South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

December 8, 2023

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

December 8, 2023
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Location:
Ramada by Wyndham Sioux Falls Airport Hotel
1301 West Russell Street
Sioux Falls, SD

Meeting Room – Galley 3

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **PA approval comparison**

New business
- **Jornay PM & Stimulant Review**
- **FDA Advisory Letter on Stimulants**
- **Epidemiology Presentation**
- **Humira shift to Skyrizi**
- **Ilaris new indication**
- **Nuzyra**
- **Vowst**

Public input accepted after individual topic discussion
Next meeting date March 1, 2023 & adjournment

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

Friday, September 8, 2023
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Matthew Stanley, DO	X
Dana Darger, RPh, Chair	X	Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	X	Clarissa Barnes, MD, DSS Staff	X
Kelley Oehlke, PharmD	X	Mary Carpenter, MD, DSS Staff	X
Lenny Petrik, PharmD	X	Mike Jockheck, DSS Staff	X
Heather Preuss, MD	X	Taylor Koerner, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:02 pm. The minutes of the March meeting were presented. Ladwig made a motion to approve. Baack seconded the motion. The motion was unanimously approved.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from April 1, 2023, to June 30, 2023. A total of 1,848 PAs were reviewed of which 89 requests (4.8%) were received via telephone, 102 requests (5.5%) were received via fax, 649 (35.2%) were reviewed electronically, and 1,007 (54.5%) PAs were received via ePA. There was a 25% decrease in PAs received compared to the previous quarter which was the result of the PAs leveling off after the 25% increase from the ePA implementation.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from April 1, 2023, to June 30, 2023. The top five therapeutic classes based on paid amount were disease-modifying anti-rheumatic agents, skin and mucous membrane agents, atypical antipsychotics, cystic fibrosis correctors, and amphetamines. These top 15 therapeutic classes comprise 22.5 % 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 9.7% of total claims. There was an increase in hepatitis C medication utilization. Baack commented on the automatic screening performed for hepatitis C for all pregnant mothers.

Old Business

Opioid CDUR edits

The committee reviewed changing the opioids and benzodiazepines CDUR edit from message to soft edit. Baack made a motion to accept the change from message to soft edit for opioids and benzodiazepines. Ladwig seconded the motion. Darger inquired if there was any public testimony. There was none. The motion was approved unanimously.

Opioid update

The committee reviewed 2Q2023 opioid outcomes compared to previous quarters from the opioid initiatives. There was a decrease in opioid utilization and utilizers during 2Q2023 with corresponding decrease in total eligibility and utilizers. Darger inquired if there was any public comment. There was none.

New Business

Vyvanse dose limit

The committee reviewed members exceeding Vyvanse 70mg/day. Darger commented literature did not support any advantages in taking doses over 70mg/day. Stanley was skeptical that increase in doses are clinically necessary. After discussion, Lagwig made a motion to add a dose limit of 70mg/day on Vyvanse. Stanley seconded the motion. Darger inquired if there were any public comments. There were none. The motion was approved unanimously.

Qelbree

Jockheck clarified the next agenda items. The committee reviewed the utilization of Qelbree and proposed step therapy with trial of atomoxetine or stimulants. Stanley commented regarding the onset of action, stimulants are immediate acting while the full response from atomoxetine takes 6 – 12 weeks; and to ensure accounting for side effects. Darger and Stanely discussed allowing different trial durations for atomoxetine vs stimulants; 30-day trial for stimulant and 60- day trial for atomoxetine. Darger inquired if there were any public comments. Patrick Harvey with Medical Affairs from Supernus Pharmaceuticals provided public testimony. Stanley made a motion to add step therapy to Qelbree with 60-day trial of atomoxetine or 30-day trial of stimulants in the last 180 days. Baack seconded the motion. The motion was approved unanimously.

Adalimumab

Jockheck provided information that there is a significant difference between the net price of biosimilars to brand. The proposed step therapy is a trial and failure of Humira before biosimilars. Darger inquired if there were any public comments. Baack made a motion add this step therapy and Van Gilder seconded the motion. The motion was approved unanimously.

Growth hormones

The committee reviewed utilization of growth hormones and proposed step therapy of the preferred products. Baack commented on the current shortages of both Genotropin and Norditropin and to allow for substitution of the preferred product when shortages occur. Baack made the motion to add Genotropin and Norditropin as preferred. Petrik seconded the motion. Darger inquired if there were any public comments. Paul Miner, National Director for Ascendis Pharmacy, provided public testimony. After discussion, Baack made the motion for trial and failure of one preferred product before allowing a second line product. Preuss seconded the motion. The motion was approved unanimously.

Rukobia

Rukobia clinical information was presented for review. Due to the narrow use profile of Rukobia, the need for clinical PA was discussed. Baack made the motion to add PA like health plan A. Van Gilder seconded the motion. Darger inquired if there was any public comment. There was none. The motion was approved unanimously.

Sotyktu

Sotyktu clinical information was presented for review. The committee discussed adding PA using the state's general psoriasis PA criteria for Sotyktu. The committee also reviewed the general psoriasis PA criteria to determine if any changes should be made. After review, Baack made the motion to carry on with the current plaque psoriasis PA and to add this PA criteria for Sotyktu. Van Gilder seconded the motion. Darger inquired if there was any public comment. There was none. The motion was approved unanimously.

Darger's last meeting will be in December. Van Gilder will assume Chairperson duties going forward.

Adjournment

The next meeting is scheduled on December 8, 2023, in Sioux Falls. The March meeting is tentatively scheduled for March 1, 2024. Baack made the motion to adjourn the meeting and Van Gilder seconded the motion. The motion to adjourn the meeting was unanimous, and the meeting adjourned at 2:32 pm CT.

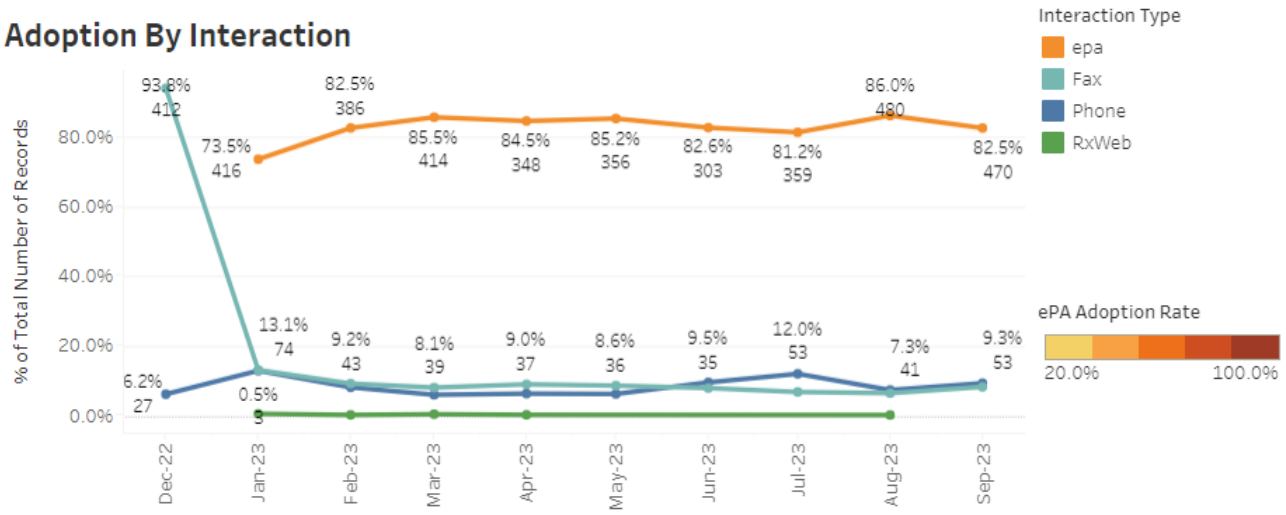
PA Report
7/1/2023 – 9/30/2023

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	2169	2169	0	100.00%	0.00%
Urgent	247	247	0	100.00%	0.00%
Grand Total	**2,416**	**2,416**	**0**		

Priority	Standard	Urgent
ePA	1,093	216
Fax	105	8
Phone	124	23
Real-Time	846	

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**2,416**	**147**	**6.0%**	**113**	**4.7%**	**846**	**35.0 %**	**1,309**	**54.2.%**

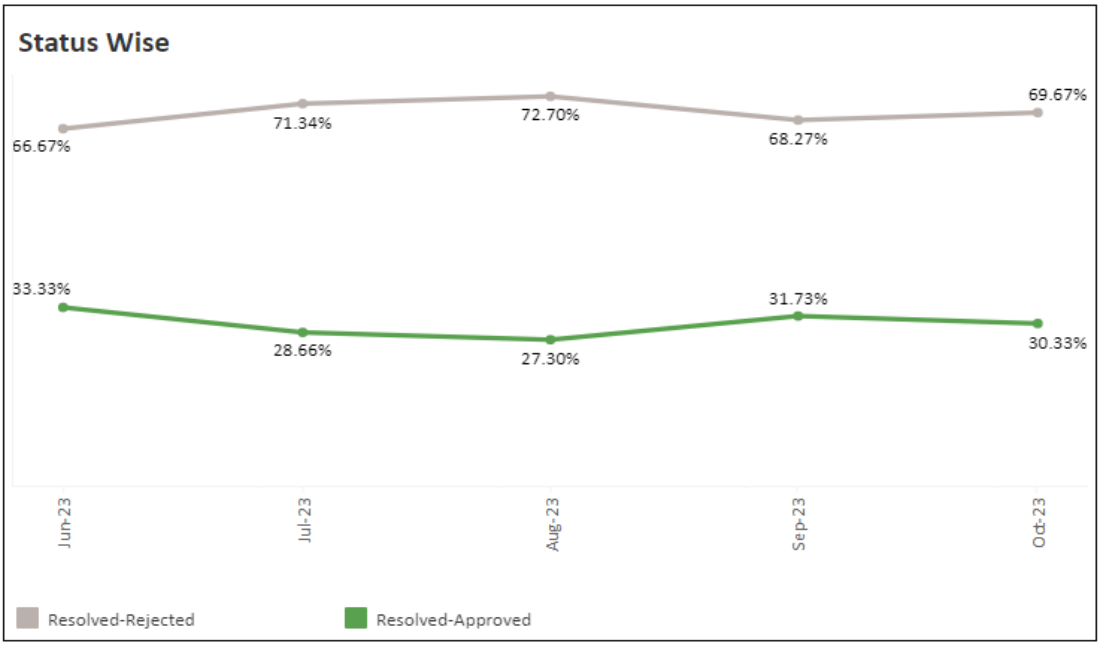


This graph shows the adoption of Interaction Types in percentage. This graph considers all resolved cases (Approved + Denied).

PA Initial Requests Summary

Month	Approved	Denied	Total
Jul-23	544	123	667
Aug-23	668	169	837
Sep-23	741	171	912
3Q23	**1,953**	**463**	**2,416**
Percent of Total	**80.84%**	**19.16%**	

SilentAuth Approvals



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIDIABETICS	406	70	476	85.29%	19.70%	, OZEMPIC
ANTIPSYCHOTICS/ANTIMANIC	412	24	436	94.50%	18.05%	, INVEGA SUSTENNA
DERMATOLOGICALS	141	68	209	67.46%	8.65%	DUPIXENT, IVERMECTIN
ANALGESICS - OPIOID	177	28	205	86.34%	8.49%	, HYDROCODONE/APAP
ANTIDEPRESSANTS	125	22	147	85.03%	6.08%	, VILAZODONE
OTHERS -	692	251	943	73.38%	39.03%	
3Q23	**1,953**	**463**	**2,416**	**80.84%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS*	406	70	476	85.29%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	412	24	436	94.50%
90 - DERMATOLOGICALS*	141	68	209	67.46%
65 - ANALGESICS - OPIOID*	177	28	205	86.34%
58 - ANTIDEPRESSANTS*	125	22	147	85.03%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	108	30	138	78.26%
52 - GASTROINTESTINAL AGENTS - MISC.*	86	26	112	76.79%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	63	47	110	57.27%
67 - MIGRAINE PRODUCTS*	77	20	97	79.38%
28 - THYROID AGENTS*	43	22	65	66.15%
72 - ANTICONVULSANTS*	46	13	59	77.97%
66 - ANALGESICS - ANTI-INFLAMMATORY*	46	12	58	79.31%
41 - ANTIHISTAMINES*	33	11	44	75.00%
16 - ANTI-INFECTIVE AGENTS - MISC.*	31	2	33	93.94%
12 - ANTIVIRALS*	21	7	28	75.00%
54 - URINARY ANTISPASMODICS*	21	6	27	77.78%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	17	4	21	80.95%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	16	3	19	84.21%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	6	10	16	37.50%
50 - ANTIEMETICS*	10	5	15	66.67%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	11	2	13	84.62%
39 - ANTIHYPERLIPIDEMICS*	8	2	10	80.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	8	1	9	88.89%
34 - CALCIUM CHANNEL BLOCKERS*	3	5	8	37.50%
40 - CARDIOVASCULAR AGENTS - MISC.*	5	3	8	62.50%
75 - MUSCULOSKELETAL THERAPY AGENTS*	2	6	8	25.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	6	0	6	100.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	5	0	5	100.00%
33 - BETA BLOCKERS*	4	1	5	80.00%
74 - NEUROMUSCULAR AGENTS*	5	0	5	100.00%
36 - ANTIHYPERTENSIVES*	1	3	4	25.00%
83 - ANTICOAGULANTS*	2	2	4	50.00%
02 - CEPHALOSPORINS*	1	2	3	33.33%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	2	3	33.33%
32 - ANTIANGINAL AGENTS*	1	1	2	50.00%
51 - DIGESTIVE AIDS*	2	0	2	100.00%
86 - OPHTHALMIC AGENTS*	1	1	2	50.00%
45 - RESPIRATORY AGENTS - MISC.*	1	0	1	100.00%
57 - ANTIANXIETY AGENTS*	0	1	1	0.00%
82 - HEMATOPOIETIC AGENTS*	1	0	1	100.00%
97 - MEDICAL DEVICES AND SUPPLIES*	0	1	1	0.00%
3Q23	**1,953**	**463**	**2,416**	
Percent of Total	**80.84%**	**19.16%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jul-23	17	89.47%	2	10.53%	19
Aug-23	15	83.33%	3	16.67%	18
Sep-23	16	80.00%	4	20.00%	20
3Q23	**48**	**84.21%**	**9**	**15.79%**	**57**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	14	0	14	100.00%
AIMOVIG	2	1	3	66.67%
DEXLANSOPRAZOLE	2	1	3	66.67%
IVERMECTIN	3	0	3	100.00%
AMLODIPINE BESYLATE	1	1	2	50.00%
HUMIRA PEN	1	1	2	50.00%
MAVYRET	2	0	2	100.00%
MYRBETRIQ	2	0	2	100.00%
XELJANZ	2	0	2	100.00%
AJOVY	1	0	1	100.00%
DALFAMPRIDINE ER	1	0	1	100.00%
DAPSONE	1	0	1	100.00%
DEXMETHYLPHENIDATE HCL ER	1	0	1	100.00%
EMGALITY	1	0	1	100.00%
ESZOPICLONE	0	1	1	0.00%
LEVOCETIRIZINE-D HCL	0	1	1	0.00%
LEVOTHYROXINE	1	0	1	100.00%
LUBIPROSTONE	1	0	1	100.00%
METHOCARBAMOL	1	0	1	100.00%
METHYLPHENIDATE HCL	0	1	1	0.00%
MODAFINIL	1	0	1	100.00%
QULIPTA	1	0	1	100.00%
REMODULIN	1	0	1	100.00%
REXULTI	1	0	1	100.00%
RINVOQ	1	0	1	100.00%
SOFOSBUVIR/VELPATASVIR	1	0	1	100.00%
SYMPAZAN	1	0	1	100.00%
SYNTHROID	1	0	1	100.00%
TIROSINT	1	0	1	100.00%
TREMFYA	1	0	1	100.00%
VELETRI	0	1	1	0.00%
VICTOZA	0	1	1	0.00%
VRAYLAR	1	0	1	100.00%
LINZESS	14	0	14	100.00%
AIMOVIG	2	1	3	66.67%
DEXLANSOPRAZOLE	2	1	3	66.67%
3Q23	**48**	**9**	**57**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 7/1/2023 – 9/30/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	13,357	$178,972.76	$13.40	6.38%
2	ANTICONVULSANTS, MISCELLANEOUS	12,272	$1,042,435.65	$84.94	5.86%
3	ATYPICAL ANTIPSYCHOTICS	9,017	$2,737,838.80	$303.63	4.30%
4	SECOND GENERATION ANTIHISTAMINES	7,606	$85,369.68	$11.22	3.63%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,045	$400,331.95	$56.82	3.36%
6	RESPIRATORY AND CNS STIMULANTS	6,792	$693,464.75	$102.10	3.24%
7	PROTON-PUMP INHIBITORS	6,507	$193,291.88	$29.71	3.11%
8	AMPHETAMINES	6,426	$1,194,348.69	$185.86	3.07%
9	ADRENALS	5,735	$653,470.58	$113.94	2.74%
10	OPIATE AGONISTS	5,650	$195,707.37	$34.64	2.70%
11	AMINOPENICILLIN ANTIBIOTICS	5,493	$79,390.93	$14.45	2.62%
12	ANXIOLYTICS,SEDATIVES,AND HYPNOTICS,MISC	4,974	$66,016.76	$13.27	2.37%
13	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,935	$716,437.55	$182.07	1.88%
14	HMG-COA REDUCTASE INHIBITORS	3,835	$45,508.62	$11.87	1.83%
15	CENTRAL ALPHA-AGONISTS	3,732	$62,978.05	$16.88	1.78%
Total		**102,376**	**$8,345,564.02**	**$81.52**	**48.86%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 7/1/2023 – 9/30/2023					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	9,017	$2,737,838.80	$303.63	4.30%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	380	$2,602,494.19	$6,848.67	0.18%
3	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	728	$2,398,183.88	$3,294.21	0.35%
4	INCRETIN MIMETICS	1,497	$1,372,681.08	$916.95	0.71%
5	CYSTIC FIBROSIS (CFTR) CORRECTORS	62	$1,370,474.75	$22,104.43	0.03%
6	ANTINEOPLASTIC AGENTS	308	$1,251,293.06	$4,062.64	0.15%
7	AMPHETAMINES	6,426	$1,194,348.69	$185.86	3.07%
8	HEMOSTATICS	52	$1,130,398.64	$21,738.44	0.02%
9	ANTICONVULSANTS, MISCELLANEOUS	12,272	$1,042,435.65	$84.94	5.86%
10	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,935	$716,437.55	$182.07	1.88%
11	RESPIRATORY AND CNS STIMULANTS	6,792	$693,464.75	$102.10	3.24%
12	ADRENALS	5,735	$653,470.58	$113.94	2.74%
13	GI DRUGS, MISCELLANEOUS	437	$516,937.14	$1,182.92	0.21%
14	LONG-ACTING INSULINS	1,336	$513,924.44	$384.67	0.64%
15	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	902	$484,868.22	$537.55	0.43%
Total		**49,879**	**$18,679,251.42**	**$374.49**	**23.81%**

Total Rx Claims from 7/1/2023 – 9/30/2023	**209,518**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 7/1/2023 – 9/30/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,594	$186,165.96	$33.28	2.67%
2	Antidepressants	SERTRALINE HCL	4,323	$57,889.49	$13.39	2.06%
3	ADHD & Narcolepsy Medications	METHYLPHENIDATE HCL	4,212	$258,825.43	$61.45	2.01%
4	Penicillins	AMOXICILLIN	4,021	$52,130.18	$12.96	1.92%
5	Antihistamines	CETIRIZINE HCL	3,960	$41,674.72	$10.52	1.89%
6	Proton Pump Inhibitors	OMEPRAZOLE	3,826	$43,668.50	$11.41	1.83%
7	Antidepressants	FLUOXETINE HCL	3,740	$46,725.57	$12.49	1.79%
8	Anticonvulsants - 2nd Generation	GABAPENTIN	3,635	$58,380.33	$16.06	1.73%
9	Antidepressants	TRAZODONE HCL	3,204	$34,527.36	$10.78	1.53%
10	Thyroid Hormones	LEVOTHYROXINE SODIUM	3,172	$37,803.39	$11.92	1.51%
11	Antidepressants	ESCITALOPRAM OXALATE	3,023	$38,524.45	$12.74	1.44%
12	ADHD & Narcolepsy Medications	VYVANSE	2,875	$951,859.30	$331.08	1.37%
13	Leukotriene Modulators	MONTELUKAST SODIUM	2,816	$36,561.48	$12.98	1.34%
14	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	2,700	$75,024.51	$27.79	1.29%
15	Biguanides & Combos	METFORMIN HCL	2,452	$29,368.70	$11.98	1.17%
16	Antiadrenergic Antihypertensives	CLONIDINE HCL	2,400	$21,518.53	$8.97	1.15%
17	Antidepressants	BUPROPION HCL	2,329	$41,970.99	$18.02	1.11%
18	Opioid Agonists & Combos	HYDROCODONE BIT/AC	2,222	$32,667.20	$14.70	1.06%
19	Statins & Combos	ATORVASTATIN CALCIUM	2,207	$25,151.25	$11.40	1.05%
20	ACE Inhibitors & Combos	LISINOPRIL	2,151	$20,346.75	$9.46	1.03%
21	Atypical Antipsychotics	ARIPIPRAZOLE	2,035	$31,168.54	$15.32	0.97%
22	Cephalosporins	CEPHALEXIN	1,948	$32,752.14	$16.81	0.93%
23	Antianxiety Agents	HYDROXYZINE HCL	1,913	$23,125.33	$12.42	0.91%
24	Antidepressants	DULOXETINE HCL E	1,874	$28,915.44	$15.43	0.89%
25	Glucocorticosteroids	PREDNISONE	1,670	$16,312.05	$9.77	0.80%
26	Anticonvulsants - 2nd Generation	LAMOTRIGINE	1,669	$22,333.21	$13.38	0.80%
27	Atypical Antipsychotics	RISPERIDONE	1,661	$20,697.11	$12.46	0.79%
28	Antihistamines	LORATADINE	1,656	$17,847.37	$10.78	0.79%
29	Antiemetics	ONDANSETRON ODT	1,630	$22,982.37	$14.10	0.78%
30	ADHD & Narcolepsy Medications	GUANFACINE ER	1,516	$25,246.14	$16.65	0.72%
31	Antianxiety Agents	BUSPIRONE HCL	1,512	$18,842.75	$12.46	0.72%
32	Atypical Antipsychotics	QUETIAPINE FUMARATE	1,491	$19,020.13	$12.76	0.71%
33↓	Penicillins	AMOXICILLIN/CLAVULANATE	1,467	$27,176.63	$18.53	0.70%
34	Nasal Steroids	FLUTICASONE PROPIONATE	1,433	$22,155.30	$15.46	0.68%
35	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,392	$20,616.06	$14.81	0.66%
36↑	Muscle Relaxants & Combos	CYCLOBENZAPRINE HCL	1,381	$13,878.76	$10.05	0.66%
37	Anticonvulsants - 2nd Generation	CLONAZEPAM	1,363	$15,340.25	$11.25	0.65%
38	Anticonvulsants - 2nd Generation	LEVETIRACETAM	1,358	$27,996.50	$20.62	0.65%
39	Proton Pump Inhibitors	PANTOPRAZOLE SODIUM	1,341	$18,701.63	$13.95	0.64%
40	Calcium Channel Blockers	AMLODIPINE BESYLATE	1,331	$12,995.55	$9.76	0.64%
41↑	Angiotensin II Receptor Antagonists & Combo	LOSARTAN POTASSIUM	1,254	$13,868.69	$11.06	0.60%
42	Anticonvulsants - 2nd Generation	TOPIRAMATE	1,252	$16,045.19	$12.82	0.60%
43↑	Antibiotics - Topical	MUPIROCIN	1,242	$18,811.47	$15.15	0.59%
44↓	Macrolides	AZITHROMYCIN	1,218	$18,507.34	$15.19	0.58%
45	Inhaled Bronchodilator	ALBUTEROL SULFATE	1,215	$23,440.14	$19.29	0.58%
46	Compounds	-	1,205	$24,624.02	$20.43	0.58%
47	H-2 Antagonists	FAMOTIDINE	1,155	$24,514.73	$21.22	0.55%
48	ADHD & Narcolepsy Medications	GUANFACINE HCL	1,144	$18,973.72	$16.59	0.55%
49	Vitamins & Supplements	FOLIC ACID	1,121	$10,224.47	$9.12	0.54%
50	Antidepressants	MIRTAZAPINE	1,112	$15,558.84	$13.99	0.53%
	Total Top 50 Drugs		**108,421**	**$2,713,455.96**	**$25.03**	**51.75%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 7/1/2023 – 9/30/2023						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	***HUMIRA/PEN/CD/UC/HS START***	166	$1,555,875.35	$9,372.74	0.08%
2	Cystic Fibrosis	TRIKAFTA	62	$1,370,474.75	$22,104.43	0.03%
3	Chronic Inflammatory Disease	DUPIXENT	313	$1,131,819.86	$3,616.04	0.15%
4	Atypical Antipsychotics	***INVEGA SUSTNA/TRNZA/HFYRA***	294	$1,021,573.87	$3,474.74	0.14%
5	ADHD & Narcolepsy Medications	VYVANSE	**2,875**	$951,859.30	$331.08	1.37%
6	Chronic Inflammatory Disease	STELARA	35	$793,623.15	$22,674.95	0.02%
7	GLP-1 Receptor Agonists	OZEMPIC	812	$735,650.65	$905.97	0.39%
8↑	Rett Syndrome Agent	DAYBUE	11	$495,367.15	$45,033.38	0.01%
9	Atypical Antipsychotics	VRAYLAR	373	$451,683.24	$1,210.95	0.18%
10	Atypical Antipsychotics	***ARISTADA/INITIO***	150	$413,438.11	$2,756.25	0.07%
11	Anticonvulsants - 2nd Generation	EPIDIOLEX	132	$390,896.38	$2,961.34	0.06%
12↑	GLP-1 Receptor Agonists	MOUNJARO	347	$341,856.27	$985.18	0.17%
13	Chronic Inflammatory Disease	***COSENTYX/SENSOREADY PEN***	48	$311,289.16	$6,485.19	0.02%
14	SGLT-2 Inhibitors & Combos	JARDIANCE	558	$300,384.75	$538.32	0.27%
15	Movement Disorder Drug Therapy	INGREZZA	39	$295,150.29	$7,567.96	0.02%
16	ADHD & Narcolepsy Medications	METHYLPHENIDATE HCL	**4,212**	$258,825.43	$61.45	2.01%
17	Chronic Inflammatory Disease	***ENBREL SURECLICK/MINI***	39	$258,265.62	$6,622.20	0.02%
18	Atypical Antipsychotics	REXULTI	194	$254,053.60	$1,309.55	0.09%
19	HIV-Multiclass Combo	BIKTARVY	68	$250,754.50	$3,687.57	0.03%
20	Chronic Inflammatory Disease	TALTZ	32	$245,877.86	$7,683.68	0.02%
21↑	Antihemophilic Products	NOVOSEVEN RT	3	$231,331.65	$77,110.55	0.00%
22	Chronic Inflammatory Disease	SKYRIZI PEN	12	$229,419.68	$19,118.31	0.01%
23	Oncology	KOSELUGO	14	$226,156.21	$16,154.02	0.01%
24	Hepatitis C	SOFOSBUVIR/VELPATASVIR	28	$216,804.13	$7,743.00	0.01%
25	Cystic Fibrosis	PULMOZYME	52	$213,769.90	$4,110.96	0.02%
26	Spinal Muscular Atrophy (SMA) Agt	EVRYSDI	8	$197,243.28	$24,655.41	0.00%
27	Anti-Infective Agents - Misc.	XIFAXAN	71	$192,681.62	$2,713.83	0.03%
28	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	**5,594**	$186,165.96	$33.28	2.67%
29	Oral Anticoagulants	***ELIQUIS/STARTER PACK***	364	$180,168.66	$494.97	0.17%
30	Glucagon-Like Peptide-2 (GLP-2) Ana	GATTEX	4	$176,845.60	$44,211.40	0.00%
31↓	GLP-1 Receptor Agonists	TRULICITY	198	$174,461.98	$881.12	0.09%
32↑	Antihemophilic Products	HEMLIBRA	7	$170,839.51	$24,405.64	0.00%
33	Atypical Antipsychotics	***ABILIFY MAINTENA/ASIMTUFII***	67	$165,423.37	$2,469.01	0.03%
34↑	Movement Disorder Drug Therapy	AUSTEDO XR	32	$164,295.09	$5,134.22	0.02%
35↑	Metabolic Modifiers	PALYNZIQ	3	$159,061.65	$53,020.55	0.00%
36↓	Antihemophilic Products	ADVATE	7	$158,409.53	$22,629.93	0.00%
37	Insulin	**LANTUS/SOLOSTAR**	390	$157,553.48	$403.98	0.19%
38	Bile Acid Synthesis Disorder Agents	CHOLBAM	7	$149,323.85	$21,331.98	0.00%
39	Antihemophilic Products	RECOMBINATE	3	$147,644.95	$49,214.98	0.00%
40	HIV-Multiclass Combo	GENVOYA	39	$144,380.28	$3,702.06	0.02%
41	Atypical Antipsychotics	CAPLYTA	102	$142,736.67	$1,399.38	0.05%
42	Antihemophilic Products	XYNTHA SOLOFUSE	3	$140,177.25	$46,725.75	0.00%
43↑	Migraine Products	NURTEC	125	$133,750.11	$1,070.00	0.06%
44	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	213	$131,086.55	$615.43	0.10%
45	ADHD & Narcolepsy Medications	QELBREE	296	$130,848.40	$442.06	0.14%
46	Chronic Inflammatory Disease	TREMFYA	10	$128,600.70	$12,860.07	0.00%
47↑	Irritable Bowel Syndrome (IBS) Agts	LINZESS	259	$125,545.78	$484.73	0.12%
48↑	Oncology	REVLIMID	6	$122,544.31	$20,424.05	0.00%
49↑	Anaphylaxis Therapy Agents	EPINEPHRINE	409	$122,317.33	$299.06	0.20%
50↓	Antihemophilic Products	ALPROLIX	9	$122,156.55	$13,572.95	0.00%
	Total Top 50 Drugs		**19,095**	**$16,770,463.32**	**$878.26**	**9.11%**

Old Business

PA Approval Comparison

South Dakota Medicaid:

Month	Approved	Denied	Total
Jul-23	544	123	667
Aug-23	668	169	837
Sep-23	741	171	912
3Q23	**1,953**	**463**	**2,416**
Percent of Total	**80.84%**	**19.16%**	

State A:

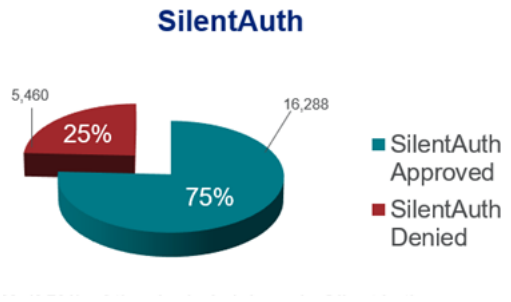
Month	Approved	Denied	Total
Jul-23	429	439	868
Aug-23	537	528	1065
Sep-23	437	387	824
3Q23	**1,403**	**1,354**	2,757
Percent of Total	**50.89%**	**49.11%**	

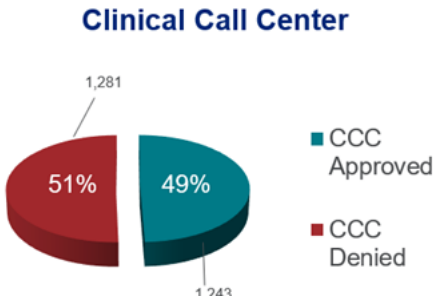
State B:

Month	Approved	Denied	Total
Initial PAs	7,021	8,571	15,592
1St Level of Appeals	564	307	871
2nd Level of Appeals	26	36	62
3Q23	**7,611**	**8,914**	**16,525**
Percent of Total	**46.05%**	**53.94%**	

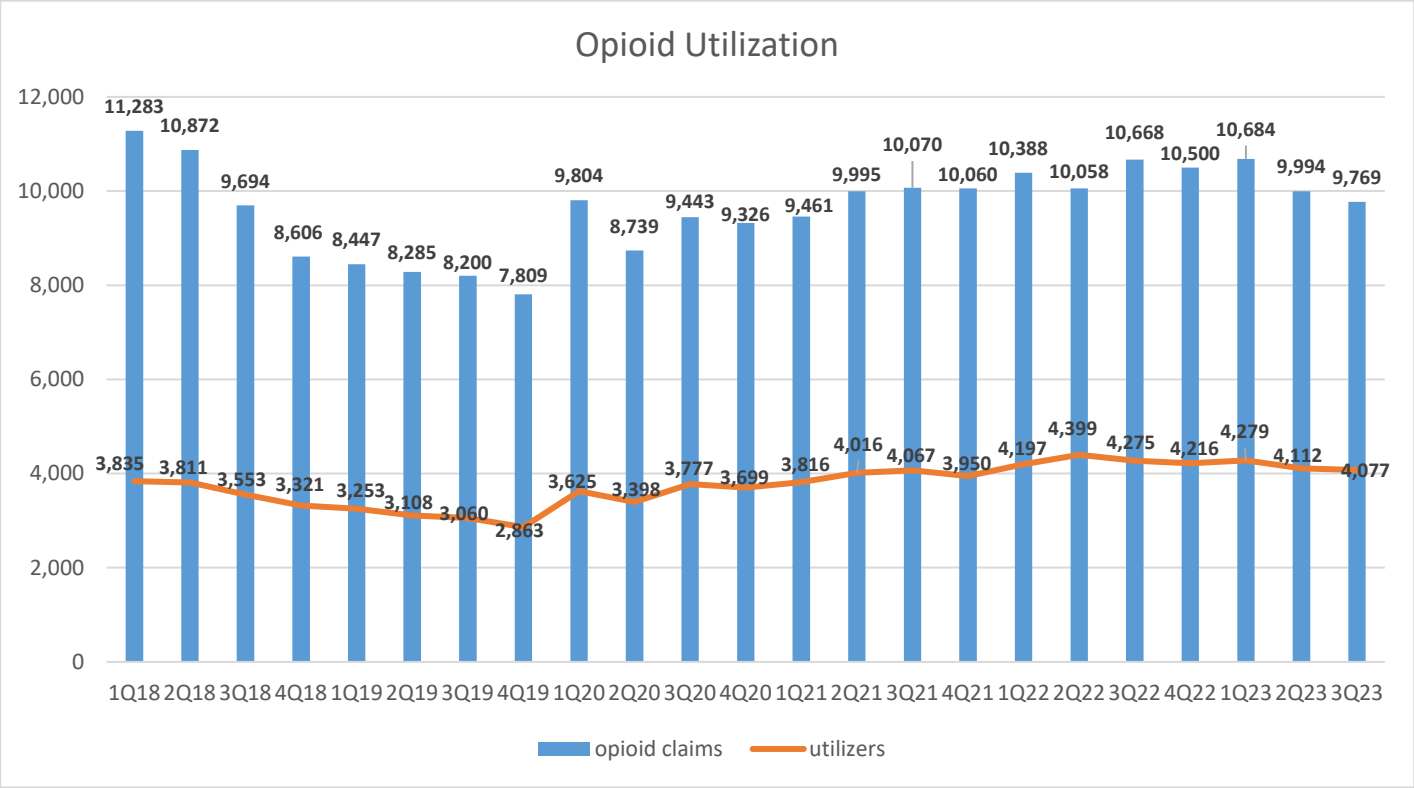
State C:

Month	Approved	Denied	Total
SilentAuth	16,288	5,460	21,748
Clinical Call Center	1,243	1,281	2,524
3Q23	**20,656**	**8,252**	**28,908**
Percent of Total	**71%**	**29%**	





Opioid Summary



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

Opioid Initiatives:

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

Other Initiatives:

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

Total Eligibility and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%
3Q2023	131,292	26,218	19.9%

Opioid Utilization Snapshot

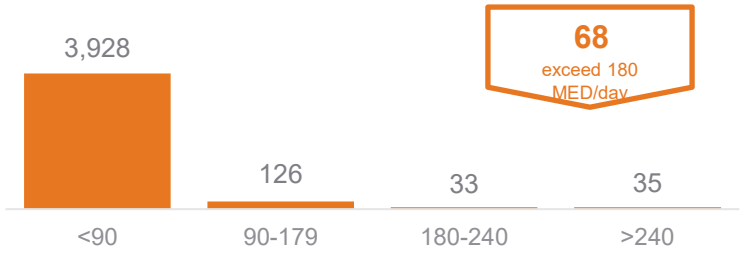
SDM 2Q2023
Mar 23 to Jun 23

Opioid Claims **9,994**
2.9% prescription claims filled for an opioid
0.9% higher than Medicaid FFS benchmark

Utilizers **4,122**
29% are high utilizers [1]
1.6% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



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

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

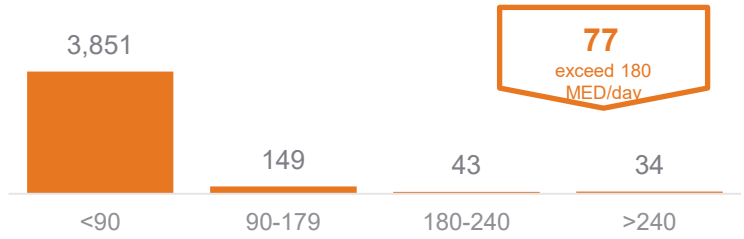
3Q2023
Jun 23 to Sep 23

Opioid Claims **9,769**
3.0% prescription claims filled for an opioid
0.2% higher than Medicaid FFS benchmark

Utilizers **4,077**
28.6% are high utilizers [1]
1.0% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



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

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

OPTUMRx®

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

Opioid Utilization

SDM 3Q2023
Opportunities date range: Jun - Sep 2023
Benchmark: MEDICAID MANAGED

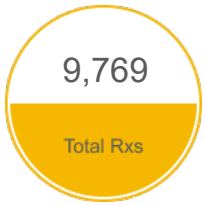
Utilizers: 4,077

3.0% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.0% of all prescriptions this period, which is 0.2% higher than the benchmark
- 1,166 high opioid utilizers were identified this period, which is 1.0% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
13.7%

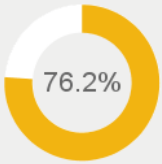
Opioid utilizers

HIGH UTILIZERS
28.6%
1,166 high utilizers

1.0% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

76.2% of all opioid Rxs were filled for short acting opioids. **1,671** Rxs were for medication assisted therapy (MAT) and **176** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT –Medication Assisted Therapy (buprenorphine, etc)
Overdose rescue therapy – opioid overdose reversals w/naloxone
MME – relative potency of an opioid to a morphine dose

Utilizers by cumulative MED

77 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,851	149	43	34

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

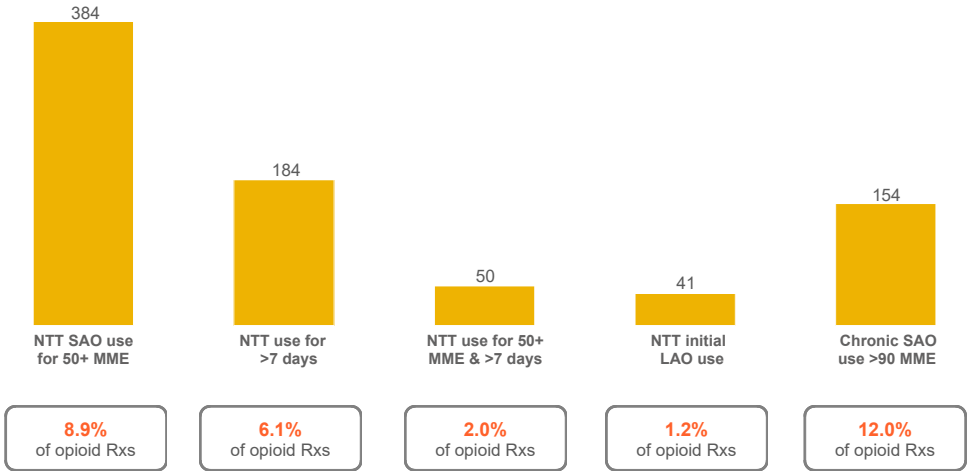
Opioid Opportunity Assessment

SDM 3Q2023
Opportunities date range: Jun - Sep 2023
Benchmark: MEDICAID MANAGED

Percent non-compliant: 13.7%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



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

DID YOU KNOW?

46 opioid utilizing members use 3 or more pharmacies and 292 opioid utilizing members use 3 or more prescribers.

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

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
760	547	725	356	144

Anticonvulsants –view definition

New Business

History of Stimulant Reviews

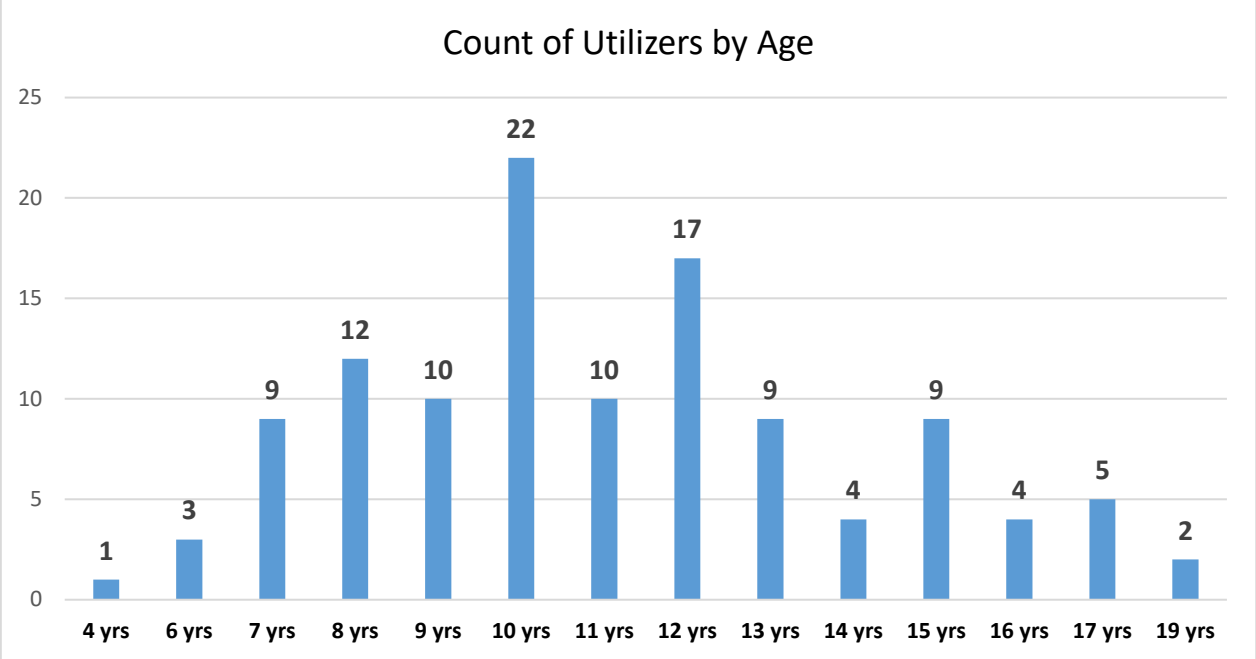
- March 2019 P&T meeting – reviewed utilization of all members on ADD/ADHD medications
- June 2019 P&T meeting – reviewed utilization of members aged 1-20 years old vs 21 years old & older
- September 2019 P&T meeting – reviewed utilization of members aged 26 years old & older
- December 2020 P&T meeting – reviewed utilization of members 21 years & older
- March 2021 P&T meeting – reviewed utilization of members 21 years & older

Jornay PM ER (methylphenidate)

- Increased utilization
- Candidate for step therapy?

Time frame: 7/1/2023 – 9/30/2023

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
Jornay PM ER cap • 20mg, 40mg, 60mg, 80mg 100mg	272	$110,065.30	$404.65	29.3 per 28.9 days	117	< 20
	6	$2,464.59	$410.77	29 per 29 days	2	30, 33



Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Quantity/DS	Utilizers	Age Range
methylphenidate cap ER • 10mg, 20mg, 30mg 40mg, 50mg	341	$27,224.70	$79.84	30.1 per 29 days	170	5 – 19
	24	$1,928.55	$80.36	27.7 per 27.7 days	11	25 – 51
methylphenidate tab ER • 18mg, 20mg, 27mg, 36mg, 54mg, 72mg	2,193	$155,369.62	$78.85	31.6 per 30.5 days	392	4 – 20
	261	$24,346.65	$93.28	32.7 per 29.3 days	102	21 – 64

Stimulant Utilization of Members 21 years and older

	4Q2020				3Q2023			
Class	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizers**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizers**
Amphetamines amphet/dextroamphetamine, ADDERALL/XR, ADZENYS XR, MYDAVIS, VYVANSE & generic	1,686	$210,736.90	$124.99	550	2,199	$326,929.78	$148.67	825
Respiratory & CNS Stimulants AZSTARYS, CONCERTA, COTEMPLA XR, DAYTRANA, JORNAY PM, QUILLICHEW, RITALIN/LA, FOCALIN/XR, methylphenidate/ER, dexmethylphenidate/ER	420	$28,706.59	$68.35	148	550	$43,130.93	$78.42	213

*IHS excluded

Stimulant Utilization Review of Members taking IR and ER

Time frame: 1/1/2023 – 10/31/2023

Members 20 years and younger	
Total Members 20 years and younger	6,986
Number of Members receiving Vyvanse with IR	100
Number of Members receiving ER with IR	383
Number of Members - change due to shortage?	9

Members 21 years and older	
Total Members 21 years and older	1,629
Number of Members receiving Vyvanse with IR	51
Number of Members receiving ER with IR	73
Number of Members - change due to shortage?	11

State PA Criteria Comparison

State Medicaid	**PA Criteria**	
State A	PA for ages < 6 years with QL	Non-preferred- PA for all ages
State B	PA for ages 21 years & older	Non-preferred- PA for all ages
State C	• Ages 20 years & older requires a valid diagnosis • >1 ER product at a time not permitted, (2 different strengths of same product is permitted) • IR formulation needs to be same chemical entity as ER formulation to be used concurrently (e.g., Adderall XR + Adderall IR), unless otherwise specified in PA	
State D	Preferred stimulants have a PA bypass for patients less than 20 years of age with max dose 80 mg/day. Preferred stimulants have PA for everyone 21 years and older with max dose 60 mg/day.	Non-preferred- PA for all ages
South Dakota	Qelbree step therapy effective 1/1/2023 -trial of atomoxetine OR stimulants	

U.S. FOOD & DRUG ADMINISTRATION

August 1, 2023

Dear Americans,

As leaders of the U.S. Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA), we recognize the important role that prescription stimulants play in the treatment of conditions such as attention-deficit/hyperactivity disorder (ADHD), binge eating disorder, and uncontrollable episodes of deep sleep (narcolepsy). The lack of availability of certain medications in recent months has been understandably frustrating for patients and their families.

Given the interest related to access to these medications, we want to provide an update on the ongoing actions being taken to resolve the shortages of prescription stimulant medications. In addition, we want to acknowledge important issues that will need to be addressed through longer-term coordination by a variety of entities involved in this effort. This is not a problem that the FDA and DEA can solve on our own. We are urging all stakeholders to work together to resolve these shortages as quickly as possible.

The FDA and DEA do not manufacture drugs and cannot require a pharmaceutical company to make a drug, make more of a drug, or change the distribution of a drug. That said, we are working closely with numerous manufacturers, agencies, and others in the supply chain to understand, prevent, and reduce the impact of these shortages.

The current shortage of stimulant medications is the result of many factors. It began last fall due to a manufacturing delay experienced by one drug maker. While this delay has since resolved, we are continuing to experience its effects in combination with record-high prescription rates of stimulant medications. Data show that, from 2012 to 2021, overall dispensing of stimulants (including amphetamine products and other stimulants) increased by 45.5 percent in the United States. According to a U.S. Centers for Disease Control and Prevention report, particularly during 2020–2021, when virtual prescribing was permitted on a widespread basis during the COVID-19 Public Health Emergency, the percentages in certain age groups grew by more than 10 percent. We are calling on key stakeholders, including manufacturers, distributors, pharmacies, and payors, to do all they can to ensure access for patients when a medication is appropriately prescribed. We want to make sure those who need stimulant medications have access. However, it is also an appropriate time to take a closer look at how we can best ensure these drugs are being prescribed thoughtfully and responsibly.

Stimulants are controlled substances with a high potential for abuse, which can lead to addiction and overdose. Therefore, there are limits (also known as quotas) set by DEA for how much of these drugs can be produced. However, for amphetamine medications, in 2022, manufacturers did not produce the full amount that these limits permitted them to make. Based on DEA's internal analysis of inventory, manufacturing, and sales data submitted by manufacturers of amphetamine products, manufacturers only sold approximately 70 percent of their allotted quota

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

for the year, and there were approximately 1 billion more doses that they could have produced but did not make or ship. Data for 2023 so far show a similar trend.

We (DEA and the FDA) have called on manufacturers to confirm they are working to increase production to meet their allotted quota amount. If any individual manufacturer does not wish to increase production, we have asked that manufacturer to relinquish their remaining 2023 quota allotment. This would allow DEA to redistribute that allotment to manufacturers that will increase production. DEA is also committed to reviewing and improving our quota process.

The FDA is asking professional groups and healthcare providers to accelerate efforts to support appropriate diagnosis and treatment of ADHD, such as further development of additional clinical guidelines for ADHD in adults. In recognition of this need, FDA awarded a grant to the National Academies of Sciences, Engineering, and Medicine (NASEM) to support a scientific meeting on ADHD in adults and considerations for diagnosis and treatment. FDA also recognizes that further research is needed into the diagnosis and treatment of ADHD and believes that research can help inform the development of alternative treatments and an understanding of the behavioral and societal issues leading to widespread misuse of these medications in certain groups.

FDA has already taken steps to support the development of alternative treatment options. In 2020, for instance, FDA permitted marketing of a game-based digital therapeutic to improve attention function in children with ADHD. This device offers a non-drug option for improving symptoms associated with ADHD in children. There are also non-stimulant medications approved to treat ADHD, including one approved in 2021. Additionally, to address continuing concerns of misuse, addiction and overdose of prescription stimulants, the FDA recently issued a drug safety communication and required updates to the labeling to standardize prescribing information and clearly inform patients, caregivers and healthcare professionals of these risks.

FDA and DEA will continue to do all we can to prevent stimulant drug shortages, limit their impact, and resolve them as quickly as possible. We will consider additional actions to prevent non-medical use and identify efforts to better understand and strengthen the supply chain. We also hope that we can all work together to assure that those who need stimulant medications can get them based on the best clinical knowledge about when they are effective, and avoid them when there is no indication for their use.

We will continue to work together and with all of you to mitigate this drug shortage and provide up to date information.

Sincerely,

Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration

Anne M. Milgram
Administrator
Drug Enforcement Administration

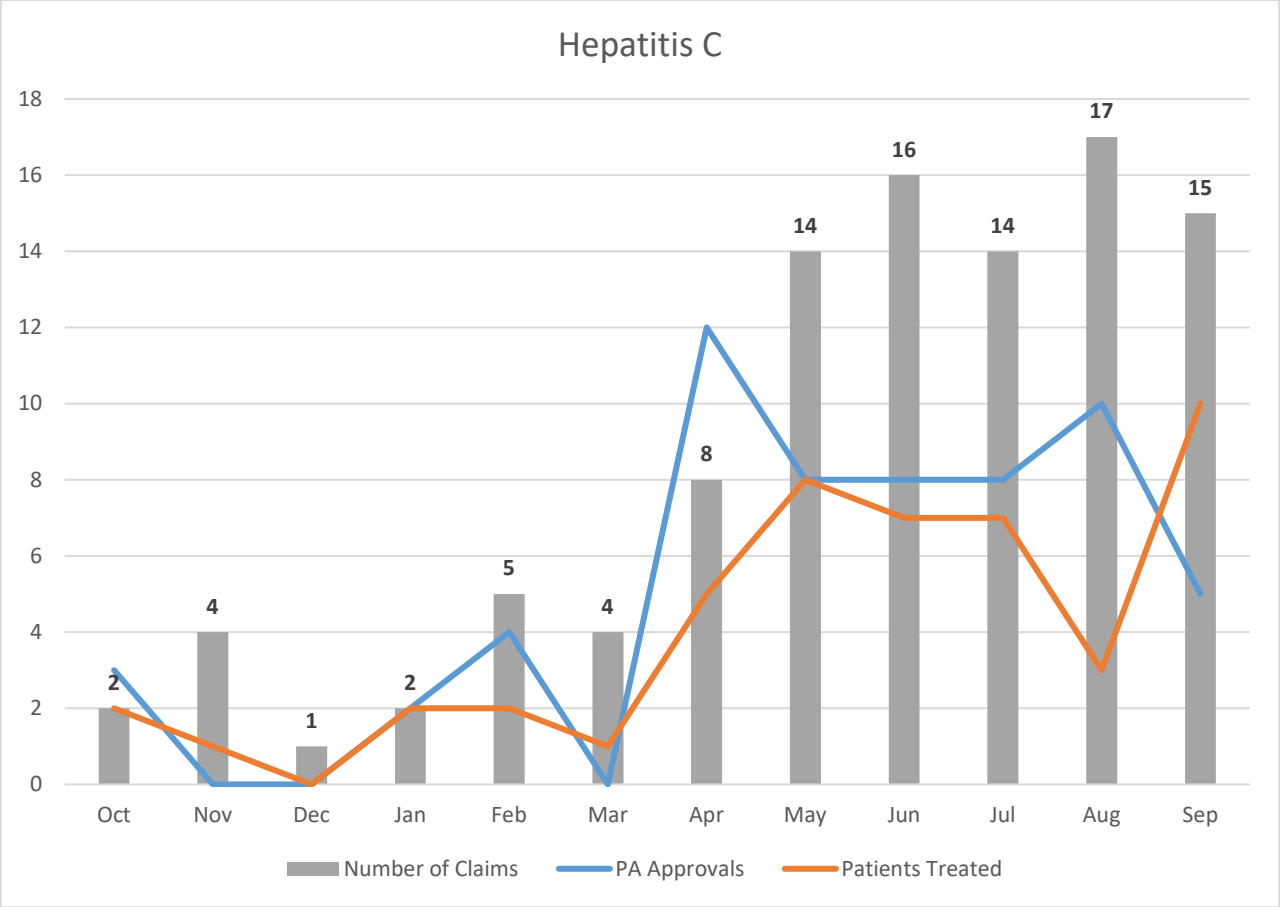
New Business

Hepatitis C Review

Time Frame: October 2022 – September 2023

	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep
PA Approvals	3	0	0	2	4	0	12	8	8	8	10	5
Patients Treated*	2	1	0	2	2	1	5	8	7	7	3	10
Number of Claims	2	4	1	2	5	4	8	14	16	14	17	15

*Patients counted once in the first month of treatment



Demographics of Patients Treated

Age Range & Gender

Age Range	Total	Female	Male
20 years & younger	**1**	1	
21 – 30	**9**	8	1
31 – 40	**17**	15	2
41 – 50	**6**	5	1
51 – 60	**10**	6	4
61 – 64	**5**	3	2
Total	**48**	38	10

Humira shift to Skyrizi

- Lookback period started on 1/1/2022
- During 1/1/2022 to 9/30/2023 reviewed claims to find patients who switched from Humira to Skyrizi
    - 110 patients taking Humira only
    - No shifts from Humira to Skyrizi seen during this time period
    - 6 patients who switched to the following drugs: Actemra, Cosentyx, Enbrel, Orencia, Otelza, Rinvoq, Stelara, leflunomide
        - Some patients switched to one drug
        - Some patients switched to two drugs
        - Some patients switched to one drug and switched back to Humira

Ilaris (canakinumab) – new indication

On August 25, 2023, the FDA approved Novartis' Ilaris (canakinumab), for the symptomatic treatment of adult patients with gout flares in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Proposed criteria:

1. Diagnosis of gout flares **AND**
2. Patient is ≥ 18 years of age **AND**
3. Prescribed by or in consultation with a rheumatologist **AND**
4. The medication will not be used in combination with another biologic agent **AND**
5. Patient has had an inadequate response to, intolerance to, or contraindication oral systemic agent(s) such as NSAIDs **and/or** colchicine

Health plan:

Will require diagnosis; trial and failure, contraindication, or intolerance to ALL of the following: NSAID, colchicine, corticosteroids; **and** patient has not received Ilaris in the last 12 weeks.

Nuzyra (omadacycline)

State A

1. Trial and failure of at least one other tetracycline product (minocycline, doxycycline, etc.) in the past 30 days **OR**
2. The prescriber submitted valid medical justification for use of omadacycline over other tetracycline products (pharmacist review required)

State B

1. What is the member's age?
2. What is the diagnosis?
    a. Community-acquired bacterial pneumonia (CABP)
    b. Acute bacterial skin and skin structure infection (ABSSSI)
3. Was the member started and stabilized on the medication while in the hospital and this request is a continuation of therapy?
4. Which formulation is being requested?
5. Is the member not able to switch to oral therapy?
6. Where will the medication be administered?
    a. Home or LTC – approve for 14 days
    b. Clinic or physician's office – deny

State C

1. Patient must be greater than or equal to 18 years of age
2. If patient is female and of childbearing potential, it has been confirmed patient is NOT pregnant
3. Patient has one of the following diagnoses:
    - Community-acquired bacterial pneumonia (CABP) caused or suspected by one of the following susceptible organisms: Streptococcus pneumoniae, Staphylococcus aureus (methicillin-susceptible isolates; MSSA), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydophila pneumoniae
    - Acute bacterial skin and skin structure infections (ABSSSI) caused or suspected by one of the following susceptible organisms: S. aureus [methicillin-susceptible and -resistant isolates], Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus group (includes S. anginosus, S. intermedius, and S. constellatus), Enterococcus faecalis, Enterobacter cloacae, and K. pneumoniae
4. One of the following:
    4.1 Continuing treatment from an acute care facility/hospital discharge OR
    4.2 Patient meets one of the following conditions:
        - If Culture & Sensitivity (C&S) report is available, patient must have tried/failed or have a contraindication or adverse effect to at least 2 preferred antibiotic agents susceptible to the isolated pathogen
        - If provider is unable to provide a C&S report, patient must have tried/failed or have a contraindication or adverse reaction to at least 2 preferred antibiotics indicated for the member's diagnosis
5. Patient's total treatment duration does not exceed 14 days
6. Patient dosing follows FDA-approved dosing instructions

Vowst (fecal microbiota spores, live-brpk)

State A

1. Patient is ≥ 18 years old
2. Treatment is to prevent the recurrence of Clostridioides difficile infection (CDI)
3. Patient has had three or more episodes of CDI within the past year
4. Submission of medical records (e.g. chart notes, lab test) of a positive C. difficile stool test with toxin A/B results within the previous 30 days;
5. Patient has completed a full treatment course with ONE of the following antibiotic therapies 2 to 4 days prior to initiating Vowst:
    - Fidaxomicin
    - Vancomycin
6. Prescriber by or in consultation with an infectious disease specialist or gastroenterologist;
7. The agent will not to be used in combination with other products for prevention of CDI, such as Zinplava or Rebyota

Health plan

1. Diagnosis of recurrent clostridioides difficile infection (CDI) as defined by both of the following:
    - Presence of diarrhea defined as a passage of 3 or more loose bowel movements within a 24-hour period for 2 consecutive days
    - A positive stool test for C.difficile toxin or toxigenic C.difficile
2. Patient is 18 years of age or older
3. Patient has a history of two or more recurrent episodes of CDI within 12 months
4. All of the following:
    - Patient has completed at least 10 consecutive days of one of the following antibiotic therapies 2-4 days prior to initiating Vowst:
        - oral vancomycin
        - Dificid (fidaxomicin)
    - Patient has completed the recommended course of magnesium citrate the day before and at least 8 hours prior to initiating Vowst
    - Previous episode of CDI is under control (e.g., less than 3 unformed/loose [i.e., Bristol Stool Scale type 6-7] stools/day for 2 consecutive days)
5. Prescribed by or in consultation with one of the following:
    - Gastroenterologist
    - Infectious disease specialist

South Dakota Medicaid

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

- Patient must be 18 years of age or older **AND**
- Patient must have a diagnosis of Clostridium difficile-associated diarrhea (CDAD) **AND**
- Patient must have been treated per the current guidelines and failed one of the following:
    - Initial episode (mild to moderate severity) – metronidazole
    - Initial episode (severe) – vancomycin
    - Initial episode (severe, complicated) – vancomycin and metronidazole
    - First recurrence – same regimen as first episode
    - Second recurrence – oral vancomycin in tapered regimen

Optum Rx®

Therapeutic Class Overview

Tetracyclines

Introduction

- The tetracycline class of antibiotics, discovered in the 1940s, has been widely used for its broad-spectrum bacteriostatic activity (*Nelson and Levy 2011*).
  - The tetracyclines are useful in treating aerobic gram-positive, gram-negative bacteria, and atypical pathogens (eg, *Rickettsia* species [spp], *Borrelia* spp, *Treponema* spp, *Chlamydia* spp). However, these drugs have little activity against fungi and viruses (*May 2022*).
  - The tetracyclines have a number of indications, some of which include acne, rosacea, sexually-transmitted diseases, acute bacterial skin and skin structure infections (ABSSSIs), urinary tract infections, respiratory tract infections, and various other infections (see Table 2 for the labelled indications for the individual agents) *(May 2022)*.
  - The antimicrobial activity is generally similar between the tetracyclines, although some differences in the relative degree of activity against certain pathogens do exist among the various agents (*May 2022*).
- Tetracyclines function by binding reversibly to the 30S ribosomal subunit at a position that blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. Protein synthesis is ultimately inhibited, leading to a bacteriostatic effect (*May 2022*).
- With regard to resistance, once resistance develops to one of the drugs in this class, it is typically conferred to all tetracyclines. However, there are differences in resistance among species of bacteria *(May 2022)*.
- Doxycycline and minocycline are the most frequently prescribed drugs in this class (*May 2022*).
- Newer generation oral tetracyclines approved by the Food and Drug Administration (FDA) include Nuzyra (omadacycline) and Seysara (sarecycline). Omadacycline was approved for community-acquired bacterial pneumonia (CABP) and ABSSSIs (including cellulitis, wound infection, and major cutaneous abscess); while sarecycline was approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age (*Drugs@FDA 2023, FDA multi-discipline review [Nuzyra] 2018*).
  - CABP is an acute infection of the pulmonary parenchyma in patients who have acquired the infection in the community. CABP is a common and potentially serious illness, and is associated with considerable morbidity and mortality, particularly in older adults and those with major comorbidities (*File 2022*).
    - *Streptococcus pneumoniae* is the most commonly identified bacterial cause of CABP worldwide. Other common pathogens identified in CABP include *Haemophilus influenzae*; atypical bacteria *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp.; and oropharyngeal aerobes and anaerobes (in the setting of aspiration). Viruses are also common causes of CABP (*FDA multi-discipline review [Nuzyra] 2018, File 2023*).
  - Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments (*Zaenglein et al 2016, The Medical Letter 2016*).
    - The tetracycline class of antibiotics should be considered first-line therapy in moderate to severe acne, except when contraindicated (*Zaenglein et al 2016)*. In addition to sarecycline, other products in this class that are utilized for acne treatment include tetracycline, doxycycline, and minocycline (*Graber 2022*).
- This review includes mainly oral tetracyclines. Topicals tetracyclines, including oral/topical kits, are excluded from this review.
- Medispan class: Antibiotic; Tetracycline Derivative

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Avidoxy (doxycycline monohydrate) tablets	✔
demeclocycline HCl tablets	✔
doxycycline hyclate tablets	✔
Doryx (doxycycline hyclate) delayed-release tablets	✔
Doryx MPC (doxycycline hyclate) delayed-release tablets	-
minocycline HCl extended-release tablets	✔
minocycline HCl capsules, tablets	✔
Minolira (minocycline HCl) extended-release tablets	-
Mondoxyne NL (doxycycline monohydrate) capsules	✔

Drug	Alternative Available (same molecular entity)*
Nuzyra (omadacycline) tablets, injection	-
Oracea (doxycycline monohydrate) delayed-release capsules	✔
Seysara (sarecycline) tablets	-
Solodyn (minocycline HCl) extended-release tablets	✔
TargaDOX (doxycycline hyclate) tablets	✔
tetracycline HCl capsule	✔
Vibramycin (doxycycline monohydrate) suspension	✔
Vibramycin (doxycycline hyclate) capsules	✔
Ximino (minocycline HCl) extended-release capsules	✔

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

(*Drugs@FDA 2023, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2023*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Demeclocycline	Doxycycline	Minocycline	Omadacycline	Sarecycline	Tetracycline
Alternative Treatment for Selected Infections When Penicillin is Contraindicated						
Gonococcal infections, uncomplicated	✔	✔ *	✔ *			
Listeriosis	✔		✔ *			
Syphilis	✔	✔	✔ *			✔
Vincent's infection	✔	✔	✔ *			✔
Yaws	✔	✔	✔ *			✔
Central Nervous System						
Treatment of asymptomatic meningococcal carriers			✔ *			
Dermatological						
Acne	✔ †	✔ †	✔ ‡		✔ #	✔ †
Rosacea		✔ ##				
Skin and soft tissue infections	✔		✔ *	✔		✔
Gastrointestinal						
Acute intestinal amebiasis	✔	✔	✔ *			✔
Cholera	✔	✔	✔ *			✔
Genitourinary conditions						
Chancroid	✔	✔	✔ *			✔
Urinary tract infections	✔	✔	✔ *			✔
Ophthalmic Infections						
Conjunctivitis (inclusion)	✔	✔	✔ *			✔
Trachoma	✔	✔	✔ *			✔
Respiratory Infections						
Anthrax	✔ §	✔	✔ *§			✔ §

Indication	Demeclocycline	Doxycycline	Minocycline	Omadacycline	Sarecycline	Tetracycline
Psittacosis	✔	✔	✔ *			✔
Respiratory tract infection	✔	✔	✔ *			✔
CABP				✔		
Rickettsial Infections						
Disease caused by rickettsiae	✔	✔	✔ *			✔
Q fever	✔	✔	✔ *			✔
Rickettsialpox	✔	✔	✔ *			✔
Rocky Mountain spotted fever	✔	✔	✔ *			✔
Typhus	✔	✔	✔ *			✔
Sexually Transmitted Infections						
Endocervical infections		✔	✔ *			✔
Granuloma inguinale	✔	✔	✔ *			✔
Lymphogranuloma venereum	✔	✔	✔ *			✔
Nongonococcal urethritis	✔	✔	✔ *			
Rectal infections		✔	✔ *			✔
Urethritis, uncomplicated	✔ §	✔	✔ *§			✔
Miscellaneous						
Malaria prophylaxis		✔				
Periodontitis		✔ ‖				
Plague	✔	✔	✔ *			✔
Relapsing fever	✔	✔	✔ *			✔
Tularemia	✔	✔	✔ *			✔

*Immediate-release only.
†May be useful as adjunctive therapy.
‡Solodyn (minocycline extended-release tablets) are indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 12 years of age. Minocycline immediate-release may be useful as adjunctive therapy.
§ When penicillin is contraindicated.
‖ Periostat (doxycycline hyclate immediate-release tablets), which has now been discontinued, was indicated as adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.
Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age.
Oracea only. Note: No meaningful effect was demonstrated for generalized erythema of rosacea.

(*Prescribing information: demeclocycline 2020, Doryx 2022, Doryx MPC 2022, doxycycline tablets 2019, minocycline capsules 2022, Minolira 2018, Nuzyra 2021, Oracea 2023, Seysara 2023, Solodyn 2017, TargaDOX 2019, tetracycline 2021, Vibramycin 2022, Ximino 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.

- Limitations of use:
  - Oracea has not been evaluated in the treatment or prevention of infections. It should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

- Oracea has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea.
- The efficacy of sarecycline beyond 12 weeks and safety beyond 12 months have not been established.
- Sarecycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drug, sarecycline should be used only as indicated
- Ximino did not demonstrate any effect on non-inflammatory acne lesions. Safety of Ximino has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections.

Clinical Efficacy Summary

- There are numerous clinical trials that have demonstrated the safety and efficacy of the tetracyclines for their respective FDA-approved indications, with no significant differences observed among the agents in this class. The focus of this section, however, will be the clinical trials for omadacycline and sarecycline *(Fleischer et al 2006, Garner et al 2003, Hubbell et al 1982, Lauharanta et al 1993, Lister et al 1993, Parish et al 2005, Rosentock et al 1985).*
- For the treatment of CABP, the efficacy of omadacycline was evaluated in a phase 3, double-blind (DB), active-control (AC), parallel-group (PG), multi-center (MC), randomized controlled trial (RCT), known as the OPTIC trial. The trial included 774 patients ≥ 18 years of age with radiographically confirmed pneumonia and a pneumonia severity index/Patient Outcomes Research Team (PORT) Risk Class II, III, or IV (ie, low- to moderate-risk). Patients were treated for 7 to 14 days with omadacycline 100 mg intravenous (IV) infusion every 12 hours for 2 doses on Day 1, followed by 100 mg IV infusion once daily for ≥ 3 days, with an option to switch to 300 mg orally once daily on Day 4 (n = 386); or moxifloxacin 400 mg IV infusion once daily for ≥ 3 days, with an option to switch to 400 mg orally once daily on Day 4 (n = 388). Of note, the efficacy and safety of an oral loading dose was not evaluated in CABP (*FDA multi-discipline review [Nuzyra] 2018, Stets et al 2019*).
  - The primary endpoint was clinical success (early clinical response [ECR]) at 72 to 120 hours after the first dose, defined as survival with improvement in ≥ 2 of 4 symptoms (cough, sputum production, chest pain, dyspnea) without deterioration.
    - Clinical success was demonstrated in 81.1% of omadacycline-treated patients vs 82.7% of moxifloxacin-treated patients, with a treatment difference of -1.6% (95% confidence interval [CI], -7.1 to 3.8).
    - For the clinical success endpoint, omadacycline met an efficacy finding of noninferiority vs moxifloxacin with the lower bound of the 2-sided 95% CI being greater than the pre-specified 10% noninferiority margin (80% power).
  - The secondary endpoint of clinical response at 5 to 10 days after the last study dose was defined as improvement in signs and symptoms of CABP with no further antibacterial therapy needed.
    - Clinical response was demonstrated in 87.6% of omadacycline-treated patients vs 85.1% of moxifloxacin-treated patients, with a treatment difference of 2.5% (95% CI, -2.4 to 7.4).
- For the treatment of ABSSSI, the efficacy of omadacycline was evaluated in 2 Phase 3, DB, AC, PG, MC, RCTs, known as the OASIS-1 and OASIS-2 trials. The trials included a total of 1012 patients ≥ 18 years of age with ABSSSI and evidence of a systemic inflammatory response. Of note, both trials excluded patients with necrotizing fasciitis or diabetic foot infections (*FDA multi-discipline review [Nuzyra] 2018, O'Riordan et al 2019[a], O'Riordan et al 2019[b]*).
  - In OASIS-1, patients were treated with omadacycline 100 mg IV infusion every 12 hours for 2 doses on day 1, followed by 100 mg IV infusion once daily for ≥ 3 days, with an option to switch to 300 mg orally once daily on Day 4 (n = 386); or linezolid 600 mg IV infusion twice daily for ≥ 3 days, with an option to switch to 600 mg orally every 12 hours on Day 4 (n = 322). In OASIS-2, patients were treated with omadacycline 450 mg orally once daily for 2 days, followed by 300 mg orally once daily (n = 368); or linezolid 600 mg orally every 12 hours (n = 367). Patients in both trials were treated for 7 to 14 days.
  - In both studies, the primary endpoint was clinical success (ECR) at 48 to 72 hours after the first study dose, defined as a ≥ 20% decrease in lesion size without clinical failure.
    - In OASIS-1, clinical success was demonstrated in 84.8% of omadacycline-treated patients vs 85.5% of linezolid-treated patients, with a treatment difference of -0.7% (95% CI, -6.3 to 4.9); in OASIS-2, clinical success was demonstrated in 88% of omadacycline-treated patients vs 83% of linezolid-treated patients, with a treatment difference of 5.0% (95% CI, -0.2 to 10.3).
    - In both trials, omadacycline met an efficacy finding of noninferiority for clinical success vs linezolid with the lower bound of the 2-sided 95% CI being greater than the pre-specified 10% noninferiority margin (90% power).

- The secondary endpoint of clinical response at 7 to 14 days after the last dose was defined as survival with resolution or improvement in signs or symptoms of infection without receiving alternative antibacterial therapy and/or unplanned major surgical intervention, and sufficient resolution of infection.
  - In OASIS-1, clinical response was demonstrated in 86.1% of the omadacycline-treated patients vs 83.6% of linezolid-treated patients, with a treatment difference of 2.5% (95% CI, -3.2 to 8.2); in OASIS-2, clinical response was demonstrated in 84% of the omadacycline-treated patients vs 81% of linezolid-treated patients, with a treatment difference of 3.3% (95% CI, -2.3 to 9.0).

- The efficacy and tolerability of sarecycline 1.5 mg/kg daily (administered as 60 mg, 100 mg, or 150 mg) were evaluated in 2 phase 3, DB, PC, RCTs (*Moore et al 2018, Seysara prescribing information 2018*). Patients 9 to 45 years of age with moderate to severe acne were randomized to sarecycline or placebo once daily for 12 weeks. At baseline, the mean facial inflammatory and noninflammatory lesion counts were approximately 30 and 43, respectively. The trials assessed the proportion of patients with success on the facial investigator's global assessment (IGA) (scores range from 0 [clear] to 4 [severe]), as well as assessing lesion counts.
  - In the first trial, the proportions of patients achieving IGA success (defined as clear or almost clear and a ≥ 2-grade improvement from baseline) were 21.9% and 10.5% in the sarecycline and placebo groups, respectively ($p < 0.0001$). In the second trial, proportions were 22.6% and 15.3%, respectively ($p = 0.0038$).
  - In the first trial, the mean absolute changes in inflammatory lesion counts were -15.3 and -10.2 for sarecycline and placebo, respectively ($p < 0.001$). In the second trial, changes were -15.5 and -11.1, respectively ($p < 0.001$).
  - Improvements were also demonstrated for reductions in noninflammatory lesions and for IGA success on chest and back acne.
- A systematic review of 13 studies evaluated the safety and efficacy of commonly used oral tetracyclines (ie, sarecycline, doxycycline, minocycline, tetracycline) for the treatment of acne. Compared to placebo, most agents demonstrated statistically significant reduction in inflammatory lesions or papule count (tetracycline) compared to placebo (sarecycline, $p < 0.0001$; doxycycline 40 mg, $p < 0.006$; minocycline, $p < 0.001$; tetracycline, $p < 0.05$). The most common AEs were headache with sarecycline and doxycycline; nausea and vomiting with tetracycline; and central nervous system (CNS)/vestibular effects (eg, nausea, vomiting, dizziness, vertigo) with minocycline, mainly due to its high lipophilicity and crossing of the blood-brain barrier (*Armstrong et al 2020*).

Clinical Guidelines

CABP

- Treatment recommendations from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommend selection of empiric antimicrobial regimens for outpatient treatment of CABP are based on the presence of patient comorbidities. Routine blood cultures are no longer recommended at the time of diagnosis for outpatient or inpatient CABP. However, 2 specific situations in which sputum gram stain and culture are recommended include in hospitalized patients with severe CABP or when strong risk factors for MRSA and *Pseudomonas (P) aeruginosa* are identified (*Metlay et al 2019*).
  - Patients with no comorbidities or risk factors for MRSA or *P. aeruginosa*: Amoxicillin or doxycycline or macrolide.
  - Patients with comorbidities (ie, chronic heart, lung, liver or renal disease, diabetes mellitus, alcoholism, malignancy or asplenia):
    - Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline, OR
    - Monotherapy with respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin).
  - For initial empiric therapy of severe CABP, the 2019 guidelines suggest stronger evidence for β-lactam/macrolide combination.
  - Geographic resistance patterns are an important consideration for treatment.
- The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends the use of empirical treatment with aminopenicillin with clavulanic acid, a macrolide, or a tetracycline for acute respiratory infections with a high probability of bacterial cause (presence of increased sputum purulence in addition to increased dyspnea and/or increased sputum volume), in patients with chronic obstructive lung disease (COPD). (*GOLD 2023*).

ABSSSI

- The IDSA recommended the following in their 2014 practice guidelines for the diagnosis and management of skin and soft tissue infections (*Stevens et al 2014*):
  - Nonpurulent skin and soft tissue infections (SSTIs): cellulitis/erysipelas/necrotizing infection
    - Mild infection (ie, typical cellulitis/erysipelas with no focus of purulence)

- Patients with typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against *streptococci* such as oral penicillin or amoxicillin, cephalosporin, dicloxacillin, or clindamycin.
- Moderate infection (ie, typical cellulitis/erysipelas with systemic signs of infection)
  - For cellulitis with systemic signs of infection, IV antibiotics such as penicillin, ceftriaxone, cefazolin, or clindamycin are indicated. Coverage against methicillin-susceptible *S. aureus* (MSSA) can be considered.
- Severe infection (ie, oral antibiotic failure, systemic signs of infection, immunocompromised patients, clinical signs of deeper infection [bullae, skin sloughing, hypotension, or evidence of organ dysfunction])
  - For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or systemic inflammatory response syndrome (SIRS), vancomycin or another antimicrobial effective against both MRSA and *streptococci* is recommended.
  - In severely compromised patients, broad-spectrum antimicrobial coverage may be considered.
  - Vancomycin plus either piperacillin/tazobactam or imipenem/cilastatin, or meropenem is recommended as a reasonable empiric regimen for severe nonpurulent infections.

- Purulent SSTIs: furuncle/carbuncle/abscess
- Mild infection (ie, inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles)
  - Incision and drainage is the recommended treatment.
- Moderate infection (ie, purulent infection with systemic signs of infection)
  - The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of SIRS.
  - Empiric treatment options include sulfamethoxazole/trimethoprim (SMX/TMP) and doxycycline.
  - MRSA: SMX/TMP
  - MSSA: Dicloxacillin or cephalexin
- Severe infection (ie, failure of incision and drainage plus oral antibiotics, systemic signs of infection, immunocompromised patients)
  - An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
  - Empiric treatment options include vancomycin, daptomycin, linezolid, telavancin, and ceftaroline.
  - MRSA: any of the empiric treatments may be considered.
  - MSSA: nafcillin, cefazolin, or clindamycin.

- The Clinical practice guidelines by the IDSA for the treatment of MRSA infections recommend the following in adults and children (*Liu et al 2011*):
  - The following recommendations pertain only to the management of SSTI and pneumonia associated with MRSA disease.
  - SSTIs
    - For a cutaneous abscess, incision and drainage is the primary treatment.
      - Antibiotic therapy is recommended for abscesses associated with conditions such as severe or extensive disease or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, abscess in an area difficult to drain (eg, face and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone.
    - For outpatients with purulent cellulitis, empiric therapy for community acquired MRSA (CA-MRSA) is recommended pending culture results. Empiric therapy for infection due to β-hemolytic *streptococci* is likely to be unnecessary.
    - For outpatients with nonpurulent cellulitis, empiric therapy for infection due to β-hemolytic *streptococci* is recommended. Empiric coverage for CA-MRSA is recommended in patients who do not respond to β-lactam therapy and may be considered in those with systemic toxicity.
    - For empiric coverage of CA-MRSA in outpatients with SSTI, oral antibiotic options include clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both β-hemolytic *streptococci* and CA-MRSA is desired, options include clindamycin alone, SMX/TMP or a tetracycline in combination with a β-lactam (eg, amoxicillin), or linezolid alone.
    - For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used.
      - Tetracyclines should not be used in children < 8 years of age.

Acne

- The American Academy of Dermatology published guidelines for the management of acne vulgaris in 2015. The recommendations are as follows (*Zaenglein et al 2016*):
  - Systemic antibiotics are recommended in the management of moderate and severe acne, and forms of inflammatory acne that are resistant to topical treatments.
    - Doxycycline and minocycline are considered more effective than tetracycline, but neither agent is considered superior over the other.
    - Oral erythromycin and azithromycin can be effective; however, their use should be limited to patients who cannot use tetracyclines (eg, pregnant women or children < 8 years of age). Of note, erythromycin should be used carefully, due to the increased risk of bacterial resistance.
    - Systemic antibiotic use should be limited to the shortest possible duration, usually 3 months, in order to minimize the risk of bacterial resistance.
    - Monotherapy with systemic antibiotics is not recommended. Concomitant topical therapy (eg, benzoyl peroxide and/or retinoid) should be used with systemic antibiotics, as well as maintenance after completion of systemic antibiotic therapy.

Sexually-transmitted diseases (STDs)

- The Centers for Disease Control (CDC) published treatment guidelines for the management of STDs in 2021. The recommendations are listed below (*CDC 2021*).
  - Chancroid
    - Azithromcyin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies.
  - Granuloma inguinale
    - Azithromycin is recommended.
    - Alternative agents include doxycycline, erythromycin or SMX/TMP.
  - Lymphogranuloma venereum
    - Doxycycline for 21 days is recommended.
    - Azithromycin once weekly for 3 weeks or erythromycin for 21 days are alternative treatment options.
  - Syphilis
    - Penicillin G is the preferred drug for all stages of syphilis. Alternative agents in patients who are allergic to penicillin may include doxycycline, tetracycline, or ceftriaxone (for neurosyphilis).
    - Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized.
    - Benzathine penicillin G is recommended for primary and secondary syphilis.
    - Infants > 1 month of age with primary or secondary syphilis should be treated with benzathine penicillin G.
    - Patients with neurosyphilis should be treated with aqueous crystalline penicillin G. An alternative regimen in patients in whom compliance can be assured is procaine penicillin plus probenecid.
  - Urethritis
    - Doxycycline is recommended. Azithromycin is an alternative regimen.
  - Cervicitis
    - Doxycycline is recommended. Azithromycin is an alternative regimen.
  - Chlamydia
    - Doxycycline is recommended.
    - Alternative agents include azithromycin or levofloxacin.
    - Azithromycin is recommended in pregnant patients. An alternative agent is amoxicillin.
  - Pelvic inflammatory disease
    - Recommended parenteral regimen A: ceftriaxone plus metronidazole plus doxycycline (oral or IV).
    - Recommended parenteral regimen B: cefotetan plus doxycycline (oral or IV).
    - Recommended parenteral regimen C: cefoxitin plus doxycycline (oral or IV).
    - Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or IV) or clindamycin plus gentamicin.
    - Outpatient oral therapy may be considered in patients with mild to moderate disease. Recommended regimens include ceftriaxone plus doxycycline with metronidazole, cefoxitin and probenecid plus doxycycline with metronidazole, or another parenteral third generation cephalosporin plus doxycycline with metronidazole.
  - Epididymitis

- Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex): ceftriaxone + levofloxacin are recommended. For acute infections most likely caused by enteric organisms only: levofloxacin.
- Proctitis
  - Ceftriaxone + doxycycline are recommended.

Plague

- The 2021 CDC recommendations for the treatment and prophylaxis of plague (*Nelson et al 2021*) indicate that FDA-approved antimicrobials for treatment and prophylaxis of plague include streptomycin, ciprofloxacin, levofloxacin, moxifloxacin, and doxycycline. Although gentamicin, chloramphenicol, and SMX/TMP are not FDA approved for plague, they are effective based on clinical experience and animal data.
  - Doxycycline is an alternative agent recommended by the CDC for pneumonic or septicemic plague in non-pregnant adults and children.
  - Doxycycline is one of several first-line agents recommended for bubonic or pharyngeal plague in adults and children, and for pre- and post-exposure prophylaxis in non-pregnant adults and children potentially exposed to *Yersinia pestis.*
  - Omadacycline (adults only), tetracycline (adults and children), and minocycline (adults and children) are listed as potential alternatives for bubonic or pharyngeal plague, and for pre- and post-exposure prophylaxis after potential exposure to *Yersinia pestis*.
  - In pregnant women, doxycycline, tetracycline, or minocycline are alternative agents for pre- and post-exposure prophylaxis of *Yersinia pestis,* and doxycycline is an alternative agent for treatment of pneumonic, septicemic, bubonic, or pharyngeal plague.

Safety Summary

- The tetracyclines are contraindicated in patients hypersensitive to tetracyclines or any component in the formulations.
- Key warnings and precautions for tetracyclines:
  - Tooth discoloration and enamel hypoplasia: Use during tooth development (ie, during the last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia.
  - Inhibition of bone growth: Use during the second and third trimester of pregnancy, infancy, and childhood up to the age of 8 years may cause reversible inhibition of bone growth.
  - *C. difficile*-associated diarrhea
  - Photosensitivity: Skin protection and sun avoidance is recommended.
- Tetracyclines are generally considered safe; the most common adverse effects associated with this class are gastrointestinal in nature, eg, epigastric pain, anorexia, diarrhea, nausea, and vomiting.
- Key drug interactions with the tetracycline class include:
  - Antacids and iron preparations: Dosing should be spaced apart.
  - Methoxyflurane: Fatal renal toxicity has been reported.
  - Anticoagulants: Anticoagulant levels may increase.
  - Retinoids: Increased risk of pseudotumor cerebri (benign intracranial hypertension)
  - Urinary alkalinizers and zinc salts: Serum levels of tetracyclines may decrease.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Avidoxy, Doryx, Doryx MPC, Mondoxyne NL, TargaDOX, Vibramycin (doxycycline)	Capsules, suspension, syrup, tablets, delayed-release tablets	Oral	More severe or life-threatening infections Once or twice daily Prophylaxis of malaria	Pediatric dosing in patients who weigh < 45 kg is weight-based; patients weighing ≥ 45 kg should receive the adult dose, which may differ based on the indication.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily, starting 1 to 2 days before travel and for 4 weeks after return from travel Inhalation anthrax Twice daily for 60 days	Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer May be given with food or milk if gastric irritation occurs Tablets may be broken into thirds to provide the appropriate strength.
Oracea (doxycycline)	Capsules, delayed-release beads	Oral	Once daily in the morning	Should be taken on an empty stomach, preferably ≥ 1 prior or 2 hours after meals The dose of Oracea differs from other doxycycline formulations that are used to treat infections.
demeclocycline	Tablets	Oral	Adults: twice daily Pediatric patients > 8 years of age: 2 to 4 times daily	Pediatric dosing in weight-based. Should be used cautiously in patients with impaired renal or hepatic function (dose may need to be decreased or dosing interval extended) Should be given at least 1 hour before or 2 hours after meals Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer
minocycline	Capsules, tablets	Oral	Adults: Immediate release: 2 to 4 times daily Pediatric patients > 8 years of age: 2 times daily	Pediatric dosing is weight-based. Can be given with or without food Should be administered with adequate amounts of fluid to reduce risk of esophageal irritation/ulcer Current data are insufficient to determine if a dosage adjustment is warranted in patients with creatinine clearance (CLcr) < 80 mL/min; therefore, the total daily dosage

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				should not exceed 200 mg in 24 hours in these patients (blood urea nitrogen [BUN] and serum creatinine should be monitored).
Nuzyra (omadacycline)	Tablets, injection	IV, oral	IV: once daily infusion over 30 minutes for 7 to 14 days Oral: once daily for 7 to 14 days, plus: loading dose administered twice in CABP and once in ABSSSI)	A higher dose is recommended for ABSSSI. Fasting is recommended for at least 4 hours prior to oral omadacycline administration; with the exception of water, food and drink should be avoided for 2 hours and dairy products, antacids, or multivitamins for 4 hours post oral omadacycline administration. Safety and efficacy have not been established in pediatric patients < 18 years of age. Omadacycline should be avoided in patients < 8 years of age, due to potential adverse effects related to tooth development and bone growth.
Seysara (sarecycline)	Tablets	Oral	Once daily	Weight-based dosing
Minolira, Solodyn, Ximino (minocycline)	Extended-release tablets, extended-release capsules	Oral	Once daily	May be taken with or without food; however, food may help reduce risk of esophageal irritation A dose decrease or extend dosing interval is recommended in patients with renal impairment. Safety beyond 12 weeks has not been established (Solodyn, Minolira, Ximino).
tetracycline	Capsule	Oral	Adults: 2 to 4 times daily Pediatric patients > 8 years of age: 4 times daily	Pediatric dosing is weight-based. Should be used cautiously in patients with impaired renal function (a dose decrease or extend dosing interval is recommended) Should be administered with adequate amounts of fluid to

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				reduce risk of esophageal irritation/ulcer

See the current prescribing information for full details.

Conclusion

- The tetracyclines are broad-spectrum bacteriostatic antibiotics with activity against many aerobic gram-positive and gram-negative bacteria and atypical pathogens (eg, *Mycoplasma pneumoniae* and *Chlamydia* spp).
- Based on various treatment guidelines, the tetracyclines potentially play a role in the treatment of various infectious diseases based on their established susceptibility to certain microorganisms and FDA-approved indications.
- Within the class, no major clinically significant differences exist among the various agents; however, doxycycline and minocycline appear to be the most highly utilized.
- Tetracyclines have been associated with permanent tooth discoloration in children < 8 years of age if used repeatedly or for prolonged courses, and with accumulation in fetal bones and teeth when administered to pregnant women.
  - The newer generation tetracyclines (eg, doxycycline) are associated with a lower risk of dental staining when used ≤ 21 days in children.
  - Doxycycline has not been correlated with teratogenic effects during pregnancy and is a treatment option when other agents appear less effective.
- Tetracycline antibiotics are relatively safe, with the most common adverse events relating to gastrointestinal symptoms.
- Omadacycline, FDA-approved in 2018, provides an additional oral option for the treatment of ABSSSI due to MRSA, as well as a non-fluoroquinolone monotherapy option for CABP.
  - In CABP, a phase 3 RCT demonstrated non-inferiority with omadacycline treatment vs an appropriate comparator (ie, moxifloxacin) for clinical success (ie, ECR) in patients with low- to moderate-risk pneumonia.
  - In ABSSSI, 2 phase 3 RCTs demonstrated non-inferiority with omadacycline treatment vs an appropriate comparator (ie, linezolid) for clinical success (ie, ECR) in patients with moderate to severe skin infections.
- Sarecycline, also FDA-approved in 2018, is specifically indicated for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age.
  - Sarecycline has demonstrated efficacy vs placebo for improving the severity of acne and decreasing lesion counts, and is well tolerated.

References

- Armstrong AW, Hekmatjah J, Kircir LH. Oral tetracyclines and acne: A systematic review for dermatologists. *J Drugs Dermatol*. 2020;19(11):s6-s13.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. CDC Web site. https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf . Updated 2021. Accessed September 17, 2023.
- Demeclocycline [package insert], Bridgewater, NJ: Amneal Pharmaceuticals; December 2020.
- Doryx [package insert], Greenville, NC: Mayne Pharma USA; July 2022.
- Doryx MPC [package insert]. Greenville, NC: Mayne Pharma; July 2022.
- Doxycycline tablets [package insert], East Brunswick, NJ: Avet Pharmaceuticals, Inc.; December 2019.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed September 17, 2023.
- File T. Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults. UpToDate Web site. www.uptodate.com. Updated March 3, 2023. Accessed September 17, 2023.
- File T. Treatment of community-acquired pneumonia in adults in the outpatient setting. UpToDate Web site. www.uptodate.com. Updated April 15, 2022. Accessed September 17, 2023.
- Fleischer AB Jr, Dinehart S, Stough D, Plott RT; Solodyn Phase 2 Study Group; Solodyn Phase 3 Study Group. Safety and efficacy of a new extended-release formulation of minocycline (abstract). *Cutis*. 2006;78(4 Suppl):S21-31.
- Food and Drug Administration. Multi-discipline review: Nuzyra. 2019. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209816Orig1s000,209817Orig1s000TOC.cfm. Accessed September 17, 2023.
- Garner SE, Eady A, Popescu CM, Newton J, Li Wan, Po A. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD002086. DOI:10.1002/14651858.CD002086.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2023. https://goldcopd.org/2023-gold-report-2/. Accessed October 21, 2023.
- Graber E. Acne vulgaris: Management of moderate to severe acne. UpToDate Web site. www.uptodate.com. Updated May 20, 2022. Accessed September 17, 2023.
- Hubbell CG, Hobbs ER, Rist T, White JW. Efficacy of minocycline compared to tetracycline in treatment of acne vulgaris. *Arch Dermatol.* 1982;118:989-92.

- Lauharanta J, Saarinen K, Mustonen M, Happonen H. Single-dose oral azithromycin vs seven-day doxycycline in the treatment of non-gonococcal urethritis in males. *J Antimicrob Chemother*. 1993;31(Suppl E):S177-83.
- Lister PJ, Balechandran T, Ridgway GL, Robinson AJ. Comparison of azithromycin and doxycycline in the treatment of non-gonococcal urethritis in men. *J Antimicrob Chemother.*1993;31(Suppl E):S185-92.
- Liu C, Bayer A, Cosgrove SE, et al; for the Infectious Diseases Society of America (IDSA). Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18-55.
- Marrie T, File T. Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults. UpToDate Web site. www.uptodate.com. Updated June 11, 2018. April 8, 2019.
- May DB. Tetracyclines. UpToDate Web site. www.uptodate.com. Updated June 20, 2022. Accessed September 17, 2023.
- Medical Letter, Inc. Drugs for acne. 2016; 58(1487):13-15.
- Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. *Am J Respir Crit Care Med*. 2019:200(7);e45-e67.
- Minocycline capsules [package insert], East Windsor, NJ: Aurobindo Pharma USA; February 2022.
- Minolira [package insert], Charleston, SC: EPI Health, Inc.; June 2018.
- Moore A, Green LJ, Bruce S, et al. Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe acne vulgaris: results from two identically designed, phase 3, randomized, double-blind clinical trials. *J Drugs Dermatol*. 2018; 17(9):987-996.
- Nelson CA, Meaney-Delman D, Fleck-Derderian S, et al. Antimicrobial treatment and prophylaxis of plague: Recommendations for naturally acquired infections and bioterrorism response. *MMWR Recomm Rep.* 2021;70(3):1-27.
- Nelson ML, Levy SB. The history of tetracyclines. *Ann N Y Acad Sci*. 2011;1241:17-32.
- Nuzyra [package insert], Boston, MA: Paratek Pharmaceuticals, Inc.; May 2021.
- Oracea [package insert], Fort Worth, TX: Galderma Laboratories; January 2023.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed September 17, 2023.
- O'Riordan W, Cardenas C, Shin E, et al. Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial. *Lancet Infect Dis.* 2019[a];19(10):1080-1090. doi:10.1016/S1473-3099(19)30275-0
- O'Riordan W, Green S, Overcash JS, et al. Omadacycline for acute bacterial skin and skin-structure infections. *N Engl J Med*. 2019[b];380(6):528-538. doi: 10.1056/NEJMoa1800170.
- Parish LC, Parish JL, Routh HB, et al. The treatment of acne vulgaris with low dosage doxycycline (abstract). *Acta Dermatovenerol Croat.* 2005;13(3):156-9.
- Rosenstock J, Smith LP, Gurney M, Lee K, Weingberg WG, Longfield JN, et al. Comparison of single-dose tetracycline hydrochloride to conventional therapy of urinary tract infections. *Antimicrob Agents Chemother.*1985;27(4):652-4.
- Seysara [package insert], Exton, PA: Almirall, LLC; March 2023.
- Solodyn [package insert], Bridgewater, NJ: Valeant Pharmaceuticals, Inc.; September 2017.
- Stets R, Popescu M, Gonong JR, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. *N Engl J Med.* 2019;380(6):517-527. doi: 10.1056/NEJMoa1800201.
- Stevens DL, Bisno AL, Chambers HF, et al; for the Infectious Diseases Society of America (IDSA). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):147-159.
- TargaDOX [package insert], Scottsdale, AZ: Journey Medical Co.; March 2019.
- tetracycline capsule [package insert], Congers, NY: Chartwell Pharmaceuticals, LLC; February 2021.
- Vibramycin [package insert], New York, NY: Pfizer, Inc.; December 2022.
- Ximino [package insert], Cranbury, NJ: Sun Pharmaceuticals, Inc.; January 2021.
- Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74:945-973.

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Introduction

- *Clostridioides difficile* is a spore-forming, anaerobic, gram-positive bacillus (rod) which may cause life-threatening diarrhea and colitis, and is the leading cause of antibiotic-associated diarrhea in the United States (U.S) (*Centers for Disease Control and Prevention [CDC] Web site 2021*).
  - *C. difficile* infection (CDI) is estimated to cause approximately half a million infections in the U.S. each year, and is associated with significant morbidity and mortality, accounting for 15,000 to 30,000 deaths annually in the U.S. (*CDC Web site 2021, Fu et al 2021*).
- CDI is spread through person-to-person contact via the fecal-oral route, or from direct exposure to an environment contaminated with *C. difficile* spores (*CDC Web site 2021*).
  - Symptoms include watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness.
  - The majority of infections with *C. difficile* occur during a course of antibiotics or shortly after completing antibiotic therapy, with patients being 7 to 10 times more likely be infected with *C. difficile* while on antibiotics and during the month after (*CDC Web site 2021*).
    - Antibiotic exposure is the most important modifiable risk factor for *C. difficile*, as receipt of antibiotics may suppress the normal bowel microbiota, reduce microbiota diversity, and provide a niche for *C. difficile* spores to germinate (*Khanna et al 2022)*.
    - This disruption of the microbiota, or dysbiosis, is long-lasting, and leads to a risk of recurrent CDI (rCDI); restoration of the intestinal microbiota plays an important role to reduce recurrence (*Khanna et al 2022*).
  - rCDI is an episode of CDI, confirmed by symptoms and a positive assay, following a previous episode of CDI in the previous 2 to 8 weeks (*McDonald et al 2018*).
    - After a first diagnosis of CDI, 10 to 30% of patients develop ≥ 1 rCDI episode. The risk of recurrence increases with each successive recurrence, with a reported recurrence rate of 65% after 3 episodes of CDI (*Fu et al 2021*).
- The recommended treatment for an initial episode of CDI is use of standard-of-care (SOC) CDI-directed antimicrobial therapy such as fidaxomicin or oral vancomycin for 10 days (*Johnson et al 2021, Kelly et al 2021*).
  - While fidaxomicin and oral vancomycin effectively eliminate toxin-producing *C. difficile* bacteria, they are not sporicidal, and may disturb the gut microbiota further, which allows *C. difficile* spore germination, and may lead to continued risk of rCDI (*Khanna et al 2022*).
- Treatment regimens for rCDI vary depending on the number of recurrences and severity of the current episode.
  - In general, for a first recurrence, fidaxomicin or vancomycin are recommended, administered as either a standard 10-day course of therapy or in a tapered/pulsed regimen; bezlotoxumab may be considered as an adjunctive therapy during administration of antibiotics to reduce the risk of rCDI (*Johnson et al 2021*, *Kelly et al 2021, Zinplava prescribing information 2023)*.
  - Second or subsequent episodes of rCDI are treated similarly as the first recurrence, with additional consideration for fecal microbiota transplant (FMT), which treats rCDI through restoration of normal gut microbiota by infusion of healthy donor stool (*Johnson et al 2021*, *Kelly et al 2021)*.
    - FMT via stool bank has not been approved by the Food and Drug Administration (FDA), and the FDA has issued safety alerts related to the risk of transmissible infectious agents (*FDA safety alert 2020*).
- There are currently 2 FDA-approved fecal microbiota products, Rebyota (fecal microbiota, live-jslm) and Vowst (fecal microbiota spores, live-brpk), which aim to prevent recurrence of CDI by addressing the underlying dysbiosis through restoration of healthy gut microbiota (*Rebyota prescribing information 2023, Vowst prescribing information 2023*).
  - Vowst (fecal microbiota spores, live-brpk) is an orally administered fecal microbiota-based live biotherapeutic that received FDA approval on April 26, 2023 with Priority Review, Breakthrough Therapy, and Orphan Drug designations, for the prevention of recurrence of CDI in patients ≥ 18 years of age following antibacterial treatment for rCDI (*FDA Web site 2023, FDA Vowst Summary Basis for Regulatory Action [SBRA] 2023*).
    - Vowst is a bacterial spore suspension supplied as capsules containing between 1×10^6 and 3×10^7 of Firmicutes spore colony forming units (CFU) for oral administration.
    - Vowst is manufactured from human fecal matter sourced from qualified, pre-screened donors. The spore suspension is generated by treating fecal matter with ethanol to kill organisms that are not spores such as bacteria, fungi, parasites, and viruses, followed by filtration steps to remove solids and residual ethanol, and contains a pre-specified amount of Firmicutes spore CFU (*FDA Vowst SBRA 2023*).
- Medispan class: Live fecal microbiota (human)

Indications

- Vowst is indicated for the prevention of recurrence of CDI in individuals ≥ 18 years old following antibacterial treatment for rCDI.
  - Limitation of Use: Vowst is not indicated for treatment of CDI.
- 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

- Vowst was approved based on a Phase 3 development program that included ECOSPOR III, a multicenter (MC), placebo-controlled (PC), randomized-controlled trial (RCT), and ECOSPOR IV, a single-arm (SA), open-label (OL) trial (*Feuerstadt et al 2022, Sims et al 2023*).
  - ECOSPOR III was a Phase 3, MC, PC, RCT evaluating the safety and efficacy of Vowst for the prevention of rCDI in adult patients (*Feuerstadt et al 2022*).
    - Patients were included in the study if they had ≥ 3 episodes of CDI in the last 12 months, defined as ≥ 3 unformed bowel movements over 2 consecutive days, and a positive *C. difficile* toxin test. They had to have resolution of symptoms for ≥ 2 days after completion of 10 to 21 days of SOC CDI antibiotic therapy.
    - Patients were randomized to Vowst or placebo in a 1:1 ratio, administered within 4 days after achieving symptom control, and after completion of SOC antibiotic therapy. Patients were required to take magnesium citrate 24 hours prior to administration of Vowst to clear residual vancomycin or fidaxomicin from the gastrointestinal (GI) tract.
    - The majority of patients in ECOSPOR III were White (92%), female (67%), and had ≥ 3 episodes of CDI (ie, 2 episodes of rCDI) in the last 12 months. Patients with active inflammatory bowel disease (IBD) within ≤ 3 months, toxic megacolon, small bowel ileus, major GI surgery ≤ 3 months prior to enrollment, neutropenia, or prior administration of bezlotuxumab or FMT within ≤ 3 months were excluded.
    - Vowst significantly reduced the rate of rCDI at 8 weeks as compared to placebo (88% vs 60%, respectively), with a rate of recurrence of 12.4% vs 39.8%, representing a 68% lower risk than SOC antibiotics alone.
    - The most common adverse events (AEs) included GI symptoms (eg, flatulence, abdominal distention and pain, constipation, diarrhea, nausea, and vomiting), and the frequency of AEs was similar between both groups.
    - The authors concluded that administration of Vowst after completion of SOC CDI-directed antibiotics was superior to placebo in reducing the risk of rCDI with an observed safety profile similar to placebo.
  - ECOSPOR IV was a Phase 3, SA, OL trial evaluating the safety and rate of rCDI after administration of Vowst through 24 weeks. Patients were enrolled in 2 cohorts: Rollover patients from ECOSPOR III who had rCDI, and patients with ≥ 1 episode of rCDI (*Sims et al 2023*).
    - AEs were reported in 53.6% of patients, with the most commonly reported AEs (≥ 5%) being mild to moderate GI-related events (eg, diarrhea, flatulence, nausea, and abdominal pain). No death or serious AEs were considered treatment related.
    - Overall, rCDI rates remained low through 24 weeks at 13.7% (36/141).
    - The authors concluded that Vowst was well tolerated, and the rate of rCDI remained low during the 24-week period.

Clinical guidelines

- **Clinical practice guidelines for CDI in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA**) (*McDonald et al* 2018).
- **Clinical practice guideline by the IDSA and SHEA: 2021 focused update guidelines on the management of CDI in adults** (*Johnson et al 2021*).
  - For an initial CDI episode, the IDSA guidelines recommend a 10-day course of fidaxomicin (preferred), or oral vancomycin as an alternative. Oral metronidazole may be considered for non-severe CDI (white blood cell [WBC] ≤ 15,000 cells/mm3 and serum creatinine [SCr] < 1.5 mg/dL) if the other agents are not available.
    - Fidaxomicin is preferred per the guidelines due to studies showing lower rates of rCDI, as well as an overall narrower spectrum of activity as compared to vancomycin, potentially leading to less disruption of the gut microbiome.
  - For a first CDI recurrence, fidaxomicin is recommended as the preferred first-line therapy, with consideration for an extended and pulsed regimen. Oral vancomycin administered as a tapered or pulsed regimen is a recommended alternative regimen.

    - Bezlotuxumab is recommended as an adjunctive treatment, administered during the course of SOC antibiotics for high-risk patients (eg, age > 65 years, immunocompromised, severe CDI on presentation). Guidelines note that implementation depends upon available resources and logistics for IV administration.
  - In patients with second or subsequent CDI recurrences, fidaxomicin or vancomycin can be repeated in a pulsed or tapered regimen, with the additional recommendation of FMT. The opinion of the IDSA panel is that FMT be considered in patients with ≥ 2 recurrences of CDI who have failed appropriate antibiotic treatment.
  - Fecal microbiota products have not been incorporated into the current IDSA guidelines as publication occurred before availability of either Rebyota or Vowst.
- **ACG clinical guidelines: prevention, diagnosis, and treatment of CDI** (*Kelly et al 2021*).
  - For the initial CDI episode and first recurrence, oral vancomycin or fidaxomicin in standard 10-day courses or tapered/pulsed dosing regimens are recommended treatment options. Metronidazole may be considered for an initial episode in low-risk patients with non-severe CDI (WBC ≤ 15,000 cells/mm3 and SCr < 1.5 mg/dL.
  - In patients with a second or further recurrence, FMT via colonoscopy is recommended.
  - The ACG guidelines discuss preventative options including daily oral vancomycin taken in conjunction with non-CDI antibiotic courses, adjunctive bezlotuxumab co-administered with SOC antibiotics in patients at high risk of recurrence,
    - FMT, while mainly used as treatment for rCDI, is also recommended as a preventative agent as it restores the gut microbiome, leading to less rCDI.
  - The ACG guidelines discuss that defined microbiota consortia may enable a more targeted approach to treating the underlying dysbiosis that drives CDI; if cost-effective and safe, these products may be used early in the clinical course, even after a first CDI. At the time of publication, FDA-approved fecal microbiota products were not available.

Safety summary

- Warnings and precautions:
- *Risk of transmissible infectious agents*: Because Vowst is manufactured from human fecal matter, it may carry a risk of transmitting infectious agents; all human fecal matter donations are collected from pre-screened and qualified donors and routinely tested for a panel of transmissible pathogens.
  - The Vowst spore-containing suspension is generated by treating fecal matter with ethanol to kill organisms that are not Firmicutes spores, then filtered to remove solids and residual ethanol.
- *Potential presence of food allergens*: Vowst may contain food allergens. The potential to cause adverse reactions due to food allergens is unknown.
- The most common (≥ 5%) AEs reported within 8 weeks after administration as compared to placebo in ECOSPOR III were abdominal distention (31.1% vs 29.3%, respectively), fatigue (22.2% vs 21.7%), constipation (14.4% vs 10.9%), chills (11.1% vs 7.6%), and diarrhea (10.0% vs 4.3%).
    - The majority of events were mild to moderate in severity, occurred within 10 days of treatment and had a median duration of ≤ 5 days.
  - In ECOSPOR IV, the most common AEs included flatulence (4.2%), diarrhea (3.4%), and nausea (3.0%). There were no serious AEs considered related to Vowst.

Dosing and administration

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Vowst (fecal microbiota spores, live-brpk)	Capsule	Oral	4 capsules once daily for 3 days	• Vowst should be administered 2 to 4 days after completion of SOC CDI antibiotics. • Patients should drink 10 ounces (296 mL) of magnesium citrate ≥ 8 hours prior to the first dose. • Vowst should be administered on an empty stomach (no food or drink, except a small

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				amount of water for ≥ 8 hours) prior to the first meal of the day.

See the current prescribing information for full details.

Conclusion

- Vowst is 1 of 2 available fecal microbiota biotherapies with FDA approval for the prevention of recurrence of rCDI in patients ≥ 18 years of age following antibacterial treatment for rCDI.
  - Phase 3 data demonstrated a significant reduction in rCDI at 8 weeks with Vowst vs placebo (88% vs 60%, respectively), representing a 68% lower risk than SOC antibiotics alone *(Feuerstadt et al 2022)*.
  - Safety outcomes in 2 Phase 3 trials showed no significant difference between Vowst and placebo, with the most common AEs reported as mild to moderate GI-related events including abdominal distention, flatulence, diarrhea, and constipation (*Feuerstadt et al 2022, Sims et al 2023*).
- Vowst is available as an oral capsule, with 4 capsules taken once daily for 3 days; magnesium citrate should be administered ≤ 8 hours prior to the first dose to clear residual SOC CDI antibiotics.
  - The mechanism of action of Vowst has not yet been established but delivers a pre-specified amount of live spores (ie, Firmicutes) into the GI tract, which are associated with restorative microbiome changes.
  - The spore suspension is treated with ethanol to kill infectious agents, followed by filtration to remove solids and residual ethanol; however, warnings and precautions for Vowst include the potential to contain food allergens and the risk of transmitting infectious agents.
- Fecal microbiota products such as Vowst have not been incorporated into guidelines for the treatment of CDI, and it's place in therapy has not yet been fully established, but was studied for use in patients with ≥ 2 episodes of CDI administered after completion of SOC antibiotics for rCDI.

References

- Centers for Disease Control and Prevention (CDC). *C. diff* (*Clostridioides difficile*). July 12, 2021. https://www.cdc.gov/cdiff/index.html. Accessed July 29, 2023.
- Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an oral microbiome therapy for recurrent Clostridioides difficile infection. *N Engl J Med.* 2022;386:220-229.
- Food and Drug Administration (FDA). Fecal microbiota for transplantation: Safety alert- risk of serious adverse events likely due to transmission of pathogenic organisms. April 2020. FDA Web site. https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission. Accessed August 1, 2023.
- Food and Drug Administration (FDA). Fecal microbiota products. April 28, 2023. FDA Web site. https://www.fda.gov/vaccines-blood-biologics/fecal-microbiota-products. Accessed August 1, 2023.
- Food and Drug Administration (FDA). Summary basis for regulatory action - Vowst. 2023. FDA Web site. https://www.fda.gov/media/168002/download. Accessed August 3, 2023.
- Fu Y, Luo Y, Grinspan AM. Epidemiology of community-acquired and recurrent *Clostridioides difficile* infection. *Ther Adv Gastroenterol*. 2021;14:1-11.
- Johnson S, Lavergne V, Skinner AM, et al. Clinical practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis.* 2021;73(5):e1029-e1044.
- Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: Prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol*. 2021;116:1124-1147.
- Khanna S, Sims M, Louie TJ, et al. SER-109: an oral investigational microbiome therapeutic for patients with recurrent *Clostridioides difficile* infection (rCDI). *Antibiotics*. 2022;11:1234. doi:10.3390/antibiotics11091234.
- McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1-e48.
- Rebyota [package insert], Roseville, MN: Ferring Pharmaceuticals; December 2022.
- Sims MD, Khanna S, Feuerstadt P, et al; ECOSPOR IV Investigators. Safety and tolerability of SER-109 as an investigational microbiome therapeutic in adults with recurrent *Clostridioides difficile* infection: A phase 3, open-label, single-arm trial. JAMA Netw Open. 2023;6(2):e2255758. doi: 10.1001/jamanetworkopen.2022.55758.
- Vowst [package insert], Cambridge, MA: Seres Therapeutics, Inc; April 2023.
- Zinplava [package insert], Whitehouse Station, NJ: Merk and Co, Inc.; May 2023.