances its absorption; levels are slightly higher with rectal administration. Similarly, dihydroergotamine (DHE) also goes through extensive first pass metabolism, thus intranasal (IN) and intravenous (IV) administration bypass this and can deliver adequate plasma concentrations (*Silberstein and McCrory 2002*).
- Reyvow (lasmiditan) is a first in class 5-hydroxytryptamine (5-HT)1F receptor agonist for acute treatment of migraine attacks (triptans are 5-HT 1b/1d agonists) approved in 2019 by the Food and Drug Administration (FDA). This newer agent may play a role in patients with cardiovascular (CV) contraindications to triptans due to lack of vasoconstrictor activity (*AHS 2019*). In January 2021, the Drug Enforcement Agency (DEA) published a final rule placing lasmitidan as a Schedule V drug based on human abuse potential studies demonstrating significantly higher scores for drug liking, euphoric mood and feelings of relaxation (*Reyvow prescribing information 2021*).

- The focus of this overview will be migraine treatments including ergot alkaloids, butalbital combination products and Reyvow (lasmiditan). Injectable formulations have been excluded from this review. Codeine containing combination products are reviewed in the short acting opioids TCO.
- Medispan classes: Ergot combinations; Migraine products – ergotamine, dihydroergotamine; Analgesic combinations; Selective serotonin agonists 5-HT(1F)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cafergot (ergotamine/caffeine) tablets	✔
Migergot (ergotamine/caffeine) rectal suppository	-
Ergomar (ergotamine tartrate) sublingual tablets	-
Migranal (dihydroergotamine mesylate) nasal solution	✔
Trudhesa (dihydroergotamine mesylate) nasal spray	-
Allzital, Bupap, Tencon (butalbital/APAP) tablets or capsules	✔
Fioricet, Vtol LQ (butalbital/caffeine/APAP) capsules or oral solution	✔
Fiorinal (butalbital/caffeine/ASA) tablets	✔
Reyvow (lasmiditan) tablets	-

Abbreviations: APAP = acetaminophen, ASA = aspirin

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cafergot (ergotamine/ caffeine)	Migergot (ergotamine/ caffeine)	Ergomar (ergotamine tartrate)	Migranal, Trudhesa (dihydroergotamine mesylate)	Allzital, Bupap, Tencon (butalbital/APAP) *	Fioricet, Vtol LQ (butalbital/caffeine/ APAP) *	Fiorinal (butalbital/ caffeine/ASA)	Reyvow (lasmiditan)
Therapy to abort or prevent vascular headache (eg, migraine, migraine variants, or so-called "histaminic cephalalgia").	✔	✔	✔					
Acute treatment of migraine headaches with or without aura.				✔ ‡				✔ †
For the relief of the symptom complex of tension (or muscle contraction) headache					✔	✔	✔	

Abbreviations: APAP = acetaminophen, ASA = aspirin
Note: Safety and effectiveness of butalbital-containing products have been established in children aged 12 years and older.
* Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.
† Limitation of use (Reyvow): not indicated for the preventative treatment of migraine.
‡ Limitation of use: not indicated for the preventive treatment of migraine or for the management of hemiplegic or basilar migraine.

(*Prescribing information: Allzital 2020, Bupap 2020, Cafergot 2019, Migergot 2019, Ergomar 2020, Fioricet 2021, Fiorinal 2021, Vtol LQ 2019, Migranal 2019, Tencon 2017, Trudhesa 2021, Reyvow 2021*)

- 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

Ergot alkaloids

- Currently, ergotamine can be used in patients with frequent, moderate migraine but have been found to be less effective than triptans; in 3 head-to-head randomized controlled trials (RCTs), oral triptans (sumatriptan, eletriptan, and rizatriptan) were superior to oral ergotamine 2 mg plus caffeine 200 mg for quicker onset of headache relief and pain freedom at 2 hours . Sumatriptan, however was associated with higher incidence of headache recurrence at 48 hours (*Christie et al 2003, Diener et al 2002, The Multinational Oral Sumatriptan and Caferget Comparative Study Group 1999, Worthington et al 2013).* An early comparator trial demonstrated non-inferiority of ergotamine vs other migraine treatments such as naproxen, but with more adverse effects (AEs) such as nausea (*Sargent et al 1988*).
- A crossover (XO), double-blind trial (DB; N = 272) compared almotriptan vs ergotamine plus caffeine for acute migraine therapy; The primary endpoint was the proportion of patients achieving pain freedom at 2 hours. Patients were instructed to treat 2 migraine attacks, 1 with almotriptan 12.5 mg and the other with ergotamine 2 mg plus caffeine 200 mg. Rescue medication could be used 2 or more hours after treatment with the study drug for persistent moderate to severe pain and recurrence medication (the study medication for that attack) was allowed for patients who initially responded to the study medication but experienced a recurrence or worsening of their migraine during the first 48 hours after taking the study medication (*Láinez et al 2007*).
  - Treatment with almotriptan was associated with a significantly greater proportion of patients achieving pain freedom at 2 hours vs ergotamine plus caffeine (20.9% vs 13.7%; $p < 0.05$).
  - The XO design also assessed the benefit of one treatment over the other demonstrating that of the 20.9% who achieved pain freedom at 2 hours with almotriptan, 29% also responded to ergotamine plus caffeine; of the 13.7% who achieved pain freedom at 2 hours with ergotamine plus caffeine, 44% responded to almotriptan.
  - The study was not powered to detect the differences in safety between almotriptan vs ergotamine plus caffeine.
- A network meta-analysis (NMA) of 141 RCTs (7 studies including ergotamines) evaluated the comparative tolerability of various treatments including triptans, NSAIDs, and ergotamines, in any combination with or without caffeine or barbiturates for acute migraine. The primary outcomes were any AE, treatment-related AEs, and serious AEs. Overall, triptans and ergotamine were both associated with higher odds of any AE compared with NSAIDs, while tolerability profiles were mixed and comparable across various treatments (*Thorlund et al 2017*).
- DHE (Migranal) IN was shown to be effective in 4 RCTs. Patients treated a single moderate to severe migraine headache with a single dose of DHE IN (or placebo) and assessed pain severity over the 24 hours. Following treatment, the percentage of patients achieving headache response (rather than pain freedom) was reported at 2 hours as significant in Study 1 ($p < 0.001$) and at 4 hours in Studies 2 ($p < 0.01$), 3 ($p < 0.001$) and 4 ($p < 0.001$) (*Migranal prescribing information 2019*).
  - An analysis of 4 RCTs comparing DHE IN to placebo found a statistically significant effect size in favor of DHE (0.34; 95% confidence interval [CI], 0.10 to 0.57). This is particularly important for patients with moderate to severe attacks who are unable to tolerate oral medications due to nausea and vomiting (*Silberstein and McCrory 2003).*
  - A systematic review (SR) and meta-analysis (MA) evaluated the use of sumatriptan IN for acute migraine attacks. One study was compared to DHE IN in terms of safety and found no significant difference between both groups in terms of the incidence of all AEs within 24 hours ($p = 0.97$) or withdrawal due to AEs ($p = 0.30$) (*Menshawy 2018*).
- The FDA-approval of Trudhesa (DHE) IN was based on relative bioavailability compared to DHE IN spray (*Trudhesa prescribing information 2021*).
- Several comparative effectiveness studies have evaluated the efficacy of triptans vs ergot derivatives for the acute treatment of migraines.
  - In a multicenter, DB, double placebo, XO study compared sumatriptan subcutaneous (SC) to DHE IN and found that sumatriptan was significantly better at providing both headache relief at 2 hours and resolution ($p < 0.001$ for both endpoints). However, more AEs were reported with sumatriptan SC (43%) vs DHE IN (22%) and fewer patients

experienced headache recurrence with DHE IN (31% vs 17% with sumatriptan) (*Touchon et al 1996, Worthington et al 2013*).
  - Two Cochrane reviews evaluated sumatriptan (SC and IN) to DHE nasal spray. Results of the included studies demonstrated a higher proportion of patients being pain free at 2 hours with sumatriptan SC vs DHE nasal spray, while the efficacy data comparing sumatriptan IN to DHE nasal spray was deemed unusable. Overall, there was insufficient data available to carry out pooled analyses for any outcomes of interest to draw firm conclusions regarding efficacy between treatments (*Derry et al 2012[a], Derry et al 2012[b]).* One SR considered the 2 Cochrane reviews, among other individual studies and found DHE IN has variable to superior efficacy vs placebo in acute migraine; however, it was less effective then IN or SC sumatriptan (*Worthington et al 2013*).

Butalbital combinations – Fioricet (butalbital/caffeine/APAP) and Fiorinal (butalbital/caffeine/ASA)

- Recent clinical trials evaluating butalbital combination products (eg, butalbital/caffeine/APAP and butalbital/caffeine/ASA) for TTH are not available.
- One study has evaluated the efficacy of butalbital-containing agent for migraine headaches vs placebo and FDA-approved anti-migraine triptan medication. A Phase 3 RCT in 503 patients (88% were currently using a butalbital-containing drug) with migraine headache that severely impacted their life, directly compared Fioricet vs sumatriptan-naproxen vs placebo. The primary endpoint was the percentage of treated attacks with sustained pain free (SPF) response 2 to 24 hours after treatment with sumatriptan-naproxen vs Fioricet. SPF was defined as being pain-free from 2 through 24 hours after initial dosing without return of migraine pain or use of any rescue medication. Results demonstrated no difference in the primary endpoint between Fioricet vs sumatriptan-naproxen (6% vs 8%; OR, 1.3; p = 0.378). However, when each drug was compared to placebo, sumatriptan-naproxen was shown to have better pain relief compared to Fioricet for the secondary endpoints of pain-free, pain relief, migraine-free, complete symptom-free, and pain-free with relief of nausea, photophobia, phonophobia, and sinus/facial pain at most time points (*Derosier et al 2011, Worthington et al 2013*).

Reyvow (lasmiditan)

- The efficacy of lasmiditan in the acute treatment of migraine with or without aura was demonstrated in 2 Phase 3, DB, placebo controlled (PC) RCT trials, SAMURAI and SPARTAN (*Kuca et al 2018*, *Goadsby et al 2019*). Both studies included patients with CV risk factors, but 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.
  - In SAMURAI (N = 1856), lasmiditan pain freedom at 2 hours dosing (200 mg: 32.2%; OR, 2.6, 95% CI, 2.0 to 3.6; p < 0.001; lasmiditan 100 mg: 28.2%; OR 2.2, 95% CI, 1.6 to 3.0; p < 0.001) vs placebo (15.5%).
    - Freedom from MBS (lasmiditan 200 mg: 40.7%; OR, 1.6; 95% CI, 1.3 to 2.1; p < 0.001; lasmiditan 100 mg: 40.9%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001) vs placebo (29.5%).
  - In SPARTAN (N = 3005), lasmiditan pain freedom at 2 hours (lasmiditan 200 mg: 38.8%; OR, 2.3; 95% CI, 1.8 to 3.1; p < 0.001; lasmiditan 100 mg: 31.4%; OR, 1.7; 95% CI, 1.3 to 2.2; p < 0.001; lasmiditan 50 mg: 28.6%, OR, 1.5; 95% CI, 1.1 to 1.9; p = 0.003) vs placebo (21.3%),
    - Freedom from MBS (lasmiditan 200 mg: 48.7%, OR, 1.9; 95% CI, 1.4 to 2.4; p < 0.001; lasmiditan 100 mg: 44.2%; OR, 1.6; 95% CI, 1.2 to 2.0; p < 0.001; 50 mg: 40.8%; OR, 1.4; 95% CI, 1.1 to 1.8; p = 0.009) vs placebo (33.5%).
- GLADIATOR was an open label extension trial that randomized 2116 patients from SAMURAI and SPARTAN to receive lasmiditan 100 mg or 200 mg with the goal of evaluating long-term safety and efficacy (up to 1 year of intermittent use). A total of 962 patients (48.6%) reported ≥ 1 treatment emergent AE including dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%), similar to those in the pivotal trials. Dizziness was the most common AE leading to discontinuation (*Brandes et al 2019*).
- An analysis evaluated the safety and efficacy of a second dose of lasmiditan for rescue or headache 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*).

- A SR and MA of 3 RCTs (N=4,506) evaluated the safety and efficacy of lasmiditan for acute treatment of migraine. Overall, lasmiditan was associated with a significantly increased rate of patients experiencing pain freedom at 2 hours post-dose vs placebo (31.6% vs 17.55%), and freedom from MBS at 2 hours (42.82% vs 30.38%). However, lasmiditan was associated with higher rates of fatigue, paresthesia, and somnolence (*Yang et al 2020*). Another SR and MA of 4 RCTs (N = 4,960) concluded that while lasmiditan is effective for acute treatment of migraine, it is associated with a higher incidence of central nervous system (CNS) related side effects including dizziness, nausea, fatigue, paresthesia and somnolence ($p < 0.00001$ for all AEs) (*Hou et al 2020*).
- An Institute for Clinical and Economic Review (ICER) NMA of 33 RCTs evaluated the safety and efficacy of lasmiditan and oral CGRP antagonists (rimegepant and ubrogepant) for acute treatment of migraine to each other, placebo, and triptans. Results from PC clinical trials indicate that lasmiditan, rimegepant and ubrogepant decrease symptoms of migraine attacks (pain, phonophobia, photophobia, or nausea) and improve function compared to placebo at 2 hours, but all interventions showed lower odds of achieving pain freedom compared to triptans. Additionally, while similar rates of efficacy were demonstrated between the newer agents, lasmiditan had significantly higher rates of dizziness and discontinuation (*Atlas et al 2020*).

- The Agency for Healthcare Research and Quality (AHRQ) evaluated the comparative effectiveness of various pharmacotherapies used for the treatment of migraine headaches (*Halker Singh et al 2020*). Sixteen RCTs with 2,615 patients specifically studied the efficacy of ergotamine, with or without caffeine, as well as ergotamine vs placebo or lidocaine. Endpoints included pain free or pain relief at 2 hours, pain scale at 2 hours, restored function at 1 day, pain free at 1 day, pain relief at 1-day, sustained pain free at 1 week, and sustained pain relief at 1 week. Compared to placebo, DHE IN (2 mg and 3 mg) was more likely to lead to pain free and restore function at 2 hours and 1 day. Additionally, while compared to placebo, ergotamine plus caffeine probably improves pain relief at 2 hours, but a number of RCTs failed to demonstrate significant difference in headache relief compared to placebo and was associated with more AEs, mirroring early trials.
  - Five RCTs evaluated the efficacy of lasmiditan and demonstrated probable improvement in pain relief at 2 hours and increased likelihood of being pain free at 2 hours, 1 day, 1 week, and restored function vs placebo. However, serious gastrointestinal and neurological AEs were more common with lasmiditan vs placebo.

CLINICAL GUIDELINES

- The 2019 American Headache Society (AHS) position statement on integrating new migraine treatments (*AHS 2019*) recommends the use of NSAIDs, non-opioid analgesics, APAP, or caffeinated analgesic combinations for acute treatment of mild to moderate migraine attacks. For moderate to severe attacks, the guidelines suggests DHE or triptans that respond poorly to NSAIDs or caffeinated combination products.
  - Non-oral formulations are recommended if severe nausea or vomiting are associated with a migraine attack. This can include sumatriptan (IN or inhaled), ketorolac (IN or intramuscular), or DHE (IN or SC).
  - The guidelines indicate that emerging acute treatments for migraine headache such as the CGRP antagonists indicated for acute use, 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.
  - To avoid medication overuse, patients who need to use acute treatments on a regular basis should be instructed to limit treatment to an average of 2 to 3 headache days per week, and if exceeding this limit, should be offered preventative treatment.
- The 2019 American Academy of Neurology and AHS guideline for the acute symptomatic treatment of migraine in children and adolescents (*Oskoui et al 2019*) recommends the use of ibuprofen, APAP (in children and adolescents) and triptans (mainly in adolescents) for the relief of migraine pain. Ergots alone have not been studied in children.
- The 2019 European Headache Federation aids to management of headache disorders in primary care (2nd edition) recommends a stepwise approach to treatment. This includes treating 3 attacks at each step before proceeding to the next (*Steiner et al 2019*).
  - Step 1: non-opioid analgesic plus an antiemetic (when needed).
    - Opioids are considered ineffective for migraine, and barbiturates (eg, butalbital) have no place in migraine treatment.
  - Step 2: Triptans; limited to ≤ 10 days per month.

    - Domperidone 10 mg can be added for nausea, and nasal spray or SC formulations can be used when vomiting is present.
    - ergotamine is considered a poor substitute for triptans due to low and unpredictable bioavailability, which impairs efficacy, and poor tolerability. It is no longer recommended for routine use.
  - Treatment of relapse: a repeat dose of triptan may be used, and any patient with migraine who is not well controlled on acute therapy should be offer prophylaxis in addition to acute medication.
- The 2013 Canadian Headache Society (CHS) guideline for acute drug therapy for migraine indicates that ergotamine use is problematic in migraine because of poor oral absorption, vasoconstrictive side effects, and the frequent occurrence of dose limiting side effects such as nausea, which make it difficult to achieve a therapeutic dose in patients. Thus, ergotamine is not recommended routinely for acute migraine pain. Additionally, the guideline strongly recommends avoiding the use of butorphanol and butalbital containing medications. Intranasal or SC DHE can be considered for acute treatment of moderate to severe attacks (*Worthington et al 2013*).
- The 2010 EFNS guideline for the treatment of tension headache (*Bendtsen et al 2010*) recommends the use of simple analgesics (eg, APAP, ASA, ibuprofen, naproxen, ketoprofen, diclofenac) for mild to moderate TTH. Second-line treatment includes a simple analgesic plus caffeine. The guideline recommends against the use of combination products with codeine or barbiturates due to the increased risk of developing MOH. Additionally, triptans most likely do not have a clinically relevant effect in patients with TTH and cannot be recommended.
- The 2009 European Federation of Neurological Societies (EFNS) guideline for the treatment of migraine (*Evers et al 2009)* recommends the use of NSAIDs and triptans for acute treatment of migraine attacks. In very severe attacks, IV ASA or SC sumatriptan are drugs of first choice.

SAFETY SUMMARY

- Cafergot, Migergot, Ergomar (ergotamine/caffeine)
  - **Boxed warning**: Co-administration with potent cytochrome P450 (CYP) 3A4 inhibitors can lead to elevated serum levels of ergotamine tartrate increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications:
    - Pregnancy and nursing: Category X, potential to cause fetal harm, oxytocic effects
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
  - Warnings and precautions
    - Co-administration with potent CYP3A4 inhibitors can lead to serious AEs.
    - Ergotism (intense arterial vasoconstriction), fibrotic complications with long term, continuous use.
    - Drug abuse and dependence with long term use.
  - AEs
    - Vasoconstrictive complications, nausea, vomiting, rectal or anal ulcers (from suppository overuse), local edema or itching (suppository use).
  - Key drug interactions: Potent CYP3A4 inhibitors (ie, macrolide antibiotics, protease inhibitors, fluconazole, grapefruit juice, fluoxetine)

- Migranal, Trudhesa (dihydroergotamine mesylate)
  - **Boxed warning**: Co-administration with potent CYP3A4 inhibitors (ie, protease inhibitors, macrolide antibiotics) can lead to elevated serum DHE levels increasing the risk of vasospasm leading to ischemia (cerebral, extremities) which can result in amputation.
  - Contraindications
    - Co-administration with potent CYP3A4 inhibitors
    - Ischemic heart disease, coronary artery vasospasm (including Prinzmetal's variant angina),
    - Do not use within 24 hours of taking sumatriptan, ergotamine-containing or ergot-type medications, or methysergide.
    - Should not be used in patients with hemiplegic or basilar type migraines.
    - Peripheral vascular disease, coronary heart disease, impaired hepatic or renal function, sepsis.
    - Pregnancy and nursing: Potential to cause fetal harm, oxytocic effects
    - Should not be used with peripheral or central vasoconstrictors due to synergistic elevation in blood pressure.

- Patients with uncontrolled hypertension, peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment.
- Patients with hypersensitivity to ergot alkaloids

- Warnings and precautions
  - Only use where a clear diagnosis of migraine has been established.
  - Co-administration with potent CYP3A4 inhibitors
  - Fibrotic complications (eg, pleural and retroperitoneal fibrosis) with prolonged daily use.
  - Risk of myocardial ischemia or infarction and other cardiac AEs and death have occurred. Patients with risk factors predictive of coronary artery disease (CAD) who have had a sufficient CV evaluation, should have the first dose of DHE administered in a physician's office unless they have previously received it. Long term users of DHE should have regular CV evaluations.
  - Cerebrovascular events (eg, cerebral hemorrhage, subarachnoid hemorrhage and stroke) and fatalities
  - Increases in blood pressure
  - Local irritation
  - Additional warnings and precautions for Trudhesa include:
    - Medication overuse headache that may require detox
    - Risk of preterm labor in pregnant women
- AEs: Rhinitis, pharyngitis, nausea, vomiting, altered sense of taste, application site reaction, dizziness.
- Key drug interactions: Vasoconstrictors, sumatriptan, beta-blockers, nicotine.

- Bupap, Tencon, Allzital (butalbital/APAP) and Fioricet, Vtol LQ (butalbital/caffeine/APAP)
  - **Boxed warning**: Hepatotoxicity with the use of APAP > 4000 mg per day, and often occurs due to more than one APAP containing product taken at a time.
  - Contraindications: Hypersensitivity to any component, patients with porphyria.
  - Warnings and precautions
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended.
    - APAP: Hypersensitivity, anaphylaxis, serious skin reactions
  - AEs (most common): Drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.
  - Drug interactions: Alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.

- Fiorinal (butalbital/caffeine/ASA)
  - Contraindications
    - Hypersensitivity or intolerance to ASA, caffeine, or butalbital.
    - Patients with a hemorrhagic diathesis (eg, hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage).
    - Patients with nasal polyps, angioedema and bronchospastic reactivity to ASA or other NSAID.
    - Peptic ulcer or other serious gastrointestinal lesions.
    - Patients with porphyria.
  - Warnings and precautions
    - ASA component: Anaphylaxis, bleeding risk
    - Butalbital is habit-forming and potentially abusable, especially following prolonged use of high doses of barbiturates, thus extended use is not recommended
  - AEs (most common): Drowsiness, dizziness

- Reyvow (lasmiditan)
  - Contraindications: None
  - Warnings and precautions: Driving impairment, CNS depression particularly in combination with alcohol or other CNS depressants, serotonin syndrome, medication overuse headache that may require detoxification.
  - AE (most common): Dizziness, fatigue, paresthesia, and sedation.

- Key drug interactions
  - Heart lowering drugs: Reyvow may further lower heart rate when used concomitantly
  - Avoid concomitant use with P-glycoprotein and breast cancer resistant protein substrates.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cafergot (ergotamine/ caffeine)	Tablets	Oral	Two tablets at start of attack; 1 additional tablet every 30 minutes if needed.	Maximum 6 tablets per attack or 10 tablets per week. Dose should start at the first sign of an attack.
Migergot (ergotamine/ caffeine) rectal suppository	Suppository	Rectal	One suppository at the start of attack; second suppository after 1 hour if needed for full relief.	Maximum 2 suppositories per attack, 5 suppositories per week. Should not be used for chronic daily administration.
Ergomar (ergotamine tartrate)	Sublingual tablets	Oral	One tablet at the start of an attack; 1 additional tablet every 30 minutes.	Maximum 5 tablets per attack or 10 tablets per week.
Migranal (dihydroergotamine mesylate)	Nasal solution	Nasal	Four sprays; 1 spray in each nostril; 1 additional spray in each nostril after 15 minutes	Maximum 3 mg in 24 hours and 4 mg in 7 days. Prior to use, the spray should be primed with 4 pumps. The applicator should be discarded with any remaining drug after 8 hours. Should not be used for chronic daily administration.
Trudhesa (dihydroergotamine mesylate)	Nasal spray	Nasal	1 dose (2 sprays); 1 spray in each nostril. Dose can be repeated a minimum of 1 hour after the first dose.	Maximum 2 doses (4 sprays) in a 24-hour period or 3 doses (6 sprays) within a 7-day period. Discard device and vial after 2 doses have been used. Prior to use, the spray should be primed with 4 pumps. Prior to initiation, a CV evaluation is recommended.
Bupap, Tencon, Allzital (butalbital/APAP)	Tablet, capsule	Oral	One to two tablets or capsules every 4 hours.	Maximum 6 tablets or capsule
Fioricet, Vtol LQ (butalbital/caffeine/APAP)	Capsule, oral solution	Oral	Capsule: 1 or 2 two tablets every 4 hours.	Capsule: Maximum 6 tablets Oral solution: Maximum 6 tablespoons.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Oral solution: 1 or 2 tablespoons (15 or 30 mL) every 4 hours	
Fiorinal (butalbital/caffeine/ASA)	Tablet	Oral	One to two tablets every 4 hours.	Maximum 6 tablets.
Reyvow (lasmiditan)	Tablet	Oral	One tablet (50 mg, 100 mg, or 200 mg), as needed.	Maximum 1 tablet every 24 hours. Maximum 4 tablets in 30 days. Should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery. A second dose has not been shown to be effective for the same migraine attack.

Abbreviations: APAP = acetaminophen, ASA = aspirin

- Ergotamine tartrate
  - Should only be used for migraine headaches. It is not effective for other types of headaches and it lacks analgesic properties.
  - Should not be used for daily, chronic administration.
  - Overdosage
    - Patients should be advised to report any of the following immediately: numbness or tingling in the fingers or toes, muscle pain in the arms and legs, weakness in the legs, pain in the chest or temporary speeding or slowing of the heart rate, vomiting, cyanosis of the extremities.

- Fiorinal, Fioricet (butalbital component)
  - May impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery
  - Concomitant use of alcohol and other CNS depressants may produce an additive CNS depression, and should be avoided.
  - Butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.
  - Acute barbiturate poisoning causing drowsiness, confusion, and coma, respiratory depression, hypotension, hypovolemic shock.

- Reyvow
  - .Drug abuse and dependence: lasmitidan is a schedule V controlled substance; Phase 2 and 3 studies have demonstrated the potential to produce euphoria or hallucinations at therapeutic doses (about 1% of patients). Patients should be evaluated/observed for risk of drug abuse/misuse.

- See the current prescribing information for full details

CONCLUSION

- Ergot alkaloids, butalbital combinations and lasmiditan are 3 classes of analgesics commonly used to treat primary headache types including migraine and TTH. Use with ergot alkaloids and butalbital combinations should be limited to treating 2 to 3 headache days a week in order to minimize the risk of MOH.

- Currently guidelines do not have recommendations in place for the use of ergotamine/caffeine combination therapies. Ergotamine tartrate has low bioavailability after oral administration due to extensive first-pass metabolism but may be enhanced with caffeine. DHE nasal spray administration bypasses this and can deliver adequate plasma concentrations for effective treatment. For moderate to severe attacks, AHS guidelines recommend the use of non-oral formulations such as DHE IN if severe nausea or vomiting are associated with a migraine attack.
- The approach to acute migraine treatment is directed by the severity of attacks, where mild to moderate migraines without nausea and vomiting can be treated with simple analgesics (eg, NSAIDs, APAP), and moderate to severe attacks are treated more migraine specific agents.
- Butalbital combinations are FDA-approved for muscular headache or TTH and use has been studied in adults and pediatric patients aged ≥ 12 years. All butalbital-containing agents are paired with APAP or ASA with or without caffeine. NSAIDs and ASA are widely prescribed as acute medications for migraine. NSAIDs are still the mainstay for acute TTH, because they are less likely to lead to MOH compared to butalbital or APAP. The use of butalbital for patients with TTH may be considered in situations where NSAIDs are relatively contraindicated (eg, late in pregnancy) or when simple analgesics with caffeine are ineffective. Combination agents of butalbital with APAP may be used when other analgesics are contraindicated due to ulcers or severe renal failure. Butalbital with ASA may be used in hepatic failure.
  - The treatments of choice for TTH includes the use of simple analgesics (eg, APAP, NSAIDs, ASA) followed by combination analgesics containing caffeine plus a simple analgesic. Guidelines for the treatment of TTH recommends against the use of combination products with codeine or butalbital due to the increased risk of developing MOH.
- The ergot alkaloids include formulations of ergotamine tartrate (available orally and rectally) and DHE (available intranasally and as injectable forms). With the advent of triptans, the use of oral ergot alkaloids have been largely displaced in migraine therapy, as they have been found to be less effective than triptans in head-to-head trials and often reported to have poor tolerability with nausea frequently reported. The ergot alkaloids are associated with increased risk of vascular events, so use in patients with peripheral vascular disease, coronary heart disease, or other certain CV indications are contraindicated.
- Lasmiditan is a first-in class selective 5HT-1F receptor agonist that has demonstrated efficacy in achieving pain freedom and MBS freedom 2 hours after treatment in clinical trials. According to guidelines from the AHS, lasmiditan may play a role in patients who have failed, have contraindications to, or who cannot tolerate triptans.
  - Lasmiditan is associated with driving impairment, and an inability to self-assess the degree of impairment, which is a limitation to use. Patients should be advised not to operate a vehicle (or other machinery) for at least 8 hours after administration. Common AEs include dizziness, fatigue, paresthesia, and sedation.
- Guidelines for acute migraine recommend lasmiditan as a specific therapy option on par with the CGRP inhibitors; however, safety issues may limit use. Ergot alkaloids have smaller place-in-therapy and based on efficacy and safety outcomes, European guidelines recommend avoiding ergotamine's, while US and Canada guidelines cite it as an option for acute migraine use.

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