South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 23, 2022

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

September 23, 2022
1:00 – 3:00 PM

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_ZmY4MTdjMDktZDU3Zi00MTMyLWEzMWMtMGUzNDBkN2EyZTFk%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: 118 380 296 3

Join by phone
+1 952-222-7450
Phone Conference ID: 409 206 862#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Performance Measures**
- **Narrow Therapeutic Index (NTI) drugs**
- **Oseltamivir**
- **Xifaxan**
- **Doxepin (sedative hypnotics)**
- **Vuity utilization**
- **Opioid & muscle relaxant**
- **Opioid & stimulant**
- **Opioid update**

New business
- **Fleqsuvy**
- **Seglentis**

Public input accepted after individual topic discussion
Next meeting date December 2, 2022 & adjournment

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

Friday, June 10, 2022
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	X
Mikel Holland, MD	-	Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	-	Mike Jockheck, DSS Staff	X
Kelley Oehlke, PharmD	X	Matthew Ballard, DSS Staff	X
Lenny Petrik, PharmD	-	Sarah Aker, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:06 pm. The agenda for today's meeting was presented. Baack made a motion to approve the agenda. Oehlke seconded the motion. The motion was unanimously approved. The minutes of the March meeting were presented. Baack made a motion to approve. Stanley seconded the motion. The motion was unanimously approved.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from January 1, 2022, to March 31, 2022. A total of 1,736 PAs were reviewed of which 104 requests (6%) were received via telephone and 968 requests (55.8%) were received via fax, and 664 (38.2%) were reviewed via electronically. There was a 1.38% increase of PAs received compared to the previous quarter.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2022, to March 31, 2022. 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 amphetamines. These top 15 therapeutic classes make up 25.08 % 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 9.67 % of total claims. Of note, Humira citrate-free utilization accounted for 72% of the utilization for Humira and Xarelto made its 1st quarter debut on the top 50 drugs by paid amount. Darger requested an in-depth utilization review of Xifaxan and the need to discuss biosimilars at future meetings.

Old Business

Narrow Therapeutic Index (NTI) drugs

Darger provided a brief beginning history of NTI drugs. The committee reviewed the NTI utilization. It was noted that there was no utilization for brand digoxin and lithium, and no utilization of procainamide and quinidine. The committee discussed many aspects of NTI utilization. Stanley commented on anticonvulsant usage for mood stabilization should not be an issue when initiating therapy. Darger pinpointed levothyroxine capsule utilization. Van Gilder commented that the price of Jantoven is the same as warfarin; and Coumadin is no longer made. Jockheck inquired about removing those drugs from NTI status for drug with no brand utilization and no utilization. Darger inquired if there was any public comment. There were none. Baack made a motion to remove from the NTI list those drugs with no brand

utilization and no utilization including warfarin and Jantoven. Van Gilder seconded the motion. The motion was unanimously approved. The committee requested to review NTI utilization more in-depth at the next meeting excluding pancreatic enzymes. For anticonvulsants, the committee wanted to review age breakdown and if the prescriber was in psychiatry to ascertain if the diagnosis was for epilepsy or mood stabilizer. Van Gilder commented on Keppra brand solution utilization compared to generic.

Sedative Hypnotics
The committee reviewed the sedative hypnotic utilization from first quarter 2022. Committee reviewed the proposed dual orexin receptor agonists (DORAs) prior authorization (PA). Darger inquired if there was any public comment. There was none. Van Gilder made a motion to add PA with the following criteria: 18 years and older, 14-day trial of zolpidem IR, quantity of 1 per day, duplicate therapy of other sedative hypnotics, benzodiazepines, or another DORAs not allowed. Baack seconded the motion. The motion was unanimously approved. Darger requested to review doxepin in-depth at the next meeting.

Vuity and pilocarpine drops
The committee reviewed utilization for Vuity and pilocarpine drugs. Jockheck suggested bringing utilization back to the next meeting to clearly see utilization.

Cyclobenzaprine
The committee reviewed the PA approvals/denials and utilization for cyclobenzaprine. Currently, the 5mg has a quantity limit of 2 tablets per day and 10mg has none. After discussion, Oehlke made a motion to add a quantity limit of 90 tablets per 30 days for cyclobenzaprine 5mg and 90 tablets per 30 days for cyclobenzaprine 10mg. Baack seconded the motion. Darger inquired if there was any public comment. There was none. Motion was approved unanimously.

Opioid and muscle relaxant combination
The committee reviewed an in-depth analysis of six members on 4 or more different opioid and muscle relaxation combination drugs. The committee requested further review of members taking more than 90 MME and muscle relaxants, excluding cancer diagnosis and spinal cord injury; the focus is on reviewing chronic non-terminal diagnosis with prescriber information including Narcan prescription history.

Opioid update
The committee reviewed 1Q2022 opioid outcomes compared to previous quarters from the opioid initiatives. There was a slight increase in opioid utilization and opioid utilizers during first quarter which corresponded accordingly with an increase in total eligible members.

New Business

Performance Measures
Sarah Aker, Medicaid Director, asked for the committee's feedback on South Dakota's adult and child core set performance measurements that are tied to medications. Jen Lavinger, Sr Data Analyst, presented the Core Set Measures review on ADHD medications, antidepressants and antipsychotics, asthma medications, contraceptives, and opioids. Committee requested additional time to review the information and a more comprehensive analysis of the measures for ADHD medications and diabetes monitoring.

Opioid & BZD
The committee reviewed an in-depth analysis of members taking opioids and benzodiazepines concomitantly including demographics, number of different drugs, different pharmacies, and different prescribers.

Opioid & stimulants

The committee reviewed an in-depth analysis of members taking opioids and stimulants concomitantly, including demographics, number of different drugs, different pharmacies, and different prescribers. The committee requested additional information for members taking opioids, stimulants, and sedative hypnotics, including those members taking more than 90 MME.

Adjournment

The next meeting is scheduled on September 23, 2022. The December meeting is tentatively scheduled for December 2, 2022. Baack made a motion to adjourn the meeting and Oehlke seconded the motion. The motion passed unanimously, and the meeting adjourned at 3:05 pm.

PA Report
4/1/2022 – 6/30/2022

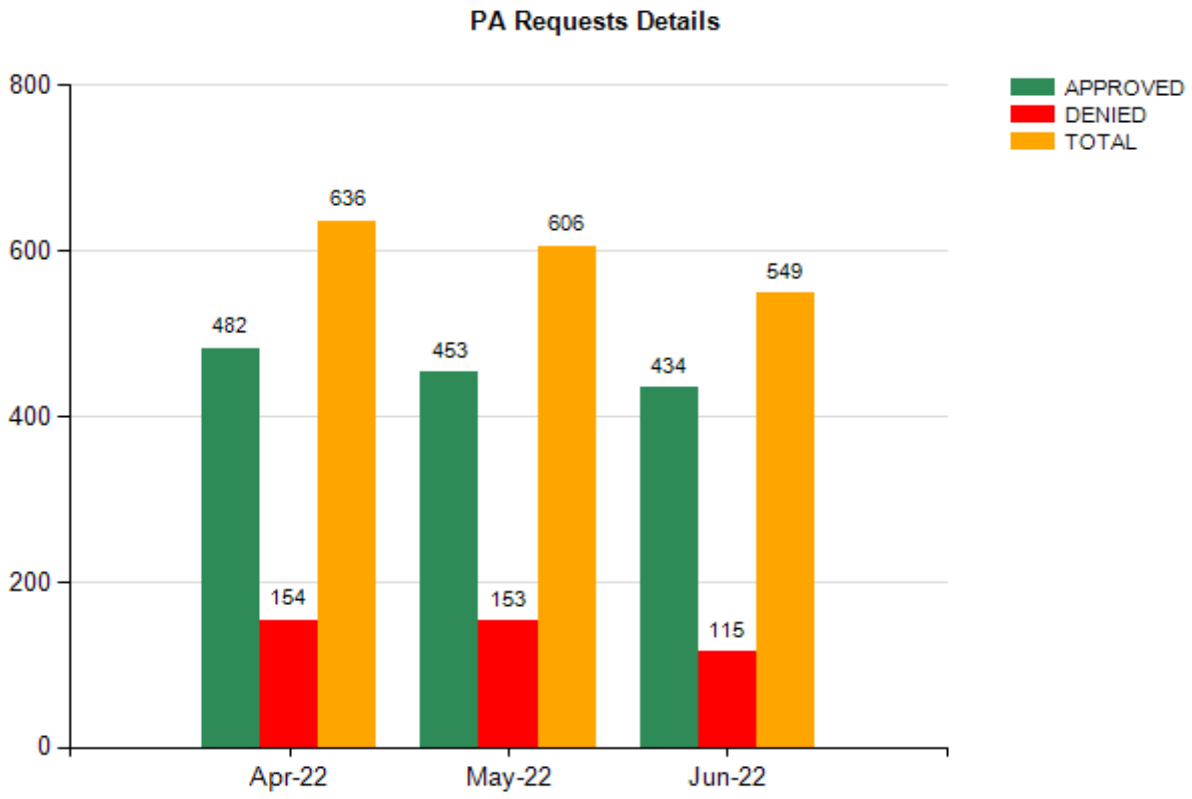
Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	1,757	1757	0	100.00%	0.00%
Urgent	34	34	0	100.00%	0.00%
Grand Total	**1,791**	**1,791**	**0**		

Drug Class	# of Requests	Phone Requests		Fax Requests		Real-Time PA	
		#	%	#	%	#	%
Total	**1,791**	**117**	**6.5%**	**1,031**	**57.6%**	**643**	**35.9%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Apr-22	482	154	636
May-22	453	153	606
Jun-22	434	115	549
2Q22	**1,369**	**422**	**1,791**
Percent of Total	**76.44%**	**23.56%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIPSYCHOTIC/ANTIMANIC	325	16	341	95.31%	19.04%	, INVEGA SUSTENNA
ANTIDIABETICS*	191	26	217	88.02%	12.12%	, OZEMPIC
ANALGESICS - OPIOID*	112	79	191	58.64%	10.66%	HYDROCODONE/APAP, TRAMADOL
DERMATOLOGICALS*	104	78	182	57.14%	10.16%	DUPIXENT, MALATHION
ANTIDEPRESSANTS*	130	21	151	86.09%	8.43%	, ESCITALOPRAM OXALATE
OTHERS -	507	202	709	71.51%	39.59%	
2Q22	**1,369**	**422**	**1,791**	**76.44%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	325	16	341	95.31%
27 - ANTIDIABETICS*	191	26	217	88.02%
58 - ANTIDEPRESSANTS*	130	21	151	86.09%
65 - ANALGESICS - OPIOID*	112	79	191	58.64%
90 - DERMATOLOGICALS*	104	78	182	57.14%
52 - GASTROINTESTINAL AGENTS - MISC.*	85	17	102	83.33%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	69	7	76	90.79%
66 - ANALGESICS - ANTI-INFLAMMATORY*	55	16	71	77.46%
67 - MIGRAINE PRODUCTS*	51	54	105	48.57%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	40	31	71	56.34%
41 - ANTIHISTAMINES*	38	5	43	88.37%
72 - ANTICONVULSANTS*	22	5	27	81.48%
16 - ANTI-INFECTIVE AGENTS - MISC.*	21	2	23	91.30%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	18	1	19	94.74%
75 - MUSCULOSKELETAL THERAPY AGENTS*	15	4	19	78.95%
54 - URINARY ANTISPASMODICS*	15	7	22	68.18%
50 - ANTIEMETICS*	13	5	18	72.22%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	7	0	7	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	7	1	8	87.50%
39 - ANTIHYPERLIPIDEMICS*	7	1	8	87.50%
83 - ANTICOAGULANTS*	7	1	8	87.50%
33 - BETA BLOCKERS*	7	3	10	70.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	7	8	15	46.67%
12 - ANTIVIRALS*	4	23	27	14.81%
02 - CEPHALOSPORINS*	3	0	3	100.00%
34 - CALCIUM CHANNEL BLOCKERS*	3	0	3	100.00%
36 - ANTIHYPERTENSIVES*	3	0	3	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	3	0	3	100.00%
11 - ANTIFUNGALS*	2	0	2	100.00%
03 - MACROLIDES*	2	2	4	50.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	2	3	5	40.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
04 - TETRACYCLINES*	0	1	1	0.00%
45 - RESPIRATORY AGENTS - MISC.*	0	2	2	0.00%
51 - DIGESTIVE AIDS*	0	1	1	0.00%
86 - OPHTHALMIC AGENTS*	0	2	2	0.00%
2Q22	**1,369**	**422**	**1,791**	
Percent of Total	**76.44%**	**23.56%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Apr-22	18	75.00%	6	25.00%	24
May-22	16	57.14%	12	42.86%	28
Jun-22	19	76.00%	6	24.00%	25
2Q22	**53**	**68.83%**	**24**	**31.17%**	**77**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LUBIPROSTONE	5	0	5	100.00%
NORDITROPIN FLEXPRO	5	0	5	100.00%
AIMOVIG	4	1	5	80.00%
DUPIXENT	4	0	4	100.00%
AJOVY	3	0	3	100.00%
EMGALITY	3	2	5	60.00%
MALATHION	3	0	3	100.00%
AMITIZA	2	0	2	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	2	0	2	100.00%
HYDROCODONE BITARTRATE/APAP	2	0	2	100.00%
MAVYRET	2	9	11	18.18%
NURTEC	2	1	3	66.67%
QULIPTA	2	0	2	100.00%
STELARA	2	0	2	100.00%
BELBUCA	1	0	1	100.00%
CYCLOBENZAPRINE HYDROCHLORIDE	1	0	1	100.00%
EPIDIOLEX	1	1	2	50.00%
ESOMEPRAZOLE MAGNESIUM	1	0	1	100.00%
HUMIRA PEN	1	0	1	100.00%
LATUDA	1	0	1	100.00%
LINZESS	1	0	1	100.00%
MORPHINE SULFATE	1	0	1	100.00%
MORPHINE SULFATE ER	1	0	1	100.00%
OTEZLA	1	0	1	100.00%
OXYCODONE/ACETAMINOPHEN	1	0	1	100.00%
TRAMADOL HCL	1	0	1	100.00%
BUPRENORPHINE	0	1	1	0.00%
DOXYLAMINE SUCCINATE/PYRIDOXINE HCL	0	1	1	0.00%
ENBREL SURECLICK	0	1	1	0.00%
IVERMECTIN	0	1	1	0.00%
LANSOPRAZOLE	0	1	1	0.00%
MODAFINIL	0	1	1	0.00%
RISPERIDONE	0	1	1	0.00%
SOFOSBUVIR/VELPATASVIR	0	1	1	0.00%
UBRELVY	0	1	1	0.00%
VIBERZI	0	1	1	0.00%
2Q22	**53**	**24**	**77**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2022 – 6/30/2022					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	15,436	$201,936.40	$13.08	6.94%
2	ANTICONVULSANTS, MISCELLANEOUS	12,274	$1,115,580.65	$90.89	5.52%
3	ATYPICAL ANTIPSYCHOTICS	9,755	$3,045,339.33	$312.18	4.39%
4	SECOND GENERATION ANTIHISTAMINES	7,849	$89,419.72	$11.39	3.53%
5	RESPIRATORY AND CNS STIMULANTS	7,390	$536,550.18	$72.60	3.32%
6	AMPHETAMINES	7,301	$1,273,540.03	$174.43	3.28%
7	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,277	$486,601.07	$66.87	3.27%
8	PROTON-PUMP INHIBITORS	6,775	$195,035.18	$28.79	3.05%
9	AMINOPENICILLIN ANTIBIOTICS	6,319	$90,421.38	$14.31	2.84%
10	ADRENALS	6,073	$683,693.93	$112.58	2.73%
11	OPIATE AGONISTS	5,887	$185,792.44	$31.56	2.65%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	5,093	$68,377.31	$13.43	2.29%
13	CONTRACEPTIVES	4,129	$125,744.70	$30.45	1.86%
14	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	4,036	$215,330.99	$53.35	1.81%
15	ANTIDEPRESSANTS, MISCELLANEOUS	3,920	$87,564.27	$22.34	1.76%
Total		**109,514**	**$8,400,927.58**	**$76.71**	**49.23%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2022 – 6/30/2022					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	***ATYPICAL ANTIPSYCHOTICS***	9,755	$3,045,339.33	$312.18	4.39%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	401	$2,538,251.87	$6,329.81	0.18%
3	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	686	$1,922,433.93	$2,802.38	0.31%
4	CYSTIC FIBROSIS (CFTR) CORRECTORS	71	$1,499,159.31	$21,114.92	0.03%
5	HEMOSTATICS	62	$1,343,365.29	$21,667.18	0.03%
6	AMPHETAMINES	7,301	$1,273,540.03	$174.43	3.28%
7	ANTICONVULSANTS, MISCELLANEOUS	12,274	$1,115,580.65	$90.89	5.52%
8	ANTINEOPLASTIC AGENTS	306	$918,230.45	$3,000.75	0.14%
9	INCRETIN MIMETICS	1,024	$863,216.49	$842.98	0.46%
10	ADRENALS	6,073	$683,693.93	$112.58	2.73%
11	LONG-ACTING INSULINS	1,446	$649,060.29	$448.87	0.65%
12	RAPID-ACTING INSULINS	1,384	$577,702.45	$417.42	0.62%
13	RESPIRATORY AND CNS STIMULANTS	7,390	$536,550.18	$72.60	3.32%
14	GI DRUGS, MISCELLANEOUS	429	$523,986.05	$1,221.41	0.19%
15	***SELECTIVE BETA-2-ADRENERGIC AGONISTS***	7,277	$486,601.07	$66.87	3.27%
Total		**55,879**	**$17,976,711.32**	**$321.71**	**25.12%**

Total Rx Claims from 4/1/2022 –4/30/2022	**222,444**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2022 – 6/30/2022						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	**FLUOXETINE HCL**	5,469	$69,511.71	$12.71	2.46%
2	***RESPIRATORY AND CNS STIMULANTS***	METHYLPHENIDATE HCL	5,130	$247,310.98	$48.21	2.31%
3	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	**SERTRALINE HCL**	4,842	$58,064.38	$11.99	2.18%
4	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	4,667	$59,475.66	$12.74	2.10%
5	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE HCL	4,583	$48,571.72	$10.60	2.06%
6	***SELECTIVE BETA-2-ADRENERGIC AGONISTS***	ALBUTEROL SULFATE HFA	4,112	$159,597.64	$38.81	1.85%
7	PROTON-PUMP INHIBITORS	**OMEPRAZOLE**	4,039	$46,546.67	$11.52	1.82%
8	***AMPHETAMINES***	VYVANSE	3,647	$1,160,928.22	$318.32	1.64%
9	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	3,585	$45,642.49	$12.73	1.61%
10	ANTICONVULSANTS, MISC	GABAPENTIN	3,525	$57,647.67	$16.35	1.58%
11	AMPHETAMINES	AMPHETAMINE/DEXTROAM	3,490	$89,575.74	$25.67	1.57%
12	SEROTONIN MODULATORS	TRAZODONE HCL	3,477	$34,381.35	$9.89	1.56%
13	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,446	$46,243.27	$13.42	1.55%
14	THYROID AGENTS	LEVOTHYROXINE SODIUM	3,004	$45,686.45	$15.21	1.35%
15	ANTIDEPRESSANTS, MISC	BUPROPION HCL	2,619	$53,879.03	$20.57	1.18%
16	CENTRAL ALPHA-AGONISTS	CLONIDINE HCL	2,418	$22,191.58	$9.18	1.09%
17	OPIATE AGONISTS	HYDROCODONE BITARTR/AC	2,338	$34,289.19	$14.67	1.05%
18	ANGIOTENSIN-CONVERTING ENZYME INHIBIT	LISINOPRIL	2,232	$21,818.20	$9.78	1.00%
19	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,224	$32,909.68	$14.80	1.00%
20	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	2,144	$24,852.29	$11.59	0.96%
21	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE ER	2,041	$35,675.83	$17.48	0.92%
22	ANXIOLYTICS, SEDATIVES, & HYPNOTICS, MISC	HYDROXYZINE HCL	1,929	$24,701.23	$12.81	0.87%
23	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,877	$23,155.02	$12.34	0.84%
24	ANTICONVULSANTS, MISC	LAMOTRIGINE	1,847	$26,198.16	$14.18	0.83%
25	1ST GENERATION CEPHALOSPORIN ANTIBIOTIC	CEPHALEXIN	1,785	$28,558.84	$16.00	0.80%
26	SEL. SEROTONIN, NOREPI REUPTAKE INHIBITOR	DULOXETINE HCL	1,750	$25,760.41	$14.72	0.79%
27	SECOND GENERATION ANTIHISTAMINES	LORATADINE	1,741	$19,346.80	$11.11	0.78%
28	ADRENALS	PREDNISONE	1,704	$16,797.11	$9.86	0.77%
29	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONATE	1,673	$24,292.64	$14.52	0.75%
30	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,670	$20,905.94	$12.52	0.75%
31	5-HT3 RECEPTOR ANTAGONISTS	ONDANSETRON ODT	1,665	$24,506.52	$14.72	0.75%
32	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANATE	1,649	$30,893.02	$18.73	0.74%
33	BIGUANIDES	METFORMIN HCL	1,545	$16,198.94	$10.48	0.69%
34	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,541	$17,073.67	$11.08	0.69%
35	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	1,533	$24,959.09	$16.28	0.69%
36	CORTICOSTEROID -SKIN, MUCOUS MEMBRANE	TRIAMCINOLONE ACETONID	1,506	$23,178.27	$15.39	0.68%
37*	ANXIOLYTICS, SEDATIVES, & HYPNOTICS, MISC	**BUSPIRONE HCL**	1,497	$19,425.17	$12.98	0.67%
38	COMPOUNDS	-	1,405	$33,833.34	$24.08	0.63%
39	CENTRALLY ACTING SKELETAL MUSCLE RELAX	CYCLOBENZAPRINE HCL	1,386	$14,497.81	$10.46	0.62%
40	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	1,384	$25,469.52	$18.40	0.62%
41	ANTICONVULSANTS, MISC	LEVETIRACETAM	1,327	$28,058.42	$21.14	0.60%
42	ANTICONVULSANTS, MISC	TOPIRAMATE	1,311	$17,080.19	$13.03	0.59%
43	3RD GENERATION CEPHALOSPORIN ANTIBIO	CEFDINIR	1,308	$27,277.15	$20.85	0.59%
44	PROTON-PUMP INHIBITORS	PANTOPRAZOLE SODIUM	1,307	$17,726.41	$13.56	0.59%
45	DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,304	$12,790.31	$9.81	0.59%
46	ANTIDEPRESSANTS, MISC	MIRTAZAPINE	1,191	$16,525.29	$13.88	0.54%
47	VITAMIN D	VITAMIN D	1,179	$11,759.73	$9.97	0.53%
48*	ANGIOTENSIN II RECEPTOR ANTAGONISTS	LOSARTAN POTASSIUM	1,146	$13,918.20	$12.15	0.52%
49*	BETA-ADRENERGIC BLOCKING AGENTS	METOPROLOL SUC ER	1,124	$14,449.55	$12.86	0.51%
50*	VITAMIN B COMPLEX	FOLIC ACID	1,121	$10,134.39	$9.04	0.50%
	Total Top 50 Drugs		**114,192**	**$2,979,686.95**	**$26.09**	**51.34%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2022 – 6/30/2022						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	DISEASE-MODIFYING ANTIRHEUMATIC AGT	**HUMIRA, PEN**	168	$1,421,948.59	$8,463.98	0.08%
2	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	55	$1,233,931.51	$22,435.12	0.02%
3	***AMPHETAMINES***	VYVANSE	3,647	$1,160,928.22	$318.32	1.64%
4	ATYPICAL ANTIPSYCHOTICS	**INVEGA SUSTENNA/TRINZA**	346	$916,771.95	$2,649.63	0.16%
5	SKIN & MUCOUS MEMBRANE AGENTS, MISC	STELARA	37	$803,973.67	$21,729.02	0.02%
6	SKIN/MUCOUS MBRNE/INTERLEUKIN ANTAG	DUPIXENT	193	$631,068.86	$3,269.79	0.09%
7	ATYPICAL ANTIPSYCHOTICS	LATUDA	457	$593,148.52	$1,297.92	0.21%
8	INCRETIN MIMETICS	OZEMPIC	563	$473,334.02	$840.74	0.25%
9	ATYPICAL ANTIPSYCHOTICS	**ARISTADA & INITIO**	162	$425,263.97	$2,625.09	0.07%
10	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	342	$391,587.24	$1,144.99	0.15%
11	HEMOSTATICS	HEMLIBRA	7	$341,128.07	$48,732.58	0.00%
12	DISEASE-MODIFYING ANTIRHEUMATIC AGT	**COSENTYX, SENSOREADY**	50	$321,743.31	$6,434.87	0.02%
13	ANTICONVULSANTS, MISC	EPIDIOLEX	122	$273,954.88	$2,245.53	0.05%
14*	DISEASE-MODIFYING ANTIRHEUMATIC AGT	**ENBREL, MINI, SURECLICK**	45	$267,718.78	$5,949.31	0.02%
15*	SODIUM-GLUC COTRANSPORT-2 INHIBITOR	JARDIANCE	515	$266,377.73	$517.24	0.23%
16	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	16	$265,227.80	$16,576.74	0.01%
17	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	74	$251,814.91	$3,402.90	0.03%
18	HEMOSTATICS	ADVATE	10	$248,514.54	$24,851.45	0.00%
19	***RESPIRATORY AND CNS STIMULANTS***	METHYLPHENIDATE HCL	5,130	$247,310.98	$48.21	2.31%
20	MUCOLYTIC AGENTS	PULMOZYME	57	$242,191.12	$4,248.97	0.03%
21	LONG-ACTING INSULINS	**LANTUS & SOLOSTAR**	609	$240,556.75	$395.00	0.27%
22	ATYPICAL ANTIPSYCHOTICS	REXULTI	199	$239,441.39	$1,203.22	0.09%
23*	ENZYMES	PALYNZIQ	6	$235,683.30	$39,280.55	0.00%
24	RAPID-ACTING INSULINS	**INSULIN ASPART, FLEX**	656	$235,153.82	$358.47	0.29%
25	INCRETIN MIMETICS	TRULICITY	267	$228,639.94	$856.33	0.12%
26	VESICULAR MONOAMINE TRANSPORT2 INHIB	INGREZZA	31	$218,492.85	$7,048.16	0.01%
27	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	63	$216,180.50	$3,431.44	0.03%
28*	HEMOSTATICS	RECOMBINATE	5	$216,125.05	$43,225.01	0.00%
29*	GI DRUGS, MISC	GATTEX	5	$214,620.00	$42,924.00	0.00%
30	SKIN & MUCOUS MEMBRANE AGENTS, MISC.	TALTZ	27	$213,497.35	$7,907.31	0.01%
31*	ADRENALS	FLOVENT HFA	867	$206,951.64	$238.70	0.39%
32	RAPID-ACTING INSULINS	**NOVOLOG, FLEXPEN/PENFIL**	357	$202,059.62	$565.99	0.16%
33	SKIN & MUCOUS MEMBRANE AGENTS, MISC	**SKYRIZI & PEN**	10	$182,807.00	$18,280.70	0.00%
34*	OTHER MISCELLANEOUS THERAPEUTIC AGT	EVRYSDI	8	$182,385.84	$22,798.23	0.00%
35	RIFAMYCIN ANTIBIOTICS	XIFAXAN	73	$180,503.58	$2,472.65	0.03%
36	HEMOSTATICS	HUMATE-P	13	$172,280.55	$13,252.35	0.01%
37	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	309	$167,174.38	$541.02	0.14%
38	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	66	$160,554.18	$2,432.64	0.03%
39	***SELECTIVE BETA-2-ADRENERGIC AGONISTS***	ALBUTEROL SULFATE HFA	4,112	$159,597.64	$38.81	1.85%
40	HEMOSTATICS	NOVOSEVEN RT	2	$148,821.10	$74,410.55	0.00%
41	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	402	$144,664.56	$359.86	0.18%
42	SKIN & MUCOUS MEMBRANE AGENTS, MISC.	TREMFYA	11	$138,496.49	$12,590.59	0.00%
43	LONG-ACTING INSULINS	**LEVEMIR & FLEXTOUCH**	281	$136,012.81	$484.03	0.13%
44	DIRECT FACTOR XA INHIBITORS	**ELIQUIS & STARTER**	306	$135,318.14	$442.22	0.14%
45*	VASODILATING AGENTS	OPSUMIT	12	$134,311.92	$11,192.66	0.01%
46*	HEMOSTATICS	XYNTHA SOLOFUSE	3	$129,753.39	$43,251.13	0.00%
47	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	36	$125,846.82	$3,495.75	0.02%
48*	ANTICONVULSANTS, MISC	VIMPAT	139	$125,668.27	$904.09	0.06%
49	GI DRUGS, MISCELLANEOUS	CHOLBAM	6	$124,413.30	$20,735.55	0.00%
50	DIPEPTIDYL PEPTIDASE-4 INHIBITORS	JANUVIA	244	$116,627.28	$477.98	0.11%
	Total Top 50 Drugs		**20,871**	**$15,869,537.55**	**$760.36**	**9.38%**

Old Business

Performance Measures

Narrow Therapeutic Index (NTI) Drugs

FDA US Food & Drug Administration FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs: Narrow therapeutic index drugs are drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.

South Dakota NTI drug list

Therapeutic Class	Example Brand Names:
• carbamazepine	Tegretol
• cyclosporine	Neoral, Sandimmune
• ~~digoxin~~	~~Lanoxin, Digitek~~
• lamotrigine	Lamictal/XR
• levetiracetam	Keppra
• ~~lithium~~	~~Lithobid, Eskalith~~
• Pancreatic Drug Products	Creon, Pancreaze
• phenytoin	Dilantin, Phenytek
• ~~procainamide~~	~~Pronestyl, Procanbid~~
• ~~quinidine~~	~~Quinidex, Quinaglute, Quinamm~~
• thyroid preparations	Synthroid, Levothroid, Armour Thyroid
• theophylline	Aminophylline, Elixophyllin, Theo-24, Theo-Dur, Theo-chron, Uniphyl
• topiramate	Topamax
• valproic Acid	Depakene
• ~~warfarin~~	~~Coumadin, Jantoven~~

Other States' NTI drug list:

State A
- Coumadin
- Dilantin
- Lanoxin
- Premarin
- Provera
- Synthroid
- Tegretol

State B
- Dilantin
- Tegretol

NTI Utilization

Time frame: 4/1/2022 to 7/31/2022

Carbamazepine	Total Rx	Paid Amount	Paid/Rx	Utilizers
carbamazepine 200mg	132	$3,652.84	$27.67	42
carbamazepine SUSP 100/5ml	44	$3,340.24	$75.91	9
carbamazepine CAP 100mg ER	17	$627.07	$36.89	5
carbamazepine CAP 200mg ER	26	$1,836.41	$70.63	9
carbamazepine CAP 300mg ER	21	$3,078.8	$146.61	7
Epitol 200mg TAB	3	$66.33	$22.11	2
TEGRETOL-XR TAB 100MG	4	$456.08	$114.02	1
carbamazepine TAB 100mg ER	19	$2,180.71	$114.77	6
carbamazepine TAB 200mg ER	43	$4,452.81	$103.55	13
carbamazepine TAB 400mg ER	41	$3,942.91	$96.17	12
carbamazepine CHW 100mg	51	$2,806.38	$55.03	14

*Red font denotes brand utilization

Lamotrigine	Total Rx	Paid Amount	Paid/Rx	Utilizers
lamotrigine TAB 25mg	599	$7,543.67	$12.59	270
LAMICTAL TAB 100MG	12	$15,975.24	$1,331.27	3
lamotrigine TAB 100mg	824	$12,088.68	$14.67	307
LAMICTAL TAB 150MG	4	$4,305.52	$1,076.38	1
lamotrigine TAB 150mg	393	$5,117.83	$13.02	134
LAMICTAL TAB 200MG	12	$19,088.64	$1,590.72	3
lamotrigine TAB 200mg	582	$8,670.93	$14.90	185
lamotrigine TAB 25mg ER	5	$333.04	$66.61	3
lamotrigine TAB 50mg ER	27	$1,719.46	$63.68	11
lamotrigine TAB 100mg ER	45	$4,643.52	$103.19	16
LAMICTAL XR TAB 200MG	8	$22,892.06	$2,861.51	2
lamotrigine TAB 200mg ER	43	$2,627.89	$61.11	13
lamotrigine TAB 250mg ER	8	$325.04	$40.63	3
LAMICTAL XR TAB 300MG	4	$10,339.88	$2,584.97	1
lamotrigine TAB 300mg ER	24	$4,631.83	$192.99	8
lamotrigine CHW 5mg	10	$301.48	$30.15	3
lamotrigine CHW 25mg	46	$3,016.34	$65.57	14
lamotrigine TAB 25mg ODT	6	$5,608.62	$934.77	2
lamotrigine TAB 50mg ODT	10	$1,564.39	$156.44	3
lamotrigine kit starter 49	1	$555.25	$555.25	1

*Red font denotes brand utilization

Phenytoin	Total Rx	Paid Amount	Paid/Rx	Utilizers
DILANTIN CHW 50MG	8	$1,454.52	$181.82	2
phenytoin CHW 50mg	24	$749.15	$31.21	7
phenytoin SUS 125/5ml	14	$447.87	$31.99	4
DILANTIN CAP 30MG	7	$925.67	$132.24	2
phenytoin EX CAP 100mg	136	$3,690.88	$27.14	38
phenytoin EX CAP 200mg	2	$88.60	$44.30	1
phenytoin EX CAP 300mg	3	$231.09	$77.03	1

*Red font denotes brand utilization

Levetiracetam	Total Rx	Paid Amount	Paid/Rx	Utilizers
KEPPRA SOL 100MG/ML	9	$16,488.84	$1,832.09	2
levetiracetam SOL 100mg/ml	627	$13,815.02	$22.03	178
KEPPRA XR TAB 750MG	4	$5,754.52	$1,438.63	1
levetiracetam TAB 250mg	124	$2,160.03	$17.42	48
KEPPRA TAB 500MG	8	$6,381.36	$797.67	2
SPRITAM TAB 500MG	1	$567.02	$567.02	1
levetiracetam TAB 500mg	610	$11,496.77	$18.85	220
KEPPRA TAB 750MG	4	$294.99	$73.75	1
SPRITAM TAB 750MG	3	$1,790.08	$596.69	1
levetiracetam TAB 750mg	144	$3,208.33	$22.28	49
levetiracetam TAB 1000mg	255	$6,523.27	$25.58	80
levetiracetam TAB 500mg ER	40	$1,315.02	$32.88	14
levetiracetam TAB 750mg ER	16	$577.50	$36.09	6

*Red font denotes brand utilization

Topiramate	Total Rx	Paid Amount	Paid/Rx	Utilizers
topiramate TAB 25mg	558	$6,309.48	$11.31	237
TOPAMAX TAB 50MG	4	$2,979.83	$744.96	2
topiramate TAB 50mg	634	$7,531.57	$11.88	224
topiramate TAB 100mg	391	$5,195.68	$13.29	127
TOPAMAX TAB 200MG	3	$3,573.12	$1,191.04	1
topiramate TAB 200mg	123	$1,944.74	$15.81	35
topiramate CAP 15mg	15	$952.50	$63.50	5
topiramate CAP 25mg	8	$388.65	$48.58	3
topiramate CAP ER 25mg	9	$1,609.66	$178.85	4
topiramate CAP ER 50mg	11	$3,104.93	$282.27	4
topiramate CAP ER 100mg	7	$2,817.51	$402.50	3
EPRONTIA SOL 25MG/ML	3	$2,026.65	$675.55	1
TROKENDI XR CAP 50MG	16	$7,822.55	$488.91	5
TROKENDI XR CAP 100MG	4	$10,388.68	$2,597.17	1

*Red font denotes brand utilization

Valproic Acid	Total Rx	Paid Amount	Paid/Rx	Utilizers
valproic acid SOL 250/5ML	299	$5,801.40	$19.40	61
valproic acid CAP 250MG	73	$3,025.80	$41.45	24
DEPAKOTE SPR CAP 125MG	20	$5,731.81	$286.59	5
divalproex CAP 125mg	162	$10,621.26	$65.56	48
divalproex TAB 125mg DR	42	$660.37	$15.72	13
DEPAKOTE TAB 250MG DR	4	$1,644.60	$411.15	1
divalproex TAB 250mg DR	244	$3,728.37	$15.28	77
divalproex TAB 500mg DR	369	$7,248.67	$19.64	104
divalproex ER TAB 250mg	195	$4,297.45	$22.04	61
DEPAKOTE ER TAB 500MG	12	$8,156.17	$679.68	3
divalproex ER TAB 500mg	446	$10,149.69	$22.76	127

*Red font denotes brand utilization

Anticonvulsant Prescribers of brand utilization

Total of 36 members taking brand anticonvulsants

A. 7 members are under 18 years old
    a) 5 members – Neurology or Pediatric Neurology
        1. Spastic diplegic cerebral palsy
        2. Epilepsy, ADHD
        3. Epilepsy, expressive language disorder, autistic disorder
        4. Epilepsy, ADHD, developmental disorder
        5. Epilepsy, Other disorder of psychological development
    b) 2 members – Nurse Practitioner
        6. Drug-induced movement disorder, ADHD, MDD, oppositional defiant disorder
        7. Anxiety, GAD, MDD, panic disorder

B. 29 members are 18 years old and over
    a) 9 members – Neurology or Pediatric Neurology
        1. Epilepsy, Lennox-Gastaut
        2. Epilepsy
        3. Regular astigmatism bilateral
        4. Epilepsy
        5. Epilepsy, cerebral palsy
        6. Epilepsy, cerebral palsy
        7. Epilepsy, anxiety
        8. Epilepsy, cerebral palsy
        9. Epilepsy, anxiety, MDD
    b) 4 members – Internal Medicine
        1. Epilepsy, cerebral palsy
        2. Epilepsy
        3. Multiple Sclerosis
        4. Epilepsy, anxiety
    c) 2 members – Neurophysiology-Clinical
        1. Epilepsy
        2. Epilepsy
    d) 1 member – Family Practice
        1. Epilepsy
    e) 1 member – OBGYN
        1. Epilepsy, cerebral palsy
    f) 8 members – Nurse Practitioner or NP-Family Health
        1. Epilepsy, Lennox-Gastaut
        2. Cerebral palsy, quadriplegia
        3. Epilepsy
        4. Epilepsy
        5. Epilepsy, bipolar, MDD GAD, anxiety
        6. Anxiety, PTSD, borderline personality disorder, episodic tension-type headache
        7. MDD, ADHD
        8. Anxiety, personality disorder, schizoaffective disorder
    g) 2 members – Physician Assistant
        1. Epilepsy
        2. Epilepsy, cerebral palsy
    h) 2 members – Resident
        1. Epilepsy, panic disorder, GAD, anxiety
        2. Epilepsy, cerebral palsy

Cyclosporine	Total Rx	Paid Amount	Paid/Rx	Utilizers
NEORAL CAP 25MG	1	$76.74	$76.74	1
cyclosporine CAP 25mg MOD	15	$897.27	$59.82	4
cyclosporine CAP 100mg MOD	10	$949.58	$94.96	3
NEORAL SOL 100MG/ML	4	$2,029.41	$507.35	1

*Red font denotes brand utilization

Theophylline	Total Rx	Paid Amount	Paid/Rx	Utilizers
THEO-24 CAP 100MG CR	4	$379.56	$94.89	1
THEO-24 CAP 300MG CR	2	$321.56	$160.78	1
theophylline TAB 300mg ER	5	$198.65	$39.73	2
theophylline TAB 400mg ER	3	$90.78	$30.26	1

*Red font denotes brand utilization

Thyroid Preparations	Total Rx	Paid Amount	Paid/Rx	Utilizers
ARMOUR THYROID TAB 15MG	25	$692.03	$27.68	8
ARMOUR THYROID TAB 30MG	18	$700.04	$38.89	6
ARMOUR THYROID TAB 60MG	24	$803.40	$33.48	8
ARMOUR THYROID TAB 90MG	20	$1,091.04	$54.55	6
ARMOUR THYROID TAB 120MG	17	$923.55	$54.33	6
ARMOUR THYROID TAB 180MG	6	$247.43	$41.24	2
	110	**$4,457.49**	**$40.52**	**36**
NP THRYOID TAB 15MG	4	$172.92	$43.23	2
NP THRYOID TAB 30MG	25	$1,073.75	$42.95	8
NP THRYOID TAB 60MG	33	$1,479.27	$44.83	12
NP THRYOID TAB 90MG	8	$221.83	$27.73	3
NP THRYOID TAB 120MG	5	$211.16	$42.23	2
	75	**$3,158.93**	**$42.12**	**27**

*Red font denotes brand utilization

Levothyroxine	Total Rx	Paid Amount	Paid/Rx	Utilizers
TIROSINT CAP 25MCG	0		~$134.98	
TIROSINT CAP 50MCG	1	$134.90	$134.90	1
TIROSINT CAP 75MCG	4	$539.76	$134.94	1
TIROSINT CAP 100MCG	0		~$135.00	
TIROSINT CAP 112MCG	4	$540.10	$135.03	1
TIROSINT CAP 125MCG	5	$591.09	$118.22	2
TIROSINT CAP 137MCG	3	$405.32	$135.11	1
	17	**$2,211.17**	**$130.07**	**6**
TIROSINT-SOL SOL 25MCG/ML	5	$715.45	$143.09	2
TIROSINT-SOL SOL 37.5MCG/ML	3	$431.25	$143.75	1
TIROSINT-SOL SOL 50MCG/ML	2	$277.16	$138.58	1
TIROSINT-SOL SOL 75MCG/ML	1	$143.75	$143.75	1
	11	**$1,567.61**	**$142.51**	**5**

*Red font denotes brand utilization

Levothyroxine	Total Rx	Paid Amount	Paid/Rx	Utilizers
EUTHYROX TAB 25MCG	32	$120.00	$3.75	14
EUTHYROX TAB 50MCG	95	$328.42	$3.46	40
EUTHYROX TAB 75MCG	47	$178.00	$3.79	22
EUTHYROX TAB 88MCG	25	$117.00	$4.68	9
EUTHYROX TAB 100MCG	24	$112.00	$4.67	13
EUTHYROX TAB 112MCG	21	$116.00	$5.52	12
EUTHYROX TAB 125MCG	35	$139.00	$3.97	16
EUTHYROX TAB 137MCG	19	$90.00	$4.74	10
EUTHYROX TAB 150MCG	18	$75.00	$4.17	10
EUTHYROX TAB 175MCG	14	$71.00	$5.07	8
EUTHYROX TAB 200MCG	29	$109.00	$3.76	15
	359	**$1,455.42**	**$4.05**	**169**
LEVOTHYROXINE **CAP 25MCG**	5	$616.91	$123.38	2
LEVOTHYROXINE **CAP 50MCG**	9	$1,168.23	$129.80	3
LEVOTHYROXINE **CAP 88MCG**	1	$112.79	$112.79	1
LEVOTHYROXINE **CAP 112MCG**	5	$557.27	$111.45	2
LEVOTHYROXINE **CAP 137MCG**	0		~$106.29	
LEVOTHYROXINE **CAP 150MCG**	1	$137.41	$137.41	1
LEVOTHYROXINE **CAP 175MCG**	2	$222.58	$111.29	1
LEVOTHYROXINE **CAP 200MCG**	4	$666.60	$166.65	2
	27	**$3,481.79**	**$128.96**	**12**
LEVOTHYROXINE TAB 25MCG	380	$5,065.33	$13.33	138
LEVOTHYROXINE TAB 50MCG	774	$10,672.62	$13.79	270
LEVOTHYROXINE TAB 75MCG	702	$9,709.04	$13.83	259
LEVOTHYROXINE TAB 88MCG	296	$4,240.42	$14.33	106
LEVOTHYROXINE TAB 100MCG	405	$5,843.86	$14.43	150
LEVOTHYROXINE TAB 112MCG	230	$3,226.29	$14.03	85
LEVOTHYROXINE TAB 125MCG	390	$5,754.51	$14.76	143
LEVOTHYROXINE TAB 137MCG	173	$2,702.17	$15.62	63
LEVOTHYROXINE TAB 150MCG	197	$2,924.83	$14.85	86
LEVOTHYROXINE TAB 175MCG	183	$2,927.59	$16.00	77
LEVOTHYROXINE TAB 200MCG	204	$3,282.56	$16.09	74
LEVOTHYROXINE TAB 300MCG	12	$173.64	$14.47	6
LEVOXYL TAB 75MG	1	$12.80	$12.80	1
	3,947	**$56,535.66**	**$14.82**	**1,458**
SYNTHROID TAB 25MCG	17	$809.70	$47.63	6
SYNTHROID TAB 50MCG	51	$2,722.94	$53.39	15
SYNTHROID TAB 75MCG	46	$2,101.23	$45.68	16
SYNTHROID TAB 88MCG	40	$1,710.31	$42.76	14
SYNTHROID TAB 100MCG	41	$1,877.34	$45.79	13
SYNTHROID TAB 112MCG	50	$2,305.73	$46.11	17
SYNTHROID TAB 125MCG	42	$1,914.61	$45.59	16
SYNTHROID TAB 137MCG	22	$1,039.33	$47.24	8
SYNTHROID TAB 150MCG	35	$1,684.05	$48.12	12
SYNTHROID TAB 175MCG	29	$1,244.85	$42.93	9
SYNTHROID TAB 200MCG	33	$1,529.70	$46.35	10
SYNTHROID TAB 300MCG	40	$1,710.31	$42.76	14
	407	**$18,955.73**	**$46.30**	**150**

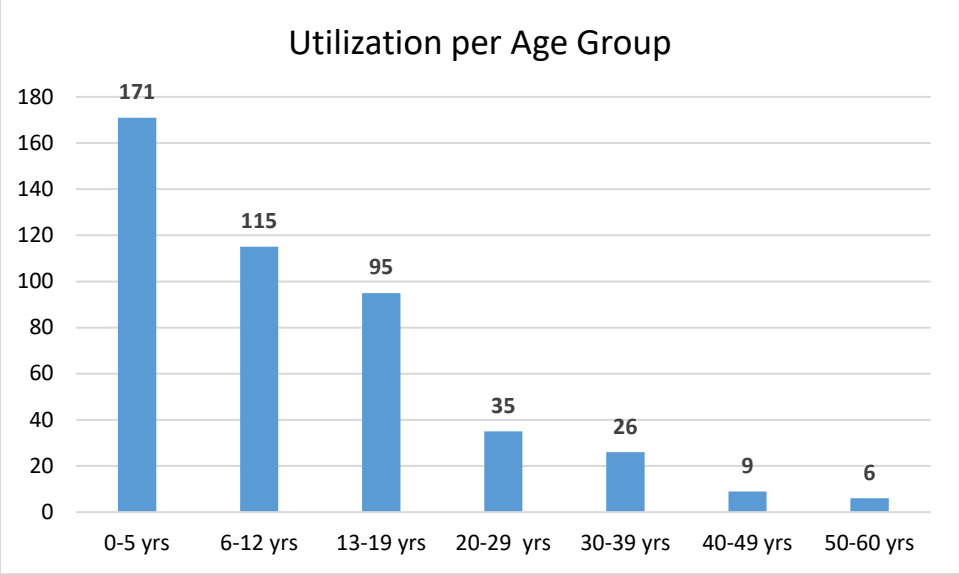
*Red font denotes brand utilization

Oseltamivir
Time frame: 10/2021 to 6/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range
oseltamivir cap 30mg	56	$1,769.20	$31.59	#10/4.75 days	49	0 – 62
oseltamivir cap 45mg	34	$1,498.89	$44.08	#9.6/5 days	34	2 – 56
oseltamivir cap 75mg	725	$16,440.99	$22.68	#9.7/5.4 days	715	6 – 61
Tamiflu cap 75mg	13	$426.43	$32.80	#10/5 days	13	9 – 35
oseltamivir susp 6mg/ml	949	$54,759.81	$57.70	#98.3/5.9 days	938	0 – 38
Tamiflu susp 6mg/ml	6	$571.03	$95.17	#100/6.2 days	6	0 – 9

Month	12/2021	1/2022	2/2022	3/2022	4/2022	5/2022	6/2022
oseltamivir 30mg	$373.98	$536.12	$163.25	$151.77	$104.96	$25.85	-
oseltamivir 45mg	$504.02	$374.23	$235.10	$63.90	$21.51	-	-
oseltamivir 75mg	$4,164.58	$6,361.93	$2,340.79	$2,173.56	$593.89	$209.27	$156.95
Tamiflu cap 75mg	$135.60	-	$243.43	$23.88	$23.52	$0	-
oseltamivir 6mg/ml	$11,855.35	$20,241.55	$11,889.54	$7,283.26	$1,973.70	$336.60	$193.86
Tamiflu 6mg/ml	-	$528.99	-	$42.04	-	-	-
TOTAL	**$17,033.53**	**$28,042.82**	**$14,872.11**	**$9,738.41**	**$2,717.58**	**$571.72**	**$350.81**

Month	10/21	11/21	12/2021	1/2022	2/2022	3/2022	4/2022	5/2022	6/2022
Total Rx	8	25	416	678	309	225	69	17	13
Paid Amount	$302.16	$846.19	$17,033.53	$28,042.82	$14,872.11	$9,738.41	$2,717.58	$571.72	$350.81
Paid/Rx	$37.77	$33.85	$40.95	$41.36	$48.13	$43.28	$39.39	$33.63	$26.98
Quantity/DS	#69/6	#51/6.6	#53/5.6	#58/5.5	#64/5.8	#59/5.7	#53/5.7	#42/5.1	#32/6.6
Utilizers	8	25	412	664	305	225	63	17	13
Age Range	0 – 17	0 – 50	0 – 60	0 – 57	0 – 61	0 – 61	0 – 62	0 – 61	0 – 46



Xifaxan
Time frame: 4/1/2022 to 6/30/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range
Xifaxan tab 550mg	73	$180,503.58	$2,472.65	#52/24.8	34	28 – 63
Xifaxan tab 200mg	0					

*Red font denotes drug is on PA

Xifaxan PA criteria:
Diagnosis of
- Travelers' diarrhea
- Hepatic encephalopathy
- Irritable bowel syndrome with diarrhea (IBS-D)

Sedative Hypnotics – doxepin review
Time frame: 4/1/2022 to 6/30/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range
doxepin tab 3mg	16	$4,175.57	$260.97	#32.8/32 days	10	15 – 57
Silenor tab 3mg	1	$122.91	$122.91	#13/13 days	1	42
doxepin tab 6mg	9	$2,167.01	$240.78	#26.7/30 days	8	15 – 45
doxepin cap 10mg	26	$473.20	$18.20	#41.5/28 days	13	23 – 61
doxepin cap 25mg	20	$356.47	$17.82	#29.7/25 days	8	28 – 60
doxepin cap 50mg	10	$242.41	$24.24	#39/30 days	5	34 – 58
doxepin cap 100mg	2	$55.69	$27.69	#30/30 days	1	44
doxepin cap 150mg	1	$49.83	$49.83	#60/30 days	1	46
doxepin conc 10mg/ml	3	$55.35	$18.45	#100/31	3	1 – 22

Indications:
Silenor/doxepin 3mg & 6mg tabs
- For treatment of insomnia characterized by difficulties with sleep maintenance

doxepin
- For treatment of major depression and/or anxiety, including psychotic depressive disorders with associated anxiety

Vuity & pilocarpine drops
Time frame: 4/1/2022 to 6/30/2022

	4Q2021				1Q2022				2Q2022			
Class	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Mbr**	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Mbr**	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Mbr**
VUITY SOL 1.25%	3	$565.18	$80.14	2	7	$565.18	$80.74	5	11	$866.06	$78.73	7
pilocarpine sol 1%	2	$142.12	$71.06	1	0				0			
pilocarpine sol 2%	0				0				0			
pilocarpine sol 4%	0				0				0			

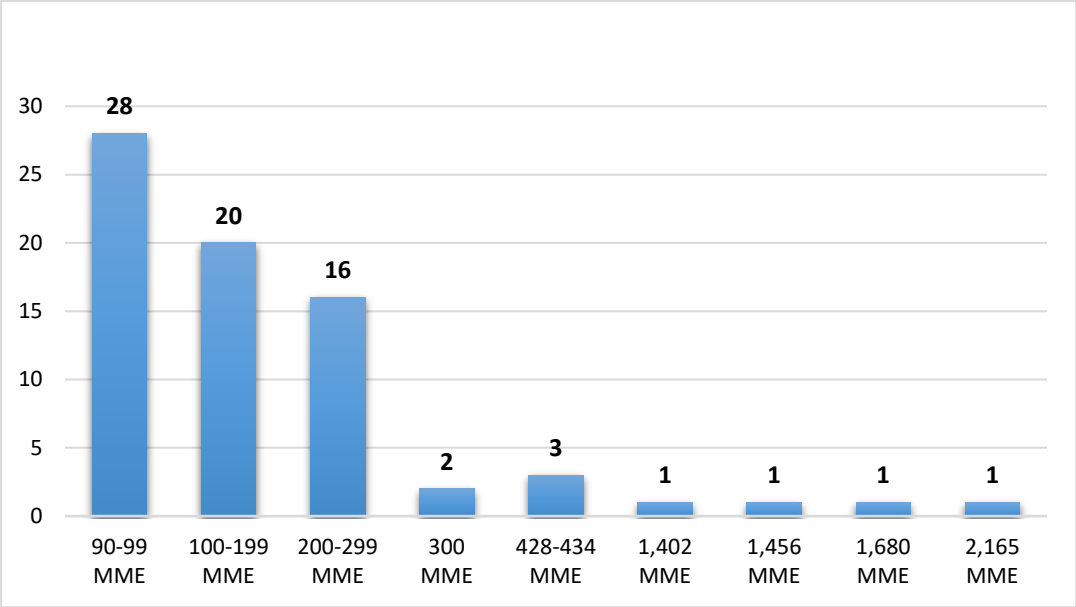
Indications:

- pilocarpine 1%, 2%, 4% solution
  - Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
  - Induction of miosis
  - Prevention of postoperative elevated IOP associated with laser surgery

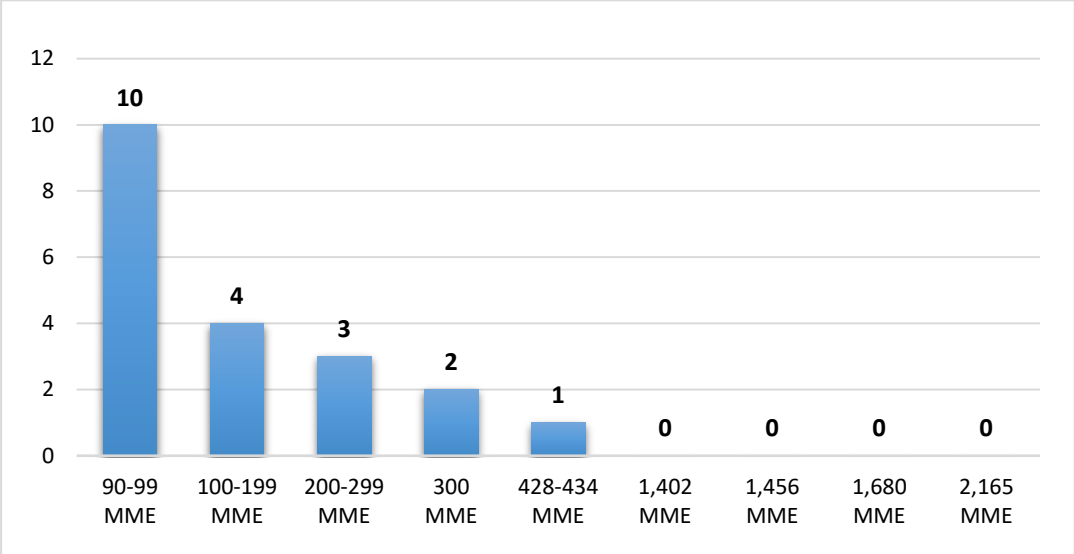
- Vuity 1.25% solution
  - Treatment of presbyopia in adults
  - 2.5ml per bottle, $32.30 per ml vs pilocarpine 15ml per bottle, $5.00 per ml

Opioid utilization over 90 MME
Time frame: 4/1/2022 to 7/31/2022

73 members with over 90 MME – not on palliative care treatment (antineoplastic and sickle cell)



20 members with Narcan/naloxone utilization (time frame 1/1/2021 to 8/31/2022)



28 members taking opioid and muscle relaxant

- 10 members have Rx filled for Narcan/naloxone

2 members taking opioid and stimulant

- 2 members have Rx filled for Narcan/naloxone

1 member taking opioid, muscle relaxant, and stimulant

- 1 member has Rx filled for Narcan/naloxone

Four members taking over 1,000 MME (No Narcan/naloxone utilization as of Jan 2021)

1. Member A – 2,165 MME (male, 29 years old)
    - Opioid utilization:
        - methadone 10mg #480/30 days
        - oxycodone 10mg #540/30 days
    - Prescriber: Hematology-Internal Medicine
    - Diagnosis: Neoplasm of colon and digestive track

2. Member B – 1,680 MME (male, 54 years old)
    - Opioid utilization: methadone 10mg #420/30 days & oxycodone
    - Prescriber: Resident
    - Diagnosis:
        - Diabetes
        - Refsum's disease (inherited condition causing vision loss, absence of the sense of smell, etc)
        - Hypertension, Varicose veins, Localized edema
        - Complete traumatic amputation at level between left hip and knee
        - Dehiscence of amputation stump
        - Acquired absence of right foot

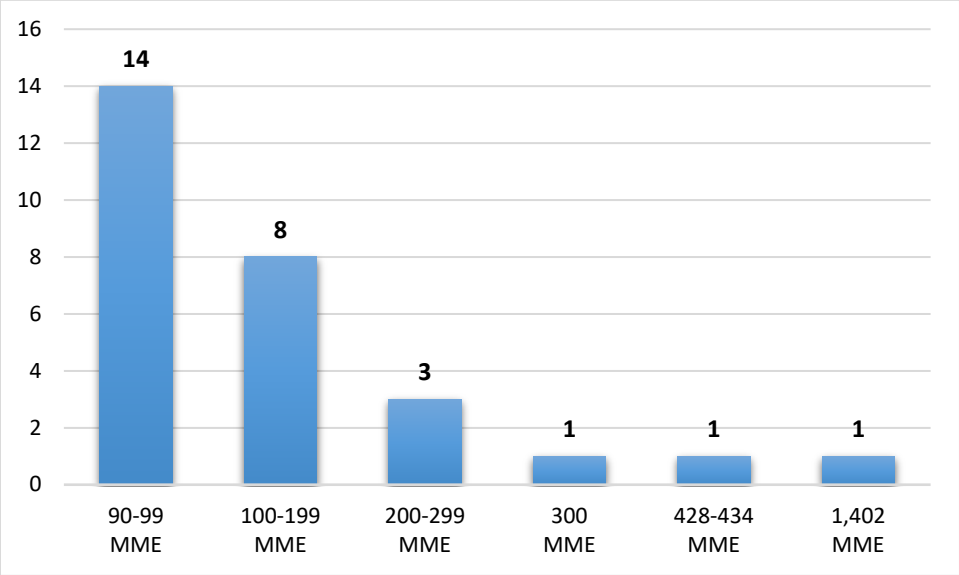
3. Member C – 1,456 MME (male, 46 years old)
    - Opioid utilization: methadone 10mg #360/30 days
    - Prescribers: Family Practice, Resident
    - Diagnosis:
        - Chronic pain
        - Cervicalgia, Low back pain
        - Pain in thoracic spine
        - Dorsalgia, unspecified
        - Abnormal weight gain
        - Long term (current) use of opiate analgesic

4. Member D – 1,402 MME (male, 40 years old)
    - Opioid utilization:
        - hydromorphone 8mg #60/30 days
        - oxycodone 30mg #300/21 days
        - Oxycontin 80mg ER #90/30 days
        - Oxycontin 40mg ER #90/30 days
        - fentanyl DIS 100mcg #20/30 days
        - carisoprodol 350mg #60/30 days
        - alprazolam 0.25mg #90/23 days
    - Prescribers: Nurse Practitioner-Family Health, Nurse Practitioner, Internal Med
    - Diagnosis:
        - Basal cell carcinoma of skin of unspecified parts of face
        - Squamous cell carcinoma of skin of unspecified parts of face
        - Malignant neoplasm of head, face and neck
        - Secondary and unspecified malignant neoplasm of lymph nodes of head, face, neck
        - Secondary malignant neoplasm of left lung & other parts of nervous system
        - Secondary malignant neoplasm of bone
        - Malignant (primary) neoplasm, unspecified

Opioid and Muscle Relaxant combination
Time frame: 4/1/2022 to 7/31/2022
IHS included

28 members taking opioid and muscle relaxant

- 10 members have Rx filled for Narcan/naloxone



1. Member E – 201 MME (female, 55 years old) – Narcan/naloxone utilization
   - Utilization:
     - oxycodone 15mg #90/30 days
     - fentanyl 50mcg/hr #10/30d ays
     - tizanidine 4mg #120/30 days
   - Prescribers: General Practice, Resident
   - Diagnosis:
     - Major depression, GAD, anxiety, Pain disorder with related psychological factors
     - Migraine
     - Carpal tunnel syndrome, Polyneuropathy
     - Other chronic pain
     - Unilateral primary osteoarthritis
     - Fibromyalgia, myalgia, Neuralgia and neuritis,
     - Pain in right arm, Pain in left arm, Pain in right finger, Pain left foot

2. Member F – 260 MME (male, 37 years old)
   - Utilization:
     - morphine 15mg #120/days
     - morphine 100mg ER #60/30 days
     - fentanyl 37.5mcg #10/30 days
     - tizanidine 4mg #360/30 days
   - Prescribers: NP-Family Health, NP, Internal Medicine
   - Diagnosis:
     - Major depressive disorder, Anxiety
     - Restless leg syndrome

- Cerebral palsy
- Other chronic pain, Chronic pain syndrome, Other muscle pain
- Periapical abscess without sinus
- Pain in left shoulder, Pain right hip, Pain in right leg, Pain in left leg
- Trochanteric bursitis in right hip

3. Member G – 297 MME (female, 48 years old) – Narcan/naloxone utilization
   - Utilization:
     - hydromorphone 4mg #90/30 days
     - methadone 10mg #90/30 days
   - Prescribers: General Practice
   - Diagnosis:
     - Personality disorder
     - Other chronic pain, Pain in unspecified joint, Pain in right shoulder, Pain in left hip
     - Sacroiliitis, Low back pain
     - Trochanteric bursitis in left hip
     - Fibromyalgia

4. Member H – 300 MME (female, 59 years old) – Narcan/naloxone utilization
   - Utilization:
     - fentanyl 100mcg #10/30 days
     - hydrocodone/APAP 10-325mg #180/30 days
     - cyclobenzaprine 10mg #90/30 days
   - Prescribers: Pain Medicine-Interventional, Family Practice
   - Diagnosis:
     - GAD, Anxiety
     - Multiple Sclerosis
     - Other chronic pain, Chronic pain syndrome
     - Bilateral primary osteoarthritis of knee
     - Unilateral primary osteoarthritis, right knee
     - Pain in right knee, Lumbago with sciatica, Low back pain
     - Other chest pain

5. Member H – 434 MME (female, 44 years old)
   - Utilization:
     - fentanyl 75mcg #10/30 days
     - fentanyl 100mcg #10/30 days
     - baclofen 10mg
   - Prescribers: Family Practice
   - Diagnosis:
     - Anxiety, Conduct disorder, Headache
     - Hallervorden-Spatz disease (an autosomal recessive disorder characterized by dystonia, parkinsonism, and iron accumulation in the brain)
     - Other specified degenerative diseases of basal ganglia
     - Chronic pain syndrome, Pain, unspecified
     - Pain in unspecified hip, Pain in right hip, Pain in left hip
     - Pain in right foot, Pain in left foot
     - Down syndrome, Encounter for palliative care

6. Member D – 1,402 MME (Male, 40 years old)

Opioid and Stimulant combination
Time frame: 4/1/2022 to 7/31/2022
IHS included

Two members taking opioid and stimulant (Rx filled for Narcan/naloxone)

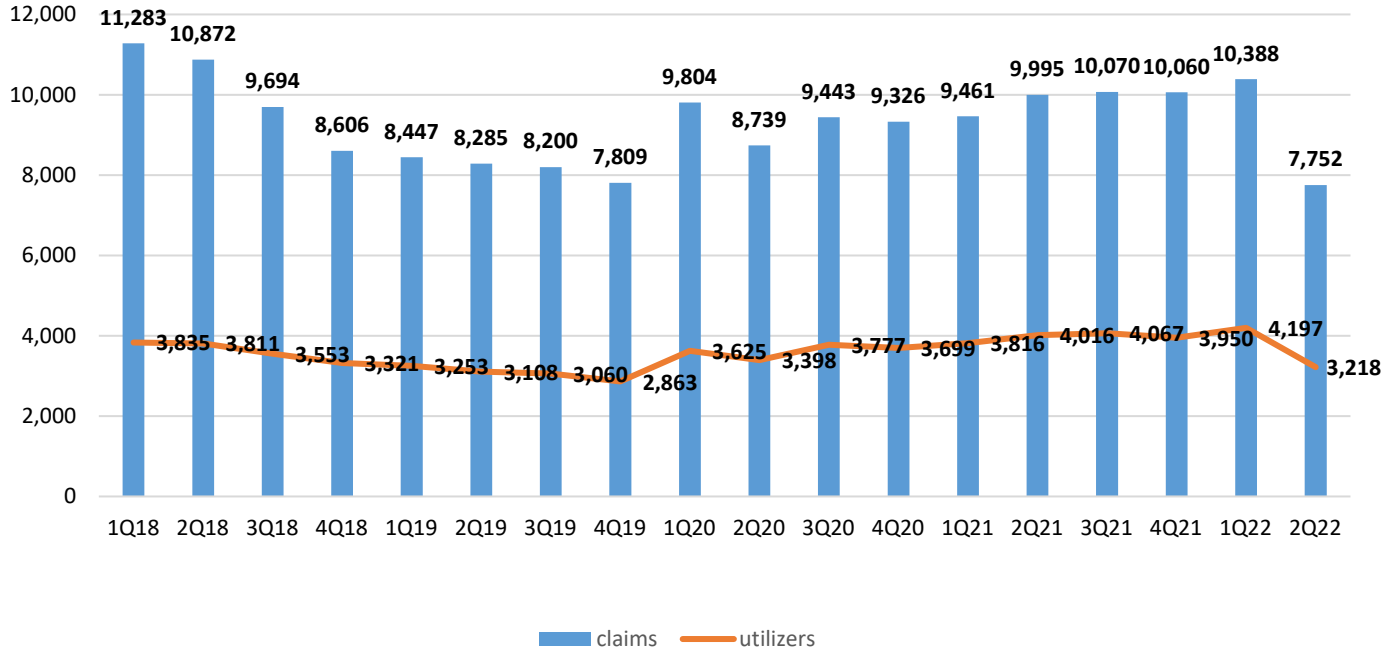
1. Member K – 93 MME (female, 63 years old)
    - Utilization:
        - methylphenidate 20mg #30/30 days
        - Vyvanse 70mg #28/28 days
        - Oxycontin 10mg CR #60/30 days
        - oxycodone/APAP 10-325mg #120/30 days
    - Prescriber: Family Practice, NP-Family Health, Psychiatry
    - Diagnosis:
        - Opioid dependence, Opioid use
        - Major depressive disorder, GAD, Anxiety, Borderline personality disorder, ADHD
        - Carpal tunnel syndrome, left upper limb
        - Polyneuropathy
        - Diverticulosis of large intestine without perforation or abscess without bleeding
        - Unilateral primary osteoarthritis
        - Primary osteoarthritis – hands, Primary osteoarthritis – shoulders
        - Pain in right shoulder, Pain in right knee
        - Spondylosis without myelopathy or radiculopathy, lumbar region
        - Pain, Other chronic pain

2. Member L – 104 MME (female, 28 years old)
    - Utilization:
        - hydromorphone 8mg #29/8 days
        - Vyvanse 70mg #30/30 days
        - Buprenorphine sub 8mg #45/30 days
        - Sublocade inj 100/0.5 #0.5/28 days
    - Prescriber: Family Practice, General Practice, Resident
    - Diagnosis:
        - Other stimulant abuse
        - Bipolar disorder, Borderline personality disorder, ADHD
        - Post-traumatic stress disorder, unspecified
        - Other chronic pain, Sacroiliitis
        - First degree perineal laceration during delivery
        - Long term (current) use of opiate analgesic
        - Imprisonment and other incarceration

One member taking opioid, muscle relaxant, and stimulant (Rx filled for Narcan/naloxone utilization)

3. Member K – 93 MME (female, 63 years old)
    - Utilization:
        - methylphenidate 20mg #30/30 days
        - Vyvanse 70mg #28/28 days
        - Oxycontin 10mg CR #60/30 days
        - oxycodone/APAP 10-325mg #120/30 days
        - baclofen 10mg #60/30 days
    - Prescriber: Family Practice, NP-Family Health, Psychiatry

Opioid Summary



- 1Q2018 to 4Q2019 excludes IHS
- 1Q2020 to current includes IHS
- March 13, 2020 – Pandemic Closure
- 2Q2022 excludes IHS

Opioid Initiatives:

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

Other Initiatives:

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

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%
4Q2021	149,034	29,257	19.3%
1Q2022	151,735	28,892	19.0%
2Q2022	154,608	28,338	18.3%

SDM

APR-JUN 2022

Opioid Utilization Snapshot

Opioid Claims

7,752

3.6% prescription claims filled for an opioid

0.3% lower than Medicaid Managed benchmark

Short acting opioids
75.2%
of opioid Rxs

MAT[2]
1,376
of opioid Rxs

Rescue Therapy[3]
130
Rx(s)

CDC Guidelines advise prescribers to manage pain with lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day

Utilizers

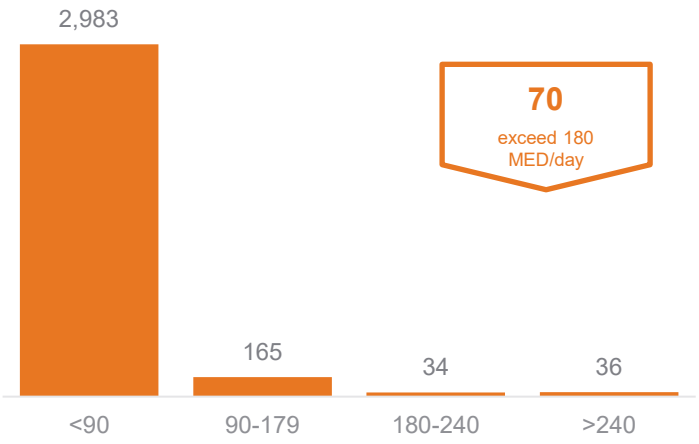
3,218

36.1% are high utilizers[1]

3.6% lower than high utilizers Medicaid Managed benchmark

Utilizers by Cumulative MED[4]

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



[1]Defined as 3+ opioid scripts within 120 days period; [2]**MAT** - Medication Assisted Therapy (e.g., buprenorphine, etc..); [3] **Overdose Rescue Therapy** – opioid overdose reversal with Narcan (naloxone), etc. [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.

SDM

APR-JUN 2022

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy

26

opioid utilizing members with 3+ pharmacies

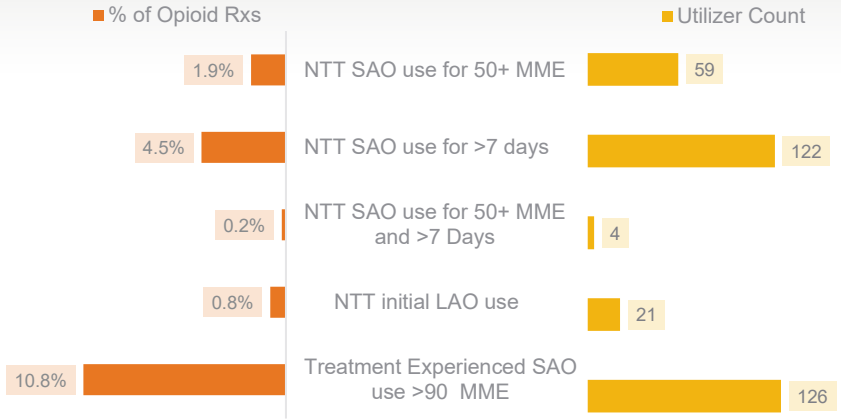
Shoppers: Poly Prescriber

233

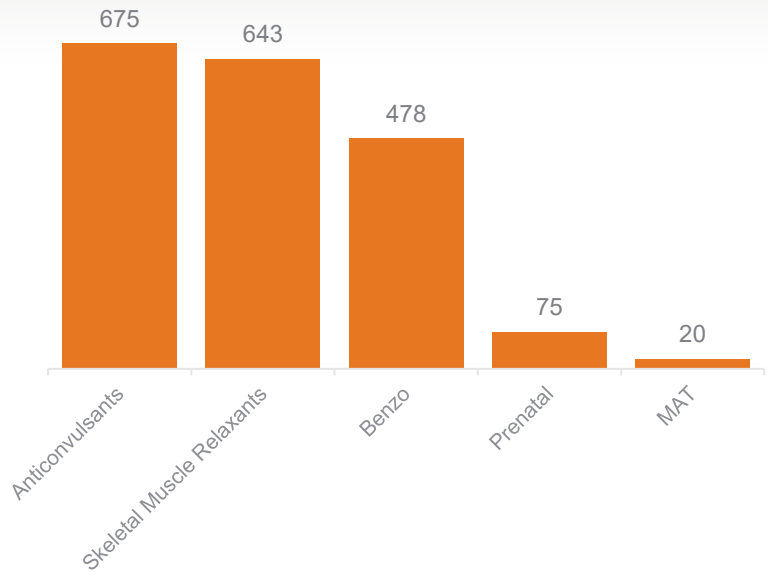
opioid utilizing members with 3+ prescribers

6.9%
of all Opioid Rxs

Non-Compliance to CDC Guidelines[7] for Opioid Prescriptions (NTT[8] and Chronic)



Utilizers with Opioid Medication Combinations[9]



OPTUMRx®

[7]JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464; [8]NTT – New To Therapy SAO – Short Acting Opioid; LAO – Long Acting Opioid;
[9]Anticonvulsants - gabapentin, pregabalin, anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

Field Definitions

Dashboard is based on the 120 days of most recent history claims.

Opioid Utilization Snapshot

Opioid claims – total number of opioid claims identified within most recent 120 days claims history
% of Opioid claims - % of opioid claims out of total claims with the period
Benchmark % (claims)- indicates percent difference of your prescription claims filled for an opioid in comparison to segment benchmark
% of Short Acting Opioids – percent of SAO scripts out of total opioid scripts
MAT Rxs – a number of Medication Assisted Therapy (e.g., buprenorphine, etc.) scripts out of total opioid scripts
Rescue Therapy – a number of Rxs for opioid overdose reversal with Narcan (naloxone), etc
Utilizer count – total number of utilizers with opioid Rxs within the period
% of high utilizers - % of utilizers with 3+ opioid scripts within 120 days period
Benchmark % (utilizers)- indicates percent difference of your opioid utilizers in comparison to segment benchmark
Utilizers by Cumulative MED (graph) - Morphine Equivalent Dose is relative potency of an opioid to standard of morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; **[Total call out]** is a sum of utilizers with 180+ MED.
MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy – a number of opioid utilizing members with 3 or more pharmacies
Shoppers: Poly Prescriber – a number of opioid utilizing members with 3 or more prescribers
Non-Compliance to CDC Guidelines for Opioid Prescriptions (NTT and Chronic) (graph) – depicts a number of members and % opioid Rxs for New To Therapy (NTT) and chronic opioid use for each of the defined categories; **% Total** – indicates total percent of opioid scripts for the categories.
Retrospective members (call out) - a retrospective review of claims indicating the number members that would have hit Orx opioid fill UMs if program was implemented during the reporting time period.
Opioid Medication Combinations of High-Risk (graph) – depicts a number of opioid utilizers for each opioid/drug type combination.

New Business

Fleqsuvy & baclofen

Time frame: 4/1/2022 to 6/30/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
baclofen tab 5mg	62	$2,441.43	$39.38	#69/25 days	30	2 – 64
baclofen tab 10mg	738	$10,852.13	$14.70	#89/27 days	323	1 – 66
baclofen tab 20mg	180	$3,781.43	$21.00	#99/29 days	63	10 – 63
baclofen sol 5mg/5ml	3	$1,079.65	$359.88	#320/32 days	2	3, 26
FLEQSUVY susp 25mg/5ml	3	$2,836.65	$945.55	#170/26 days	3	5, 6, 26
LYVISPAH granules	0					
OZOBAX solution	0					
carisoprodol tab 350mg	93	$1,257.31	$13.52	#67/25 days	34	18 – 63
SOMA tab 250mg	0					
carisoprodol/ASA/codeine	0					
chlorzoxazone tab	15	$517.26	$34.48	#71/28 days	7	34 – 64
cyclobenzaprine tab 5mg	272	$2,565.63	$9.43	#33/20 days	179	11 – 73
cyclobenzaprine tab 10mg	1,111	$11,292.28	$10.16	#44/20 days	693	11 – 72
Fexmid tab 7.5mg	0					
cyclobenzaprine cap 15mg ER (Amrix)	3	$639.90	$213.30	#30/30 days	1	43
dantrolene cap	15	$1,024.38	$68.29	#120/30 days	6	8 – 55
metaxalone tab	15	$596.10	$39.74	#16/47 days	14	32 – 63
methocarbamol tab	195	$2,647.50	$25.63	#64/22 days	108	16 – 64
orphenadrine tab ER	42	$1,140.03	$27.14	#49/26 days	22	27 – 61
tizanidine cap	39	$844.12	$21.64	#73/26days	20	23 – 59
tizanidine tab	416	$5,500.99	$13.22	#71/25 days	196	8 – 76
orphenadrine/ASA/caffeine	0					

*Red font denotes drug is on PA

Amrix (cyclobenzaprine cap ER) & Fexmid PA criteria:

- 60-day trial of cyclobenzaprine 5 mg tab OR cyclobenzaprine 10 mg tab in the past 120 days

Soma 250mg PA criteria:

- Patient has had a 6-month trial of carisoprodol 350mg within the last 120 days

State A: PA criteria for Fleqsuvy:

1. *Member is 12 to 17 years of age or unable to swallow tablets OR*
2. *Step Therapy: Try baclofen tab, chlorzoxazone, cyclobenzaprine IR, methocarbamol, orphenadrine, tizanidine tabs first*

Seglentis & tramadol
Time frame: 4/1/2022 to 6/30/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
tramadol tab 50mg	1,203	$12,771.76	$10.62	#58/15 days	595	15 – 87
tramadol tab 100mg	6	$830.32	$138.39	#90/30 days	2	54, 61
Ultram ER (tramadol tab ER)	0					
tramadol tab 100mg ER	13	$597.18	$45.94	#36/29 days	5	29 – 60
tramadol tab 200mg ER	7	$612.81	$87.54	#30/30 days	3	38 – 47
tramadol tab 300mg ER	6	$384.43	$64.07	#28/28 days	2	21, 41
tramadol/APAP tab 37.5-325	6	$76.33	$12.72	#23/9 days	3	24 – 62
Conzip (tramadol SR biphasic cap)	0					
Synapryn (tramadol susp)	0					
Qdolo (tramadol sol 5mg/ml)	0					
Seglentis (celecoxib/tramadol tab)	0					

*Red font denotes drug is on PA

Ultram ER (tramadol ER)/Conzip/Synaprn PA criteria:

- 30-day trial of tramadol IR in the past 120 days

Health plan PA criteria for Seglentis:

1. *Step Therapy: Patient has tried and failed, or is intolerant to three other non-opioid analgesics (e.g., meloxicam, ibuprofen) in the last 120 days*

INTRODUCTION

- Skeletal muscle relaxants are classified by their pharmacologic properties as either antispastic or antispasmodic agents. The antispastic agents are used to reduce spasticity that interferes with function or daily living activities, such as in cerebral palsy, multiple sclerosis (MS), and spinal cord injuries (*See and Ginsburg 2008a*). The antispastic agents include baclofen, tizanidine, and dantrolene. In contrast, the antispasmodic agents are primarily indicated as adjuncts to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal disorders. Musculoskeletal conditions include lower back pain, neck pain, tension headaches, fibromyalgia, and myofascial pain. The antispasmodic agents include carisoprodol, chlorzoxazone, cyclobenzaprine (tablet and extended-release capsule), metaxalone, methocarbamol, and orphenadrine citrate.
- Dantrolene is also used for the prevention and management of malignant hyperthermia, a potentially fatal disorder that is usually associated with the administration of certain medications during surgery. Intravenous formulations for acute treatment of malignant hyperthermia, including Dantrium Intravenous, Revonto, and Ryanodex, are considered out of the scope of this review (*See and Ginsburg 2008a*).
- Skeletal muscle relaxants are central nervous system (CNS) depressants and exert their effects either at the spinal cord or cerebral level. Well-controlled clinical studies have not conclusively demonstrated whether relief of musculoskeletal pain results from skeletal muscle relaxant effects, sedative effects, or a placebo effect of the drug (*McEvoy 2022*).
- Although skeletal muscle relaxants are not recommended as primary treatment for acute low back pain, 35% of patients are prescribed muscle relaxants for nonspecific low back pain, and 18.5% receive initial muscle relaxant therapy (*Witenko et al 2014*).
- Evidence from clinical trials of skeletal muscle relaxants is limited because of poor methodological design, insensitive assessment methods, and small numbers of patients. The choice of a skeletal muscle relaxant should be based on its adverse effect profile, tolerability, and cost (*See and Ginsberg 2008b, Witenko et al 2014*).
- Skeletal muscle relaxants, including carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine, are on the American Geriatrics Society (AGS) Beers Criteria list for potentially inappropriate medications for use in the elderly. These medications are to be avoided in elderly patients due to poor tolerability. Noted adverse effects are anticholinergic adverse effects, sedation, and increased risk of fractures. In addition, the effectiveness of these drugs at doses tolerated by the elderly is questionable (*AGS 2019*).
- This therapeutic class review focuses on the agents outlined in Table 1 for their respective FDA-approved indications.
- Medispan class: Musculoskeletal therapy agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single entity products	
Fleqsuvy (baclofen)	-
Lioresal* (baclofen)	✔
Lyvispah (baclofen)	-
Gablofen (baclofen)	✔
Ozobax (baclofen)	-
Soma (carisoprodol)	✔
Lorzone (chlorzoxazone)	✔
Parafon Forte DSC*‡ (chlorzoxazone)	✔
Amrix (cyclobenzaprine extended-release)	✔
Flexeril* (cyclobenzaprine)	✔
Dantrium (dantrolene)	✔
Skelaxin (metaxalone)	✔
Robaxin* (methocarbamol)	✔

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Drug	Generic Availability
Norflex* (orphenadrine citrate)	✔
Zanaflex (tizanidine)	✔
Combination products	
Norgesic Forte*† /Orphengesic Forte (orphenadrine/aspirin/caffeine)	✔
Soma Compound with Codeine* (carisoprodol/aspirin/codeine)	✔

*Oral branded products discontinued.
† Orphengesic Forte 50 mg/770 mg/60 mg is another brand combination product that was approved in July 2020; no AB-rated generics exist for this product.
‡Available as chlorzoxazone 250 mg, 375 mg, 500 mg, and 750 mg tablets; also marketed as Lorzone tablets in strengths of 375 mg and 750 mg, which were approved through an abbreviated new drug application (ANDA).

(*Clinical Pharmacology 2022, Drugs@FDA 2022, Drug Facts and Comparisons 2022, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2022*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications*

Generic name	Spastic conditions (includes spinal cord injury, traumatic brain injury, stroke, multiple sclerosis and/or cerebral palsy)	Acute, painful musculoskeletal conditions as an adjunct to rest, physical therapy, and other measures	Malignant hyperthermia
Single entity products			
Baclofen§	✔		
Carisoprodol		✔	
Chlorzoxazone		✔	
Cyclobenzaprine (tablet and extended-release capsule)		✔	
Dantrolene	✔†		✔‡
Metaxalone		✔	
Methocarbamol		✔	
Orphenadrine citrate		✔	
Tizanidine	✔		
Combination products			
Carisoprodol/aspirin/codeine		✔	
Orphenadrine/aspirin/caffeine		✔	

*See product prescribing information for specific indication text and any limitations of use.
†Oral dantrolene only.
‡Oral dantrolene is indicated pre-operatively to prevent or attenuate the development of signs of malignant hyperthermia and following a malignant hyperthermic crisis to prevent recurrence of signs of malignant hyperthermia.
§Limitation of use: The baclofen products Fleqsuvy, Lyvispah, and Ozobax are not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.

(Prescribing information: Amrix 2020, baclofen 2021, carisoprodol/aspirin/codeine 2021, chlorzoxazone 2020, cyclobenzaprine 2020, dantrolene sodium capsule 2020, Fleqsuvy 2022, Gablofen 2020, Lioresal 2019, Lorzone 2017; Lyvispah 2021; methocarbamol tablet 2020; orphenadrine/aspirin/caffeine 2021, orphenadrine citrate extended-release 2019, orphenadrine injection 2019, Ozobax 2020, Robaxin injectable 2017; Skelaxin 2018, Soma 2019, Zanaflex 2020)

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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

- Clinical studies evaluating the utility of skeletal muscle relaxants are limited, poorly designed, and of short duration. Much of the literature supporting the use of these agents was either published decades ago or is lacking in statistical significance and detail.
- One meta-analysis comprising randomized trials (for comparative efficacy and adverse events) and observational studies (for adverse events only) summarized the following study findings (*Chou et al 2004*):
  - There is fair evidence that baclofen, tizanidine, and dantrolene are effective compared to placebo in patients with spasticity (primarily MS).
  - There is fair evidence that baclofen and tizanidine are roughly equivalent in efficacy for patients with spasticity, but insufficient evidence to determine the efficacy of dantrolene compared to baclofen or tizanidine.
  - There is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective compared to placebo in patients with musculoskeletal conditions (primarily acute back or neck pain). Cyclobenzaprine has been evaluated the most in clinical trials and has consistently been found to be effective.
  - There is very limited or inconsistent data regarding the effectiveness of metaxalone, methocarbamol, chlorzoxazone, baclofen, or dantrolene compared to placebo in patients with musculoskeletal conditions.
  - There is insufficient evidence to determine the relative efficacy or safety of cyclobenzaprine, carisoprodol, orphenadrine, tizanidine, metaxalone, methocarbamol, and chlorzoxazone.
- A few head-to-head studies were conducted comparing the efficacy of the skeletal muscle relaxants. One study compared the improvement in pain, muscle tension, and limitation of movement between tizanidine and chlorzoxazone. There were no significant differences noted between treatment groups with respect to study endpoints (*Bragstad et al 1979*). A similarly designed trial was conducted comparing the efficacy of carisoprodol to cyclobenzaprine. Findings revealed no clinically significant differences in pain, muscle spasms, activity impairment, or overall improvement with either treatment group (*Rollings et al 1983*).
- Most available clinical trials evaluated the efficacy of skeletal muscle relaxants in comparison to placebo. The results were mixed. Several studies reported an improvement in endpoints (ie, muscle spasms, muscle cramps, lower back pain) with carisoprodol, tizanidine, cyclobenzaprine, dantrolene, and methocarbamol therapy over placebo *(Casale et al 1988, Serfer et al 2010, Vakhapova et al 2010, Weil et al 2010, Abd-Elsalam et al 2019)*. However, reported findings from another study revealed no difference in similarly reported endpoints between placebo and baclofen *(Dapas et al 1985)*.
- In patients with lower back pain, a randomized controlled trial (n = 320) compared ibuprofen plus placebo vs ibuprofen plus a muscle relaxant (baclofen, metaxalone, or tizanidine). Following a 1-week course of therapy, the addition of baclofen, metaxalone, or tizanidine to ibuprofen did not significantly improve back pain or functioning compared to ibuprofen plus placebo (*Friedman et al 2019*). Similarly, an analysis of 4 studies in patients with acute lower back pain did not find baclofen, metaxalone, tizanidine, orphenadrine, methocarbamol, or cyclobenzaprine to improve outcomes vs placebo (*Abril et al 2022*).
- One open-label trial (n = 52) compared the use of baclofen to transcutaneous electrical nerve stimulation (TENS) over a period of 4 weeks in patients with MS and diagnosed muscle spasm in the lower extremities. This trial demonstrated decreased spasticity measured on the modified Ashworth Scale (MAS) in the baclofen group, but the improvement was less than that in the TENS group. The small size and open-label design of the study limits interpretation of the results (*Shaygannejad et al 2013*).
- A systematic review evaluating the treatment of spasticity in MS included controlled trials and observational studies and concluded that oral baclofen, tizanidine, and gabapentin are first-line options due to their positive data. Use of oral dantrolene as a second-line therapy was supported by 3 small studies. Finally, despite limited evidence, the authors also recommended intrathecal baclofen in patients with severe symptoms with a suboptimal response to oral agents *(Otero-Romero et al 2016*).
- A network meta-analysis evaluating the efficacy of treatments used for spasticity in MS concluded that only cannabinoids and botulinum toxin demonstrated significant advantages over placebo. Of the skeletal muscle relaxants analyzed (baclofen, dantrolene, and tizanidine), none demonstrated an advantage over placebo for producing a

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significant improvement of spasticity. Further, botulinum toxin was found to be superior to both tizanidine and baclofen *(Fu et al 2018*).

- Another study (n = 45) compared tizanidine, cyclobenzaprine, and placebo for the treatment of myofacial pain. Although one of the co-primary endpoints, the modified Severity Symptoms Index (mSSI), demonstrated greater improvements in patients treated with cyclobenzaprine, these results were difficult to interpret due to differences in baseline measures and lack of demonstrated effects on other endpoints. The authors concluded that overall, the use of tizanidine or cyclobenzaprine was not more effective than placebo in the treatment of myofacial pain *(Alencar et al 2014)*.

CLINICAL GUIDELINES

- Few treatment guidelines addressing the appropriate use of skeletal muscle relaxants are available.
  - Guidelines from the Department of Veterans Affairs/Department of Defense on treatment of low back pain, which were published in 2019, state that there is moderate quality evidence supporting use of skeletal muscle relaxants for treatment of acute, but not chronic, low back pain. No evidence was found to support a benefit of one agent over another, therefore, adverse effect profiles of the individual agents should be considered when selecting an agent (*Pangarkar et al 2019*).
  - According to the 2017 American College of Physicians guideline on noninvasive treatments for acute, subacute, and chronic low back pain, clinicians and patients should select nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation initially. If pharmacologic therapy is needed, clinicians may choose nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants *(Qaseem et al 2017).*
  - Guidelines from the American Academy of Neurology and the Child Neurology Society on the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy, which were reaffirmed in 2019, note that for generalized spasticity that warrants treatment, diazepam should be considered for short-term use, and tizanidine may be considered. There are insufficient data to support or refute the use of dantrolene, oral baclofen, or continuous intrathecal baclofen in this setting (*Delgado et al 2010).*
  - Guidelines from the American Academy of Pediatrics (AAP) list dantrolene, baclofen, and tizanidine as potential agents for the management of spasticity, although the potentiation of seizures in children with cerebral palsy is a concern with baclofen. Muscle relaxants have been used with varying success for treatment of dystonia *(Hauer et al 2017).*

SAFETY SUMMARY

- As a class, skeletal muscle relaxants carry some risk of drowsiness and dizziness. Other shared adverse drug reactions include vertigo, nausea, vomiting, impaired vision, and neuropsychiatric effects such as mania, depression, psychosis, confusion, and amnesia.
- Blood dyscrasias such as thrombocytopenia, leukopenia, and aplastic anemia have been reported with dantrolene, metaxalone, methocarbamol, and tizanidine.
- Cardiovascular complaints associated with baclofen administration include palpitations, flushing, bradycardia, hypotension, and hypertension. Facial flushing and orthostatic hypotension have been reported with carisoprodol use. Cyclobenzaprine and methocarbamol are associated with hypotension, palpitations, and syncope. Mild hypotension, symptomatic orthostatic hypotension, and syncope have been described with tizanidine use. Pericarditis, pleural effusions, and pleural fibrosis have been described with chronic therapeutic dantrolene use.
- Gastrointestinal complaints typically include nausea, vomiting, abdominal pain, and diarrhea or constipation. Aspirin-containing products can cause gastrointestinal bleeding.
- Aspirin-containing products should not be used in patients with chicken pox, influenza, or flu symptoms due to risk for Reye's syndrome.
- Idiosyncratic, potentially fatal hepatotoxicity is associated with chronic chlorzoxazone and dantrolene use. Onset of chlorzoxazone-associated hepatotoxicity is variable, typically occurring within weeks of initiation of therapy, but occasionally occurring after ≥ 5 months. Reversible, centrilobular hepatotoxicity has recurred upon rechallenge to chlorzoxazone. Risk factors for fatal hepatic necrosis after dantrolene use include age > 30 years, chronic use > 2 months, female gender, dosages exceeding 300 mg/day, high bilirubin levels, and concomitant illness.
- Carisoprodol is contraindicated for use in patients with acute intermittent porphyria.
- Urinary retention has been associated with baclofen, cyclobenzaprine, orphenadrine, and tizanidine.
- Dantrolene and baclofen use is associated with acneiform and morbilliform rashes, respectively.

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- Allergic-type skin rashes, petechiae, or ecchymoses may occur with chlorzoxazone.
- Cyclobenzaprine and orphenadrine are associated with central and peripheral antimuscarinic symptoms.
- Cyclobenzaprine and metaxalone contain a warning for the potential of serotonin syndrome when used concomitantly with other serotonergic drugs.
- Profound muscle weakness can occur with dantrolene use, resulting in diminished protective airway reflexes.
- Severe allergic reactions have been reported with carisoprodol.
- Baclofen has been associated with movement disorders, memory impairment, muscle weakness, flapping tremor, nystagmus, diplopia, and dysarthria. Increased seizure activity, including status epilepticus, has been observed in patients with pre-existing seizure disorders.
- Sensorineural hearing loss has been described with therapeutic use of intravenous and oral dantrolene.
- Cases of dependence, withdrawal, and abuse have been reported with prolonged use of carisoprodol.
- Seizures have been reported with use of carisoprodol, although these have mostly occurred in the setting of multiple drug overdoses.
- Boxed warnings exist for dantrolene, intrathecal baclofen, and carisoprodol/aspirin/codeine. Dantrolene has a potential for inducing hepatotoxicity and symptomatic hepatitis. Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae such as high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity. Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to cytochrome (CYP) 2D6 polymorphism.
- Specific additional warnings relate to the safe administration of intrathecal baclofen preparations. Based on the risks of life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy. Some phases of therapy must be conducted in an appropriate medical setting. Additionally, a warning in the Gablofen prescribing information notes that the external surfaces of the prefilled syringes are non-sterile, and there are special considerations to prevent contamination during use.
- Skeletal muscle relaxants are on the AGS Beers Criteria list for potentially inappropriate medications for use in the elderly. They are to be avoided in elderly patients due to poor tolerability. Noted adverse effects are anticholinergic adverse effects, sedation, and increased risk of fractures *(AGS 2019)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Baclofen	Tablet, oral solution, oral suspension, oral granules, injection	Oral, Intrathecal	Tablet: 3 times daily Oral solution and suspension: 3 to 4 times daily Oral granules: 3 to 4 times daily Injection: continuous infusion via implantable pump	After the screening trial, intrathecal administration is to be done with a programmable pump labeled for intrathecal administration of baclofen. When discontinuing, the dose should be reduced slowly.
Carisoprodol	Tablet	Oral	3 times daily and at bedtime	To reduce abuse potential, limit duration of therapy to ≤ 3 weeks.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Chlorzoxazone	Tablet	Oral	3 to 4 times daily	
Cyclobenzaprine	Tablet, extended-release capsule	Oral	Tablet: 3 times daily Extended-release capsule: once daily	In patients who cannot swallow the extended release capsules, the contents of the capsule can be sprinkled over applesauce and then swallowed. Use for periods > 2 to 3 weeks is not recommended.
Dantrolene	Capsule	Oral	1 to 4 times daily	The duration of therapy depends on the indication.
Metaxalone	Tablet	Oral	3 to 4 times daily	Taking with food may enhance general CNS depression.
Methocarbamol	Tablet, injection	Oral, IV, IM	Oral: 4 times daily initially; maintenance may be every 4 hours, 3 times daily, or 4 times daily depending on the dose Injection: single dose for moderate symptoms; every 8 hours for severe symptoms for ≤ 3 consecutive days	
Orphenadrine citrate	Extended release tablet, injection	Oral, IV, IM	Oral: twice daily Injection: every 12 hours	
Tizanidine	Capsule, tablet	Oral	3 doses daily (maximum)	Capsules and tablets are not bioequivalent in the fed state.
Combination products				
Carisoprodol/ aspirin/codeine	Tablet	Oral	4 times daily	Maximum duration of therapy is up to 2 to 3 weeks.
Orphenadrine/aspirin/ caffeine	Tablet	Oral	3 to 4 times daily	

Abbreviations: CNS = central nervous system, IM = intramuscular, IV = intravenous.

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(Clinical Pharmacology 2022, Drug Facts and Comparisons 2022, Micromedex 2022)

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Single entity products					
Baclofen	Information is not available.	Safety and efficacy have not been established in children < 12 years (oral) or < 4 years (intrathecal).	Use with caution; dose adjustment may be required.	No dosage adjustment required.	Unclassified† Excreted in breast milk after oral administration; unknown whether intrathecal baclofen is excreted in breast milk; use caution
Carisoprodol	Efficacy, safety, and PK have not been established in patients > 65 years of age	Safety and efficacy have not been established in children < 16 years.	Safety and PK have not been evaluated. Excreted by kidney; use caution.	Safety and PK have not been evaluated. Metabolized in liver; use caution.	Unclassified† Data over many decades of carisoprodol use in pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Excreted in breast milk; use caution
Chlorzoxazone	Information is not available.	Information is not available.	Information is not available.	Discontinue if symptoms of liver dysfunction are observed.	Unclassified† Safe use in pregnancy has not been established Unknown whether excreted in breast milk

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Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Cyclobenzaprine (tablet and extended-release capsule)	Therapy should be initiated with a 5 mg dose and titrated slowly upward. Extended release capsules are not recommended in the elderly.	Safety and efficacy of immediate release tablets have not been established for patients < 15 years. Safety and efficacy of extended release capsules have not been established in pediatric patients.	No information is available.	Mild: start with 5 mg and titrate up. Moderate to severe: not recommended. Extended release capsules: not recommended.	Pregnancy Category B (tablet) Unclassified† (extended-release capsule) Available data from case reports have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Unknown whether excreted in breast milk
Dantrolene	Clinical studies did not include sufficient numbers of subjects age > 65 years to determine whether they respond differently than younger patients. Dose selection should be cautious.	Long-term safety in patients < 5 years has not been established.	Information is not available.	Contraindicated in active liver disease.	Unclassified† Safe use in pregnancy has not been established Should not be used by nursing mothers
Metaxalone	Elderly may be more susceptible to CNS effects. No specific dose adjustment instructions are available.	Safety and effectiveness in children ≤ 12 years of age have not been established.	Use with caution. Contraindicated in significant renal impairment.	Use with caution. Contraindicated in significant hepatic impairment.	Unclassified† Adverse fetal outcomes have not been reported, although the possibility of fetal injury cannot be ruled out.

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Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
					Unknown whether excreted in breast milk
Methocarbamol	Half-life is slightly prolonged. No specific dose adjustment instructions are available.	Safety and effectiveness in children < 16 years have not been established (tablet). Safety and effectiveness have not been established (injection).	No specific dose adjustment instructions are available for the oral tablet. Injection is contraindicated with renal pathology due to the presence of polyethylene glycol in the vehicle.	Clearance is reduced and half-life is prolonged. No specific dose adjustment instructions are available.	Unclassified† Safe use in pregnancy has not been established Unknown whether excreted in breast milk; use caution
Orphenadrine citrate	Information is not available.	Safety and effectiveness have not been established.	Information is not available.	Information is not available.	Pregnancy Category C Unknown whether excreted in breast milk
Tizanidine	Use with caution; clearance is decreased four-fold.	Safety and effectiveness have not been established.	Clearance is reduced; use with caution and with reduced doses in patients with CrCl < 25 mL/min.	Undergoes extensive metabolism; not recommended in patients with hepatic insufficiency.	Unclassified† Unknown whether excreted in breast milk; use caution
Combination products					
Carisoprodol/ aspirin/codeine	Clinical studies did not include sufficient numbers of patients > 65 years of age to determine whether they respond differently than younger patients. Dose selection should be cautious.	Contraindic-ated in patients < 12 years of age, or < 18 years of age after surgery to remove tonsils/adenoi ds. The efficacy and safety in pediatric patients <18 years of age have not been established. Do not use in children with	Avoid in severe renal failure (GFR < 10 mL/min) due to the aspirin component. In patients with less severe disease, use lower starting doses or longer dosing intervals and titrate slowly with close monitoring.	Use lower starting doses or longer dosing intervals and titrate slowly with close monitoring.	Pregnancy Category D Excreted in breast milk; avoid use

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Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
		viral illness due to the risk of Reyes syndrome with aspirin exposure. Avoid use in children aged 12 to 18 years with risk factors for respiratory depression.			
Orphenadrine/ aspirin/caffeine	Information is not available.	Safety and effectiveness have not been established. Use in children < 12 years of age is not recommended	Information is not available.	Information is not available.	Unclassified† Safe use in pregnancy has not been established Unknown whether excreted in breast milk

Abbreviations: CNS = central nervous system, CrCl = creatinine clearance, GFR = glomerular filtration rate, PK = pharmacokinetics.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
*Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.

(Clinical Pharmacology 2022; Micromedex 2022)

CONCLUSION

- Skeletal muscle relaxants are classified by their pharmacologic properties as either antispastic or antispasmodic agents. The antispastic agents include baclofen, tizanidine, and dantrolene; the antispasmodic agents include carisoprodol, chlorzoxazone, cyclobenzaprine (tablet and extended-release capsule), metaxalone, methocarbamol, and orphenadrine citrate. The mechanism of action for most of these agents is unclear but may be related in part to their sedative effects.
- Although clinical data is quite limited, skeletal muscle relaxants generally appear to be more effective than placebo in providing symptomatic relief of acute lower back pain. Skeletal muscle relaxants are generally reserved for patients who require adjunctive pharmacologic therapy and fail over-the-counter analgesics such as acetaminophen or NSAIDs.
- As a class, all skeletal muscle relaxants carry some risk of drowsiness and dizziness. Other shared adverse drug reactions may include vertigo, nausea, vomiting, impaired vision, and neuropsychiatric effects such as mania, depression, psychosis, confusion, and amnesia.
- There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety. Current evidence suggests that skeletal muscle relaxants are not as well tolerated (ie, adverse CNS effects) as NSAIDs. Additionally, clinical superiority relative to NSAIDs has not been established. According to a 2017 American College of Physicians guideline on noninvasive treatments for acute, subacute, and chronic low back pain, clinicians and patients should select

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nonpharmacologic treatment with superficial heat, massage, acupuncture, or spinal manipulation initially *(Qaseem et al 2017).* If pharmacologic therapy is needed, clinicians may choose NSAIDs or skeletal muscle relaxants.

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INTRODUCTION

- Pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, which can be influenced by varying degrees of biological, psychological and social factors (*Raja et al 2020*).
  - Pain is a subjective experience that is unique to the individual and is difficult to identify or quantify by any observer. The type of pain is often classified by its pathophysiologic etiology. Somatic pain results from the activation of pain receptors in cutaneous or deep tissues (skin, bone, joint, or connective tissues) and is generally localized and described as sharp in nature. Visceral pain involves internal areas of the body (organs) and may be poorly localized and described as an aching pain. Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2020*).
    - An individual's reaction or response to treatment of pain can be highly variable. Pain thresholds are highly individualized among patients, and responses to therapy vary between patients and even within the same patient from day to day. Pain management is multifaceted and should incorporate both pharmacological and non-pharmacological measures.
- Tramadol (Ultram) and tapentadol (Nucynta) are both centrally acting opioid analgesics that exert their analgesic effects through opioid agonist properties as well as by blocking the reuptake of norepinephrine and serotonin. Tramadol blocks norepinephrine and serotonin reuptake and has relatively weak μ-opioid receptor activity. Compared to tramadol, tapentadol has greater μ-opioid receptor activity, similar norepinephrine reuptake inhibitor activity, and weaker serotonin reuptake inhibitor activity (*Tsutaoka et al 2015*).
- Tapentadol is a schedule II-controlled substance. In the past, tramadol was not classified as a controlled substance on the Federal level; however, the Drug Enforcement Administration has moved tramadol-containing products into schedule IV as of August 18, 2014 (*Federal Register 2014*).
- Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products. Tramadol is associated with reduced cardiovascular and respiratory side effects when compared to other opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. However, cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing the tramadol-containing products long term (*Leppert et al 2005*). Based on data reported to the National Poison Data System, tapentadol was associated with more toxic effects and severe outcomes than tramadol, consistent with an opioid agonist, whereas tramadol was associated with significantly higher rates of seizures and vomiting than tapentadol (*Tsutaoka et al 2015*).
- This review includes all products that contain tramadol or tapentadol, including short-acting, extended-release (ER) and combination products.
- Medispan class: Tramadol and tapentadol are classified within the opioid agonist class.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ConZip (tramadol ER capsule)	-*
Nucynta (tapentadol tablet)	-
Nucynta ER (tapentadol ER tablet)	-
Qdolo (tramadol hydrochloride solution)	-*
Seglentis (celecoxib/tramadol hydrochloride tablet)	-
Tramadol hydrochloride ER tablet†	✔
Ultracet (tramadol hydrochloride/acetaminophen tablet)	✔
Ultram (tramadol hydrochloride tablet)	✔

* Authorized generics are marketed.
† Brand-name Ryzolt and Ultram ER (tramadol ER tablets) have been discontinued, but generic versions remain available.

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(*Drugs@FDA 2022, Orange Book: Approved drug products with therapeutic equivalence evaluations 2022*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ConZip (tramadol ER capsule)	Nucynta (tapentadol)	Nucynta ER (tapentadol ER)	Qdolo (tramadol solution)	Seglentis (celecoxib/ tramadol)	tramadol ER tablet	Ultracet (tramadol/ acetaminophen)	Ultram (tramadol)
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	✔		✔			✔		
Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.		✔			✔		✔ *	
Management of pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.				✔				✔
Management of neuropathic pain associated with diabetic peripheral neuropathy severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.			✔					

*Indicated for short-term use of 5 days or less.

(*Prescribing information: ConZip 2022, Nucynta 2021, Nucynta ER 2021, Qdolo 2021, Seglentis 2021, tramadol ER tablets 2021, Ultracet 2021, Ultram 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

Tramadol

- Tramadol has been evaluated in various settings for the management of moderate-to-moderately severe pain:
  - In patients with symptomatic osteoarthritis, tramadol (up to 400 mg daily) did not significantly improve the mean final pain intensity score compared to placebo after 3 months of treatment (2.10 vs 2.48 for tramadol and placebo, respectively, on a Likert scale of 0 [no pain] to 4 [extreme pain]; p = 0.082). The mean final pain relief score was superior in the tramadol group (0.43 vs -0.57 on a Likert scale of 3 [complete relief] to -3 [significantly worse]; p = 0.004), and both patient and investigator assessments of treatment favored tramadol over placebo (p = 0.038 and p = 0.001, respectively) (*Fleischmann et al 2001*).
  - In patients with post-tonsillectomy pain, there was no statistically significant difference in 100 mm visual analog scale (VAS) pain scores between tramadol and diclofenac over 2 weeks of treatment (mean 37.8 and 38.4 for tramadol and diclofenac, respectively; p = 0.66) (*Courtney et al 2001*).
  - In some studies, tramadol has been demonstrated to be less effective than nonsteroidal anti-inflammatory drugs (NSAIDs). In studies by O'Donnell et al, a significantly greater proportion of patients with low back pain receiving celecoxib 200 mg twice daily achieved a ≥ 30% improvement from baseline in numeric rating scale (NRS)-pain scale

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scores compared to tramadol 50 mg administered 4 times daily (63.2 vs 49.9%; p < 0.001 in 1 study and 64.1 vs 55.1%; p = 0.008 in another study) (*O'Donnell et al 2009*).
  - A systematic review of 6 double-blind, randomized trials evaluated the efficacy of tramadol compared with placebo or other active interventions for chronic neuropathic pain in adults. The endpoint of 50% or greater reduction in pain intensity, reported in 3 studies, was achieved by 53 and 30% of patients treated with tramadol and placebo, respectively (risk ratio, 2.2; 95% confidence interval [CI], 1.02 to 4.6). The analysis was limited by the use of different pain assessments in the studies and potential risks of bias. The authors stated that there is only modest information available about the use of tramadol in neuropathic pain (*Duehmke et al 2017*).
  - A systematic review evaluated the use of tramadol with or without paracetamol (acetaminophen) for cancer pain; this review included 10 randomized trials. Most comparisons of tramadol to other analgesics were limited to single, small studies and produced little useful information. One study compared the use of oral morphine to a combined group receiving tramadol, tramadol + paracetamol, or codeine + paracetamol and demonstrated reduced efficacy for the combined group compared to the morphine group (42 vs 75% of patients achieving pain reduction > 50% from baseline). In 1 trial comparing tramadol to buprenorphine, the percentage of patients who reported having no worse than mild pain was 88% and 75% in the tramadol and buprenorphine groups, respectively. The authors concluded that there is limited evidence from randomized trials that tramadol produced pain relief in some adults with cancer pain and very low quality evidence that it is not as effective as morphine (*Wiffen et al 2017*).
- Tramadol ER has been compared in clinical studies to placebo, IR tramadol, and buprenorphine:
  - Tramadol ER formulations have consistently demonstrated significant improvements in pain scores compared to placebo in patients with moderate-to-moderately severe chronic pain (*Burch et al 2007, Kean et al 2009, Fishman et al 2007*).
  - In 1 study, tramadol ER 300 mg significantly improved patient global assessment scores compared to placebo (p ≤ 0.05); however, no improvements in Western Ontario and McMaster Universities (WOMAC) pain subscale scores were reported for tramadol ER 100 mg, 200 mg or 300 mg after 12 weeks of treatment (*DeLemos et al 2011*).
  - Compared to tramadol, tramadol ER was associated with a significant reduction in 100 mm VAS scores in an 8-week crossover study of patients with chronic pain (29.9 vs 36.2 mm; p < 0.001) (*Beaulieu et al 2007*).
  - In a 12-week study comparing tramadol ER to the buprenorphine transdermal patch, the least squares mean (LSM) change from baseline in Box Scale-11 pain score between treatments was -0.17 (95% CI, -0.89 to 0.54; p value not reported), which was within the non-inferiority margin, demonstrating that buprenorphine was non-inferior to tramadol ER in patients with osteoarthritis of the hip or knee (*Karlsson et al 2009*).
- A double-blind, randomized controlled trial (N = 637) compared Seglentis (celecoxib/tramadol) to tramadol, celecoxib, and placebo for the management of moderate-to-severe acute post-operative pain following unilateral first metatarsal osteotomy with internal fixation (bunionectomy). The primary efficacy endpoint was time-weighted summed pain intensity difference over 48 hours (SPID48). It was found that patients in the Seglentis group had statistically significantly better mean SPID48 scores than any of the other groups (*ClinicalTrials.gov [NCT03108482], Seglentis Prescribing Information 2021*).
- The combination tramadol/acetaminophen has been compared to placebo, other combination opioid/acetaminophen products, and NSAIDs:
  - In patients with low back pain (n = 318), the combination of tramadol/acetaminophen was significantly more effective compared to placebo with regard to changes in VAS pain scores over 3 months (44.4 vs 52.3 mm; p = 0.015) (*Ruoff et al 2003*).
  - In a double-blind, placebo- and active-controlled, single-dose study comparing tramadol/acetaminophen to hydrocodone/acetaminophen in patients undergoing molar removal, both treatments provided statistically significant pain relief compared to placebo (p < 0.024); however, the differences were not significantly different from one another during the 8-hour evaluation period (*Fricke et al 2002*).
  - In an 8-week study comparing tramadol/acetaminophen to meloxicam or aceclofenac (not available in the U.S.) in patients with osteoarthritis, there was a similar improvement in WOMAC pain scores between the treatment arms (6.75 vs 6.51, respectively; p value not reported). Similarly, there was no statistically significant difference in the percentage of patients who reported pain relief with tramadol/acetaminophen compared to the NSAIDs (68.2 vs 78.7%; p > 0.05) (*Park et al 2012*).
  - Alfano et al reported that tramadol/acetaminophen was associated with significantly lower verbal rating scale pain scores compared to codeine/acetaminophen (1.4 ± 0.76 vs 2.52 ± 0.86; p < 0.001) in patients undergoing surgical procedures; however, the trial was only 2 days in duration (*Alfano et al 2011*).

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- The results of a 4-week trial in patients with low back pain and/or osteoarthritis pain demonstrated similar improvements in pain scores between tramadol/acetaminophen and codeine/acetaminophen (no p values reported; comparability was concluded because the bounds of the 95% CI of the difference in summary efficacy scores were < 10% of the maximum possible score) (*Mullican et al 2001*).

- A systematic review evaluated 22 randomized controlled trials evaluating tramadol with or without acetaminophen vs placebo in 6496 patients with pain due to osteoarthritis. Based on moderate quality of evidence, tramadol alone or with acetaminophen had no important benefit on mean pain reduction or function compared to the placebo control. Slightly more tramadol-treated and tramadol/acetaminophen-treated patients improved by 20% or more in pain compared to the placebo group (*Toupin et al 2019*).
- A systematic review and meta-analysis of 207 studies (N = 32,959) evaluated the comparative efficacy of outpatient treatments for acute pain from non-low back musculoskeletal injuries. Overall, topical NSAIDs, followed by oral NSAIDs and acetaminophen with or without diclofenac, showed the most convincing and attractive benefit-harm ratio for patients with acute pain from non-low back musculoskeletal injuries. Tramadol was no more effective than placebo at providing pain relief ≤ 2 hours after treatment (mean difference [MD] 0.95, 95% CI, -0.80 to 2.70) and was among the most harmful for incidence of central nervous system (CNS) and neurological related adverse events, in addition to fentanyl and opioid plus acetaminophen combinations (*Busse et al 2020).*

Tapentadol

- Several clinical studies have demonstrated the superior analgesic efficacy of tapentadol compared to placebo in the treatment of moderate to severe pain (*Daniels et al 2009, Hale et al 2009, Hartrick et al 2009, Kleinert et al 2008, Lee et al 2014, Stegman et al 2008; Viscusi et al 2019*). In addition to reducing pain intensity and providing pain relief, therapy with tapentadol was associated with a shorter time to 50% pain relief, a longer time to first dose of rescue medication, a decrease in the use of rescue medications, and a greater number of treatment responders compared to placebo (*Daniels et al 2009, Kleinert et al 2008, Lee et al 2014, Stegman et al 2008*).
- Several trials compared the efficacy of tapentadol to oxycodone:
  - In 1 study of patients who were candidates for joint replacement surgery, tapentadol significantly reduced pain intensity scores compared to placebo and was non-inferior to oxycodone for analgesia. In addition, the incidence of gastrointestinal-related adverse events was significantly lower with tapentadol compared to oxycodone ($p < 0.001$) (*Hartrick et al 2009*).
  - In a short-term (4 day) study of postoperative pain in patients who had undergone bunionectomy, both tapentadol and oxycodone significantly lowered summed pain intensity scores after 3 days of treatment compared to placebo ($p \leq 0.05$ for all); however, only the tapentadol 100 mg doses demonstrated statistically significant differences compared to placebo on day 4 ($p = 0.0284$). Tapentadol treatment was associated with a reduction in nausea, dizziness, vomiting, and constipation compared to oxycodone (p values not reported) (*Stegman et al 2008*).
  - A 3-month safety study demonstrated a lower incidence of gastrointestinal treatment-related adverse events with tapentadol compared to oxycodone (44.2 vs 63.5%). Odds ratios (tapentadol:oxycodone) showed that the incidences of somnolence and dizziness were similar. Nausea, vomiting, and constipation were significantly less likely with tapentadol compared with oxycodone. Tapentadol significantly lowered the incidence of withdrawal symptoms compared to oxycodone (17 vs 29%; $p < 0.05$) (*Hale et al 2009*).
  - A short-term (10-day) study in patients with low back pain and associated radicular leg pain demonstrated that pain relief with tapentadol was non-inferior to oxycodone. In this study, tapentadol was associated with a lower incidence of vomiting and constipation (*Biondi et al 2013*).
  - In a multicenter, randomized controlled trial in non-breastfeeding women post elective cesarean section, tapentadol therapy did not result in superior pain control or improved tolerability as compared to oxycodone (*French-O'Carroll et al 2019*).
- The effectiveness of the ER formulation of tapentadol has been demonstrated in several clinical trials:
  - In a 12-week trial of adults with osteoarthritis of the knee, significant pain relief was achieved with tapentadol ER compared to placebo (LSM difference, -0.7; 95% CI, -1.04 to -0.33). Oxycodone controlled-release (CR) reduced the average pain intensity compared to placebo for the overall maintenance period (LSM difference vs placebo, -0.3), but was not statistically significantly lower at week 12 of the maintenance period (LSM, -0.3; p value not reported). There was no significant difference in the proportion of patients in the tapentadol group and the placebo group achieving a ≥ 30% reduction in average pain intensity at week 12 of the maintenance period (43 vs 35.9%, respectively; $p = 0.058$). Significantly fewer patients in the oxycodone CR group achieved this improvement compared to placebo (24.9 vs

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35.9%; p = 0.002). A higher percentage of patients achieved a ≥ 50% reduction in average pain intensity from baseline at week 12 with tapentadol ER compared to placebo (32 vs 24.3%; p = 0.027), while significantly fewer oxycodone CR-treated patients achieved this improvement compared to placebo (17.3 vs 24.3%; p = 0.023) (*Afilalo et al 2010*).

- Buynak et al evaluated tapentadol ER compared to oxycodone ER and placebo in adults with moderate to severe lower back pain. The mean change in pain intensity from baseline to week 12 was significantly greater for tapentadol ER (LSM difference, -0.8; p < 0.001) and oxycodone CR (LSM difference, -0.9; p < 0.001) compared to placebo. The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for the tapentadol ER group and -2.1 for the placebo group (LSM difference, -0.7; p < 0.001) (*Buynak et al 2010*).
- A randomized trial compared tapentadol ER to oxycodone/naloxone ER in patients with severe, chronic low back pain with a neuropathic component. For the primary efficacy endpoint, change from baseline in the NRS-3 pain scale, tapentadol ER was superior to oxycodone/naloxone ER (LSM change, -3.7 vs -2.7; p < 0.001 for non-inferiority and p = 0.003 for superiority) (*Baron et al 2016[a]*). In addition, incidences of constipation and vomiting in this study were significantly lower with tapentadol ER compared to oxycodone/naloxone ER (p ≤ 0.045) (*Baron et al 2016[b]*).
- Schwartz et al evaluated tapentadol ER in adults with painful diabetic peripheral neuropathy in a 12-week, randomized withdrawal trial. Patients were titrated to an optimal dose of tapentadol ER during a 3-week open-label phase. Patients with at least a 1-point reduction in pain intensity were randomized to continue tapentadol ER or switch to placebo during a 12-week double-blind phase. The LSM change in average pain intensity from the start of the double-blind treatment period to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0 in the tapentadol ER group, indicating no change in pain intensity (LSM difference, -1.3; 95% CI, -1.7 to -0.92; p < 0.001). From pre-titration to week 12 of double-blind treatment, a ≥ 30% improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (p = 0.017). A ≥ 50% improvement in pain intensity was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients (p = 0.028) (*Schwartz et al 2011*).
- A second, 12-week, randomized withdrawal trial of tapentadol ER in adults with painful diabetic peripheral neuropathy was performed by Vinik et al. In this trial, the mean change in average pain intensity from the start of the double-blind treatment period to week 12 was 1.3 in the placebo group, indicating a worsening in pain intensity, and 0.28 in the tapentadol ER group (LSM difference, -0.95; 95% CI, -1.42 to -0.49; p < 0.001). From pre-titration to week 12 of double-blind treatment, a ≥ 30% improvement in pain intensity was observed in 55.4% of tapentadol ER-treated patients and 45.4% of placebo-treated patients (p = 0.032). A ≥ 50% improvement in pain intensity was observed in 40.4% of tapentadol ER-treated patients and 28.9% of placebo-treated patients (p = 0.015) (*Vinik et al 2014*).
- Kress et al evaluated tapentadol ER compared to placebo and morphine CR for managing moderate to severe malignant tumor-related pain. Patients were randomized and titrated to an optimal dose of tapentadol ER (100 mg to 250 mg twice daily) or morphine sulfate CR (40 mg to 100 mg twice daily) over 2 weeks. Patients who completed titration and had adequate pain control continued into a 4-week maintenance period during which patients who received morphine CR continued on the same medication and patients who received tapentadol ER were re-randomized to continue tapentadol ER or switch to placebo. Criteria for response during each phase were based on completion of the phase, a pain intensity score < 5, and a mean total daily dose of ≤ 20 mg/day of rescue medication (morphine sulfate IR). Based on responder rates at the end of titration, tapentadol ER was determined to be non-inferior to morphine sulfate CR (76 vs 83%, respectively). During the titration phase, incidences of treatment-related adverse events were 50% with tapentadol ER and 63.9% with morphine CR; nausea, vomiting, and dry mouth occurred less commonly with tapentadol ER than with morphine CR. During the maintenance phase, the adjusted responder rate was significantly higher with tapentadol ER (64.3%) than with placebo (47.1%) (p = 0.02). (*Kress et al 2014*).
- Imanaka et al evaluated tapentadol ER compared to oxycodone CR in Japanese and Korean patients with cancer-related pain. The primary efficacy endpoint, mean change in average pain intensity on an 11-point scale, was -2.69 and -2.57 in the tapentadol ER and oxycodone CR groups, respectively. Tapentadol was demonstrated to be non-inferior to oxycodone CR for the primary endpoint. The percentage of patients responding with ≥ 30% reduction in pain intensity was 63.5 and 59% in the tapentadol ER and oxycodone CR groups, respectively, and the percentage responding with a ≥ 50% improvement was 50 and 42.4%, respectively. In this study, tapentadol was also associated with a slightly lower incidence of some gastrointestinal adverse events than oxycodone CR (*Imanaka et al 2013*).
- In a pooled analysis of 3 studies of 2968 patients with pain due to osteoarthritis or nonmalignant lower back pain, tapentadol ER was significantly more effective compared to placebo over a 3-week treatment phase (LSM difference, -0.6; 95% CI, -0.8 to -0.39; p < 0.001) and for the overall 12-week maintenance period (-0.5; 95% CI, -0.73 to -0.34; p

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< 0.001). A similar analgesic effect was reported in patients receiving oxycodone CR; however, the responder rate was higher with tapentadol ER (p < 0.001). A significantly higher proportion of patients receiving tapentadol ER achieved a ≥ 30% and ≥ 50% improvement in pain intensity from baseline compared to oxycodone CR and placebo (p < 0.001 for both) (*Lange et al 2010*).

- A systematic review and meta-analysis of 13 studies (N = 12,814) evaluated the safety and efficacy of tapentadol IR vs oxycodone IR for acute pain. Tapentadol IR 50 mg was associated with less pain control compared with oxycodone IR (standardized mean difference [SMD] 0.25, 95% CI, 0.06 to 0.44, p < 0.01). However, there were no significant differences at higher doses (eg, 75, 100 mg) or when a titration strategy was used (*Wang et al 2020*).
- No published studies were identified that compared the analgesic efficacy of tramadol and tapentadol.

CLINICAL GUIDELINES

- Guidelines from the American College of Physicians (ACP) state that in patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with NSAIDs as first-line therapy, and tramadol or duloxetine as second-line therapy (*Qaseem et al 2017*).
- The ACP/American Academy of Family Physicians (AAFP) guideline for the nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults suggest the use of topical NSAIDs with or without menthol gel as first-line therapy to reduce pain and improve physical function. Second-line recommendations include oral NSAIDs, acetaminophen, acupressure, and/or electrical nerve stimulation. The guideline recommends against the use of opioids, including tramadol (*Qaseem et al 2020*).
- According to the American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, knee, or hip, initial pharmacological approaches include oral NSAIDs, intra-articular steroids, acetaminophen, tramadol, and duloxetine. For the hand and knee, topical NSAIDS, chondroitin, and topical capsaicin are also treatment options (*Kolasinski et al 2020*).
- A guideline from the American Academy of Orthopedic Surgeons (AAOS) states that oral narcotics, including tramadol, result in significant increase of adverse events and are not effective at improving pain or function for treatment of osteoarthritis of the knee (*AAOS 2021*).
- A practice guideline from the American College of Occupational and Environmental Medicine (ACOEM) notes that tramadol may be a better option than more potent opioids for management of chronic non-cancer pain. However, it notes that with long-term use, especially at higher doses, it may be considered equivalent to other opioids (*Hegmann et al 2014*).
- A guideline from the Orthopedic Trauma Association provides recommendations for pharmacologic and nonpharmacologic pain management strategies in acute musculoskeletal injury; this guideline includes detailed recommendations for multimodal analgesia regimens after specific injuries/procedures, as well as tapering schedules for opioid prescriptions, including tramadol (*Hsu et al 2019*).
- The National Comprehensive Cancer Network (NCCN) guidelines for the supportive care of adult patients with cancer pain state that optimal management of cancer pain is often accomplished by using a combination of pharmacologic and nonpharmacologic therapies. Pharmacologic therapies may include nonopioid analgesics (eg, acetaminophen, NSAIDs), adjuvant analgesics for neuropathic pain (eg, antidepressants, anticonvulsants, topical agents, corticosteroids), and/or opioid analgesics. Tramadol is less potent than other opioid analgesics such as morphine. Use of tapentadol is well-established for the treatment of non-cancer pain and neuropathic pain, and data suggest it may have a lower incidence of gastrointestinal adverse effects than oxycodone. However, more trials are needed to understand its role in the management of cancer pain (*NCCN Adult Cancer Pain 2022*).
- The 2022 American Diabetes Association (ADA) guideline recommends pregabalin, duloxetine, and gabapentin as initial pharmacologic therapy options for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first- or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker. Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options (*ADA 2022*).
- A guideline from the American Academy of Neurology (AAN) states that clinicians should not use tramadol and tapentadol for the treatment of painful diabetic neuropathy. If patients are currently on either drug, clinicians may offer the option of tapering off these medications and discuss alternative nonopioid therapies (*Price et al 2022*).
- Based on an updated systematic review and meta-analysis, the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) gives tramadol a weak recommendation for use in the

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management of neuropathic pain, recommending it as a second-line agent. Medications with a strong recommendation for use (first-line agents) include gabapentin, pregabalin, duloxetine, venlafaxine, and tricyclic antidepressants. Tapentadol has an inconclusive recommendation for neuropathic pain based on inconsistent findings (*Finnerup et al 2015*).

- The Canadian Pain Society recommends tramadol as a second-line agent for management of chronic neuropathic pain, and recommends tapentadol as a fourth-line agent. First-line agents include the gabapentinoid class of anticonvulsants, serotonin noradrenaline reuptake inhibitors, and tricyclic antidepressants (*Mu et al 2017*).
- The American Society of Interventional Pain Physicians (ASIPP) also published practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring.
    - Recommended agents for first line for moderate pain include tramadol, codeine, tapentadol, or hydrocodone. For severe pain, first line therapy may include hydrocodone, oxycodone, hydromorphone, or morphine.
  - Consider up to 40 morphine milligram equivalent (MME) as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose.
  - Avoid long-acting opioids for the initiation of opioid therapy.
  - Understand and educate patients of the effectiveness and adverse consequences.
  - There is similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids.
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain.
- A guideline from the Center for Disease Control and Prevention (CDC) recommends that nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function outweigh the risks to the patient. If starting opioid therapy, clinicians should prescribe IR opioids instead of ER/LA opioids. The IR opioids should be prescribed at the lowest effective dosage and for no greater quantity than needed for the expected duration of pain severe enough to require opioids (*Dowell et al 2016*).

SAFETY SUMMARY

- In July 2020, the FDA issued a drug safety communication recommending that healthcare professionals discuss the availability of naloxone with all patients receiving opioid pain relievers and consider prescribing it for patients who are at high risk or have a close contact at risk of overdose or accidental ingestion; the prescribing information of the tapentadol- and tramadol-containing products have been updated accordingly (*FDA News Release 2020, FDA Drug Safety Communication 2020*).
  - Prescribing of naloxone should be considered based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. Naloxone should also be considered if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.
- Tapentadol- and tramadol-containing products are generally contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or where resuscitation is not feasible, known or suspected gastrointestinal obstruction, hypersensitivity, and with concurrent use of monoamine oxidase inhibitors (MAOIs) within the last 14 days.
- Tramadol-containing products are contraindicated in children < 12 years of age and for postoperative management in children < 18 years of age following tonsillectomy and/or adenoidectomy.
- Tramadol- and tapentadol-containing products are included in the Risk Evaluation and Mitigation Strategy (REMS) program, to ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse. Under the requirements of the REMS, drug companies that manufacture approved opioid analgesics must ensure that training is available to healthcare providers involved in the treatment and monitoring of patients with pain. The education is intended to assist healthcare provers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The REMS also consists of training and education materials for patients, including a medication guide and a patient counseling guide, which outline patient roles and responsibilities regarding pain treatment (*FDA REMS 2021*).

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- All tramadol- and tapentadol-containing products carry a boxed warning regarding the risks of addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion and risks from concomitant use with benzodiazepines and other CNS depressants.
  - Each patient should be assessed for risk of opioid addiction, abuse, or misuse prior to prescribing tramadol and should be monitored for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids but use in such patients necessitates intensive counseling about the risks and proper use, along with intensive monitoring for signs of addiction, abuse, and misuse.
  - Patients on tramadol-containing products should be closely monitored for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases. Patients with chronic pulmonary disease, and elderly, cachectic or debilitated patients are at higher risk. Opioids can cause sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia. For patients who present with central sleep apnea, decreasing opioid dosage by tapering should be considered. Patients and caregivers should be educated on how to recognize respiratory depression with an emphasis on calling 911 in the event of known or suspected overdose.
- Tramadol- and tapentadol- containing products should not be abruptly discontinued in patients with physical dependence. No standard opioid tapering schedules are suitable for all patients so tapering should be individualized.
- Tramadol-containing products also carry additional boxed warnings regarding the risks of concomitant use of cytochrome P450 (CYP) inducers and inhibitors and ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children.
- Ultracet has an additional boxed warning noting that acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death.
- Nucynta ER has an additional boxed warning regarding co-ingestion of alcohol, which may lead to potentially fatal outcomes.
- Tramadol and tapentadol may increase the risk of seizures and serotonin syndrome in patients using concomitant serotonergic drugs. Based on data reported to the National Poison Data System, tramadol is associated with a greater risk of seizures than tapentadol (*Tsutaoka et al 2015*).
- Tramadol and tapentadol both have warnings related to CNS depression, and may have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression. Tramadol appears to be associated with reduced cardiovascular and respiratory side effects when compared to opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. However, cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing tramadol-containing products long-term (*Leppert et al 2005*). Based on data reported to the National Poison Data System, tapentadol was associated with more toxic effects and severe outcomes than tramadol, consistent with an opioid agonist (*Tsutaoka et al 2015*).
- Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype. This can lead to increased exposure to an active metabolite. Children < 12 years of age may be more susceptible to the respiratory depressant effects of tramadol, and is contraindicated in this age group. Use of tramadol should be avoided in adolescents aged 12 to 18 who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.
- Tramadol- and tapentadol-containing products may produce adrenal insufficiency and severe hypotension.
- Tramadol- and tapentadol-containing products should be used with caution in patients with increased intracranial pressure or other head injury, and should be avoided in patients with impaired consciousness or coma.
- Tramadol-containing products carry an additional warning for the risk of suicide.
- Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products. Tramadol is associated with a higher risk of vomiting than tapentadol (*Tsutaoka et al* 2015).
- Tramadol-containing products carry a warning and precaution for the increased risk of hyponatremia; most cases occurred in females over the age of 65 years old and within the first week of therapy.
- Tramadol-containing products carry a warning and precaution for the increased risk and hypoglycemia; in most cases, patients had predisposing risk factors (eg, diabetes).
- Ultracet carries additional warnings related to the acetaminophen component (eg, hepatotoxicity, serious skin reactions, concomitant use with other acetaminophen-containing products), while Seglentis carries additional warnings related to the celecoxib component (eg, cardiovascular thrombotic events; gastrointestinal bleeding, ulceration, and perforation;

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hypertension; heart failure and edema; hepatotoxicity; renal toxicity and hyperkalemia; serious skin reactions; exacerbation of asthma related to aspirin sensitivity; Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]; fetal toxicity; hematological toxicity; masking of inflammation and fever).

Special populations

- Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with tapentadol and tramadol are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Pregnant women should be advised of the potential risk to the fetus.
  - Additionally, breastfeeding is not recommended during treatment with tapentadol and tramadol due to the risk of serious adverse reactions, including excess sedation and respiratory depression in the infant.
- Elderly patients (aged ≥ 65 years) may have increased sensitivity to tapentadol and tramadol. They should be monitored closely, especially during initiation and titration.
- Nucynta IR/ER and tramadol ER products should not be used in patients with severe renal impairment; dose adjustment is recommended for the tramadol IR products in these patients.
- Patients with severe hepatic impairment should avoid use of Nucynta IR/ER, tramadol ER products, and Ultracet; Ultram may be used in these patients but modification of the dosing regimen is recommended.

Key drug interactions

- Concomitant use with MAOIs may lead to an increased risk of seizures or serotonin syndrome; use only with great caution.
- Additive serotonergic effects may occur when co-administered with serotonergic drugs.
- CYP3A4 and/or CYP2D6 inhibitors may reduce the metabolism of tramadol, thereby increasing the risk of adverse events. Carbamazepine increases tramadol metabolism and may significantly reduce its analgesic efficacy.
- Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
ConZip (tramadol ER)	capsules	Oral	Once daily	Patients should be advised to swallow whole and not to cut, chew, dissolve, or crush the capsule.
Nucynta (tapentadol)	tablets	Oral	Every 4 to 6 hours	May be given with or without food.
Nucynta ER (tapentadol ER)	tablets	Oral	Twice daily	Patients should be advised to swallow whole and not to cut, chew, dissolve, or crush the tablet.
Qdolo (tramadol hydrochloride solution)	Solution	Oral	Every 4 to 6 hours	Patients should be instructed on how to measure and take the correct dose. Patients should be strongly advised to always use a calibrated oral syringe or other oral dosing device, with metric units of measurements (eg, mL) and to never use household teaspoons or tablespoons to measure.

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Seglentis (celecoxib/tramadol)	tablets	Oral	Every 12 hours as needed	
tramadol ER	tablets	Oral	Once daily	Patients should be advised to swallow whole and not to cut, chew, dissolve, or crush the tablet.
Ultracet (tramadol/acetaminophen)	tablets	Oral	Every 4 to 6 hours	Maximum duration of treatment is 5 days.
Ultram (tramadol)	tablets	Oral	Every 4 to 6 hours	

See the current prescribing information for full details.

CONCLUSION

- Tramadol and tapentadol are both centrally acting opioid analgesics that produce analgesia through opioid agonist properties and by blocking the reuptake of norepinephrine and serotonin.
- Tramadol is available generically in IR and ER formulations as well as in combination with acetaminophen; it is also available in combination with celecoxib (branded product). ConZip, a branded capsule formulation that contains tramadol in a combination of IR and ER components, is also available along with its authorized generic. Tapentadol is available as Nucynta and Nucynta ER, and there are currently no generics available for tapentadol-containing products.
- Clinical studies have generally demonstrated that tramadol and tapentadol are effective in the management of moderate-to-moderately severe chronic pain and for the relief of moderate-to-severe conditions of acute pain including low back pain, osteoarthritis, and diabetic peripheral neuropathy. Clinical studies evaluating tapentadol (both IR and ER) have demonstrated significant pain relief compared to placebo with a similar analgesic profile compared to oxycodone (both IR and ER).
- Both formulations of tapentadol may generally be associated with a more favorable adverse event profile compared to oxycodone. There is a risk of seizures with both tramadol and tapentadol products; however, the risk appears to be higher with tramadol. Tapentadol products are classified as schedule II-controlled substances, and tramadol-containing products are classified as schedule IV controlled substances.
- Current clinical guidelines recommend tramadol as a second-line therapy for the treatment of chronic low back pain and neuropathic pain (*Finnerup et al 2015, Mu et al 2017, Qaseem et al 2017*). According to the ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, knee, or hip, initial pharmacological approaches include oral NSAIDs, intra-articular steroids, acetaminophen, tramadol, and duloxetine; however, a guideline from the AAOS does not recommended oral narcotics, including tramadol, for treatment of osteoarthritis of the knee (*AAOS 2021, Kolasinski et al 2020*). Guidelines from the ACP/AAFP do not recommend opioids (eg, tramadol or tapentadol) for acute pain from non-low back, musculoskeletal injuries (*Qaseem et al 2020*). For cancer pain, optimal management is often accomplished by using a combination of pharmacologic and non-pharmacologic therapies Tramadol is considered less potent than other opioid analgesics such as morphine. Tapentadol may have a role in the management of cancer pain, but more trials are needed (*NCCN 2022*). For the management of chronic non-cancer pain, guidance suggests that tramadol may be a better option than more potent opioids but may be an equivalent choice when used long-term (*Hegmann et al 2014*). Guidelines for diabetic neuropathy generally do not recommend the use of tramadol and tapentadol (*ADA 2022*, *Price et al 2022*).
- The CDC recommends nonpharmacologic therapy and nonopioid pharmacologic therapy as first-line treatment options for chronic pain. Opioid therapy should only be considered if expected benefits outweigh the risks, and if so, patients should be started on IR opioids at the lowest effective dosage. Patients should be given no greater quantity than needed for the expected duration of pain severe enough to require opioids (*Dowell et al 2016*).
- New recommendations from the FDA suggest that healthcare professionals discuss the availability of naloxone with all patients receiving opioid pain relievers and consider prescribing it for patients who are at high risk or have a close contact at risk of overdose or accidental ingestion.

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