South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

March 13, 2026

South Dakota
Department of
Social Services

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South Dakota Department of Social Services

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

March 13, 2026
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_NGJiMzU4YmQtZWQ2YS00MjA0LTgyMDctYjhkNGM1YzFiZGY0%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a Video Conferencing Device
teams@optum.onpexip.com
Video Conference ID: 111 893 702 34

Join by Phone
+1 952-222-7450
Phone Conference ID: 742 032 384#

Call to Order

Approval of Previous Meeting Minutes

PA Update
Review of Top 15 Therapeutic Categories/Top 50 Drugs

Old business
- **Non-Hormonal Drugs for Vasomotor Symptoms**
- **Opioid Update**

New business
- **Biosimilar PDL**
- **Brinsupri**
- **Coxanto**
- **MASH Treatments**
- **Zepbound OSA**

Public input accepted after individual topic discussion
Next meeting date June 12, 2026 (tentative) & adjournment

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

Friday, December 12, 2025
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Van Gilder called the meeting to order at 1:01 pm. The minutes of the September meeting were presented. Baack moved to approve. Oehlke seconded the motion. The motion carried unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report for the period July 1 to September 30, 2025. A total of 5,496 PAs were reviewed of which 139 requests (2.5%) were received via telephone, 100 requests (1.8%) were received via fax, 2,770 requests (50.4%) were reviewed electronically, and 2,487 requests (45.3%) were received via ePA.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims for period July 1 to September 30, 2025. The top five therapeutic classes based on paid amount were atypical antipsychotics, immunomodulator agents, incretin mimetics, tumor necrosis factor inhibitors, and interleukin-mediated agents. Collectively, the top 15 therapeutic classes accounted for 18.26% of all claims. The committee also reviewed the top 50 drugs ranked by paid amount and claim volume. The top 50 drugs by amount paid represented 9.54% of total claims.

Old Business

Vykat XR

The committee reviewed Vykat XR utilization. Van Gilder recommended the adoption of a simplified PA framework. Mae Kwong, Medical Managed Liaison from Soleno Therapeutics, provided public comment. Baack moved to proceed with Commercial D criteria, excluding prescriber requirement. Ladwig seconded the motion and it was unanimously approved.

Opioid Update

The committee reviewed opioid outcomes from the opioid initiatives, comparing results to the previous quarter. Opioid utilization and utilizers increased in Q3 2025, aligning with the broader trend across all drug utilization. The average daily opioid MME per utilizer remained stable. Van Gilder asked if there were any public comments; none were offered.

New Business

Bimzelx
The committee reviewed Bimzelx utilization. Rick Melbye, PharmD and Immunology Medical Outcomes Liaison from UCB Pharma provided public comment. The committee discussed implementing a 90-day trial for assessing response to the preferred product before permitting Bimzelx. Baack motioned to approve the criteria mandating a 90-day trial of preferred products by indication. Oehlke seconded the motion and it passed unanimously.

Dupixent
The committee reviewed new indications and PA considerations for Dupixent. Van Gilder asked if there were any public comments; none were offered. Nieuwenhuis recommended adopting State A criteria for the indication of bullous pemphigoid. Baack agreed but suggested removing the age requirement. Nieuwenhuis motioned and Baack seconded. The motion was approved unanimously.

Next the committee reviewed potential criteria for chronic spontaneous urticaria. Nieuwenhuis made the motion to approve State C criteria, requiring a trial of antihistamine and a leukotriene antagonist first, and removing the age limit. Ladwig seconded the motion. The motion was approved unanimously.

Neffy
The committee reviewed Neffy utilization. Baack inquired about the shelf life of epinephrine products. Jockheck reported that Neffy utilization is currently low but may present management challenges in the future. Van Gilder invited public comments; none were provided. Following discussion of criteria for clinically valid reasons, Nieuwenhuis moved to adopt State B with revised wording to specify “medical necessity and/or contraindication to injectable product.” Baack seconded the motion. The motion was approved unanimously.

Next, Baack made the motion to add the same criteria for Auvi-Q. Van Gilder asked if there were any public comments; none were offered. Ladwig seconded the motion. The motion was approved unanimously.

Zilbrysq
The committee reviewed medical criteria for adoption under the pharmacy side. Ladwig motioned to approve medical criteria and was seconded by Oehlke. The motion was approved unanimously. Public comment was provided by Tobin Chettiath, VP of Medical Affairs from UCB Pharma.

Vyalev
The committee reviewed medical criteria for Vyalev for adoption under the pharmacy side. A motion was made by Baack to adopt the same criteria and seconded by Ladwig. The motion was approved unanimously. Van Gilder called for public comments; none were offered.

Anzupgo
Clinical information for Anzupgo was presented for review. Public comment was provided by Brent Milovac, Medical Science Liaison at Leo Pharma. A motion was made by Baack to adopt Commercial B criteria with addition of trial of Eucrisa and Opzelura. Oehlke seconded the motion and it was approved unanimously.

Ladwig shared news of his retirement following 47 remarkable years at Lewis Drugs and as the last remaining original member of the committee. The committee expressed their appreciation and wished him well.

Adjournment

The next meeting is scheduled for March 13, 2026, with the June meeting tentatively scheduled for June 12, 2026. All motioned to adjourn and unanimously approved. The meeting adjourned at 2:31 pm CT.

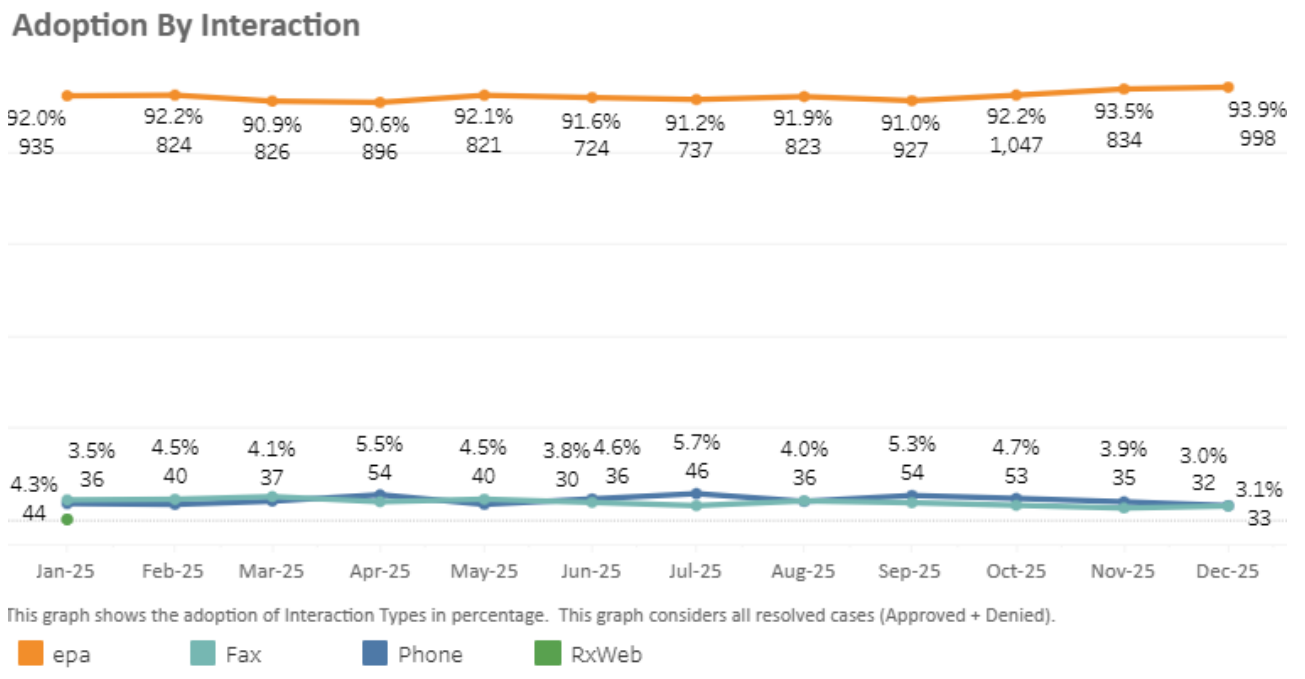
PA Report
10/1/2025 – 12/31/2025

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	7,856	7,856	0	100.00%	0.00%
Urgent	684	684	0	100.00%	0.00%
Grand Total	**8,540**	**8,540**	**0**		

Priority	Standard	Urgent
ePA	2,226	653
Fax	79	12
Phone	102	19
Real-Time	5,448	

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**8,540**	**122**	**1.43%**	**91**	**1.07%**	**5,448**	**63.8%**	**2,879**	**33.7%**



PA Initial Requests Summary

Month	Approved	Denied	Total
October-25	4,293	274	4,567
November-25	1,596	218	1,814
December-25	1,909	250	2,159
4Q25	**7,798**	**742**	**8,540**
Percent of Total	**91.31%**	**8.69%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	2554	130	2684	95.16%	31.43%	, WEGOVY
ANTIPSYCHOTICS/ANTIMANIC	2439	46	2485	98.15%	29.10%	, ARIPIPRAZOLE
ANTIDIABETICS	644	63	707	91.09%	8.28%	, OZEMPIC
MEDICAL DEVICES & SUPPLIES	365	137	502	72.71%	5.88%	, FREESTYLE
ANALGESICS - OPIOID	328	27	355	92.39%	4.16%	HYDROCODONE/APAP
OTHERS -	1468	339	1807	81.24%	21.16%	
4Q25	**7,798**	**742**	**8,540**	**91.31%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
October-25	25	55.56%	20	44.44%	45
November-25	19	63.33%	11	36.67%	30
December-25	15	83.33%	3	16.67%	18
4Q25	59	63.44%	34	36.56%	93

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	2554	130	2684	95.16%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	2439	46	2485	98.15%
27 - ANTIDIABETICS*	644	63	707	91.09%
97 - MEDICAL DEVICES AND SUPPLIES*	365	137	502	72.71%
65 - ANALGESICS - OPIOID*	328	27	355	92.39%
90 - DERMATOLOGICALS*	212	46	258	82.17%
58 - ANTIDEPRESSANTS*	227	28	255	89.02%
67 - MIGRAINE PRODUCTS*	199	36	235	84.68%
52 - GASTROINTESTINAL AGENTS - MISC.*	201	14	215	93.49%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	134	15	149	89.93%
66 - ANALGESICS - ANTI-INFLAMMATORY*	89	22	111	80.18%
12 - ANTIVIRALS*	54	12	66	81.82%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	48	10	58	82.76%
54 - URINARY ANTISPASMODICS*	34	23	57	59.65%
72 - ANTICONVULSANTS*	34	7	41	82.93%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	13	19	32	40.63%
41 - ANTIHISTAMINES*	23	5	28	82.14%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	23	4	27	85.19%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	26	1	27	96.30%
94 - DIAGNOSTIC PRODUCTS*	7	19	26	26.92%
28 - THYROID AGENTS*	22	3	25	88.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	17	7	24	70.83%
39 - ANTIHYPERLIPIDEMICS*	11	11	22	50.00%
50 - ANTIEMETICS*	16	4	20	80.00%
33 - BETA BLOCKERS*	11	8	19	57.89%
75 - MUSCULOSKELETAL THERAPY AGENTS*	6	11	17	35.29%
16 - ANTI-INFECTIVE AGENTS - MISC.*	10	0	10	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	2	7	9	22.22%
34 - CALCIUM CHANNEL BLOCKERS*	5	3	8	62.50%
83 - ANTICOAGULANTS*	6	2	8	75.00%
36 - ANTIHYPERTENSIVES*	3	4	7	42.86%
01 - PENICILLINS*	4	2	6	66.67%
40 - CARDIOVASCULAR AGENTS - MISC.*	6	0	6	100.00%
82 - HEMATOPOIETIC AGENTS*	5	1	6	83.33%
64 - ANALGESICS - NONNARCOTIC*	0	5	5	0.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	5	0	5	100.00%
03 - MACROLIDES*	2	2	4	50.00%
56 - GENITOURINARY AGENTS - MISCELLANEOUS*	3	1	4	75.00%
57 - ANTIANXIETY AGENTS*	1	2	3	33.33%
02 - CEPHALOSPORINS*	1	1	2	50.00%
11 - ANTIFUNGALS*	1	1	2	50.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	2	0	2	100.00%
45 - RESPIRATORY AGENTS - MISC.*	2	0	2	100.00%
74 - NEUROMUSCULAR AGENTS*	0	2	2	0.00%
15 - ANTHELMINTICS*	1	0	1	100.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	1	0	1	100.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	0	1	100.00%
86 - OPHTHALMIC AGENTS*	0	1	1	0.00%
4Q25	**7,798**	**742**	**8,540**	
Percent of Total	**97.31%**	**8.69%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
DEXCOM G7	4	3	7	57.14%
FREESTYLE LIBRE 3 PLUS/ FREESTYLE LIBRE 3	6	0	6	100.00%
AJOVY	4	1	5	80.00%
LUBIPROSTONE	3	1	4	75.00%
WEGOVY	2	2	4	50.00%
DEXMETHYLPHENIDATE ER	0	3	3	0.00%
LYBALVI	2	1	3	66.67%
OLANZAPINE	3	0	3	100.00%
OZEMPIC	0	3	3	0.00%
QUILLICHEW ER	0	3	3	0.00%
BELSOMRA	0	2	2	0.00%
FIDAXOMICIN	2	0	2	100.00%
GEMTESA	0	2	2	0.00%
LINZESS	1	1	2	50.00%
MODAFINIL	2	0	2	100.00%
MOUNJARO	1	1	2	50.00%
NORDITROPIN FLEXPRO	1	1	2	50.00%
VOQUEZNA	1	1	2	50.00%
ADAPALENE/BENZOYL PEROXIDE	1	0	1	100.00%
ARMODAFINIL	1	0	1	100.00%
AUVELITY	1	0	1	100.00%
CIBINQO	0	1	1	0.00%
COBENFY	1	0	1	100.00%
CONTOUR NEXT BLOOD GLUCOSE TEST	1	0	1	100.00%
EBGLYSS	1	0	1	100.00%
ENBREL SURECLICK	0	1	1	0.00%
EVEROLIMUS	1	0	1	100.00%
EVRYSDI	1	0	1	100.00%
GLUCOCARD SHINE TEST STRIPS	1	0	1	100.00%
HUMATROPE	0	1	1	0.00%
INGREZZA	1	0	1	100.00%
IVERMECTIN	1	0	1	100.00%
JOURNAVX	0	1	1	0.00%
KINERET	1	0	1	100.00%
LENVIMA 20 MG DAILY DOSE	1	0	1	100.00%
LISDEXAMFETAMINE	1	0	1	100.00%
LONSURF	1	0	1	100.00%
MAVYRET	1	0	1	100.00%
MEMANTINE	1	0	1	100.00%
METHOCARBAMOL	0	1	1	0.00%
MIRABEGRON ER	1	0	1	100.00%
NEMLUVIO	1	0	1	100.00%
NURTEC	1	0	1	100.00%
ONETOUCH VERIO TEST STRIPS	0	1	1	0.00%
OPZELURA	0	1	1	0.00%
OTEZLA/OTEZLA XR	1	1	2	50.00%
OXYCODONE/APAP	1	0	1	100.00%
QELBREE	0	1	1	0.00%
TREMFYA	1	0	1	100.00%
UBRELVY	1	0	1	100.00%
VILAZODONE	1	0	1	100.00%
WINLEVI	1	0	1	100.00%
ZURZUVAE	1	0	1	100.00%
4Q25	**59**	**34**	**93**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 9/1/2025 – 12/31/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPT	18,787	$250,370.77	$13.33	5.85%
2	ATYPICAL ANTIPSYCHOTICS	12,715	$5,081,927.10	$399.68	3.96%
3	RESPIRATORY AND CNS STIMULANTS	10,804	$1,191,632.66	$110.30	3.36%
4	SELECTIVE BETA-2-ADRENERGICS	9,905	$490,373.89	$49.51	3.08%
5	PROTON-PUMP INHIBITORS	9,898	$233,834.12	$23.62	3.08%
6	AMPHETAMINES	9,867	$734,818.87	$74.47	3.07%
7	ADRENALS	9,149	$1,105,011.50	$120.78	2.85%
8	GABA-MEDIATED ANTICONVULSANTS	8,823	$171,913.30	$19.48	2.75%
9	SECOND GENERATION ANTIHISTAMINES	8,552	$93,319.16	$10.91	2.66%
10	OPIOID AGONISTS	8,131	$245,697.65	$30.22	2.53%
11	SEROTONIN MODULATORS	7,928	$224,260.52	$28.29	2.47%
12	AMINOPENICILLIN ANTIBIOTICS	7,769	$118,092.88	$15.20	2.42%
13	ANTICONVULSANTS, MISC	7,561	$1,101,866.92	$145.73	2.35%
14	HMG-COA REDUCTASE INHIBITORS	7,245	$85,747.15	$11.84	2.26%
15	BETA-ADRENERGIC BLOCKING	6,332	$93,809.11	$14.82	1.97%
Total		**143,466**	**$11,222,675.60**	**$78.23**	**44.66%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 9/1/2025 – 12/31/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	12,715	$5,081,927.10	$399.68	3.96%
2	IMMUNOMODULATORY AGENTS	1,055	$4,999,682.95	$4,739.04	0.33%
3	INCRETIN MIMETICS	3,868	$3,875,346.79	$1,001.90	1.20%
4	TUMOR NECROSIS FACTOR INHIBITORS	372	$3,087,393.96	$8,299.45	0.12%
5	INTERLEUKIN-MEDIATED AGENTS	204	$2,427,393.41	$11,898.99	0.06%
6	ANTINEOPLASTIC AGENTS	419	$2,107,832.42	$5,030.63	0.13%
7	CYSTIC FIBROSIS (CFTR)	69	$1,866,041.29	$27,044.08	0.02%
8	HIV INTEGRASE INHIBITOR	338	$1,340,603.34	$3,966.28	0.11%
9	HEMOSTATICS	60	$1,306,518.41	$21,775.31	0.02%
10	RESPIRATORY AND CNS STIMULANTS	10,804	$1,191,632.66	$110.30	3.36%
11	SODIUM-GLUCOSE CO-TRANSPORT 2 (SGLT2)	2,145	$1,172,247.70	$546.50	0.67%
12	ADRENALS	9,149	$1,105,011.50	$120.78	2.85%
13	ANTICONVULSANTS, MISC	7,561	$1,101,866.92	$145.73	2.35%
14	CALCITONIN GENE-RELATED PEPTIDE	1,130	$1,068,634.27	$945.69	0.35%
15	DEVICES	4,493	$772,468.02	$171.93	1.40%
Total		**54,382**	**$32,502,600.74**	**$597.71**	**16.93%**

Total Rx Claims from 9/1/2025 – 12/31/2025	**321,212**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 9/1/2025 – 12/31/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Antidepressants	FLUOXETINE	6,417	$81,602.26	$12.72	2.00%
2	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,934	$179,509.43	$30.25	1.85%
3	Antidepressants	**SERTRALINE**	5,896	$76,987.07	$13.06	1.84%
4	Anticonvulsants - 2nd Generation	GABAPENTIN	5,891	$87,708.69	$14.89	1.83%
5	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,871	$288,453.41	$49.13	1.83%
6	Proton Pump Inhibitors	**OMEPRAZOLE**	5,687	$66,762.96	$11.74	1.77%
7	Antidepressants	TRAZODONE	5,443	$64,339.57	$11.82	1.69%
8	Penicillins	AMOXICILLIN	5,259	$72,010.07	$13.69	1.64%
9	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	5,095	$152,624.12	$29.96	1.59%
10	Thyroid Hormones	LEVOTHYROXINE	4,817	$54,454.15	$11.30	1.50%
11	Antidepressants	ESCITALOPRAM	4,777	$59,400.35	$12.43	1.49%
12	Antidepressants	**BUPROPION**	4,714	$73,995.66	$15.70	1.47%
13	Antihistamines	**CETIRIZINE**	4,388	$45,319.63	$10.33	1.37%
14	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,294	$456,153.46	$106.23	1.34%
15	Statins & Combos	ATORVASTATIN	4,172	$49,071.07	$11.76	1.30%
16	Biguanides & Combos	**METFORMIN**	3,981	$50,358.03	$12.65	1.24%
17	ACE Inhibitors & Combos	LISINOPRIL	3,676	$37,658.73	$10.24	1.14%
18	Antianxiety Agents	**HYDROXYZINE HCL**	3,368	$44,239.11	$13.14	1.05%
19	Antidepressants	DULOXETINE	3,300	$50,004.85	$15.15	1.03%
20	ADHD & Narcolepsy Medications	GUANFACINE	3,206	$50,735.24	$15.83	1.00%
21	Antiadrenergic Antihypertensives	CLONIDINE	3,087	$30,973.07	$10.03	0.96%
22	Antianxiety Agents	**BUSPIRONE**	2,971	$40,088.91	$13.49	0.92%
23	Opioid Agonists & Combos	HYDROCODONE/AC	2,968	$50,965.35	$17.17	0.92%
24	Leukotriene Modulators	MONTELUKAST	2,957	$37,193.10	$12.58	0.92%
25↑	Macrolides	AZITHROMYCIN	2,842	$41,351.89	$14.55	0.88%
26	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	2,826	$31,976.01	$11.31	0.88%
27	Antiemetics	ONDANSETRON ODT	2,788	$38,876.50	$13.94	0.87%
28	Glucocorticosteroids	PREDNISONE	2,783	$27,122.30	$9.75	0.87%
29	Calcium Channel Blockers	AMLODIPINE	2,584	$27,387.29	$10.60	0.80%
30	Atypical Antipsychotics	ARIPIPRAZOLE	2,524	$35,956.35	$14.25	0.79%
31	Penicillins	AMOXICILLIN/CLAVULANATE	2,501	$44,286.64	$17.71	0.78%
32	Statins & Combos	ROSUVASTATIN	2,407	$28,404.71	$11.80	0.75%
33	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,398	$31,538.84	$13.15	0.75%
34	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,379	$24,871.63	$10.45	0.74%
35	Proton Pump Inhibitors	PANTOPRAZOLE	2,347	$28,856.63	$12.30	0.73%
36	Atypical Antipsychotics	QUETIAPINE	2,288	$31,260.04	$13.66	0.71%
37	Beta Blockers & Combos	METOPROLOL ER	2,240	$28,082.86	$12.54	0.70%
38	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,145	$28,740.13	$13.40	0.67%
39	GLP-1 Receptor Agonists	MOUNJARO	2,076	$2,155,570.73	$1,038.33	0.65%
40	Cephalosporins	CEPHALEXIN	2,069	$31,567.37	$15.26	0.64%
41	Anticonvulsants - 2nd Generation	CLONAZEPAM	2,028	$23,308.76	$11.49	0.63%
42	Opioid Agonists & Combos	OXYCODONE	1,955	$28,769.61	$14.72	0.61%
43	Nonsteroidal Anti-Inflammatory	MELOXICAM	1,952	$21,119.57	$10.82	0.61%
44	Atypical Antipsychotics	RISPERIDONE	1,904	$25,921.59	$13.61	0.59%
45	Antidepressants	**VENLAFAXINE**	1,891	$28,589.64	$15.12	0.59%
46	Antidepressants	MIRTAZAPINE	1,890	$26,039.92	$13.78	0.59%
47↑	Inhaled Bronchodilator	ALBUTEROL SULFATE	1,860	$37,668.72	$20.25	0.58%
48	Nasal Steroids	FLUTICASONE PROPIONATE	1,833	$31,815.61	$17.36	0.57%
49	Diuretics & Combos	SPIRONOLACTONE	1,792	$25,070.32	$13.99	0.56%
50	H-2 Antagonists	FAMOTIDINE	1,707	$22,904.14	$13.42	0.53%
	Total Top 50 Drugs		**166,178**	**$5,107,666.09**	**$30.74**	**51.73%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 9/1/2025 – 12/31/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	DUPIXENT	721	$2,925,196.13	$4,057.14	0.22%
2	Chronic Inflammatory Disease	**HUMIRA**	248	$2,223,420.09	$8,965.40	0.08%
3	GLP-1 Receptor Agonists	MOUNJARO	2,076	$2,155,570.73	$1,038.33	0.65%
4	Cystic Fibrosis	TRIKAFTA	59	$1,602,554.55	$27,161.94	0.02%
5	Atypical Antipsychotics	**INVEGA SUSTENNA/TRINZA/HAFYERA**	441	$1,500,967.18	$3,403.55	0.14%
6	GLP-1 Receptor Agonists	OZEMPIC	1,425	$1,375,711.52	$965.41	0.44%
7	Chronic Inflammatory Disease	**SKYRIZI/PEN**	63	$1,357,337.99	$21,545.05	0.02%
8	Atypical Antipsychotics	VRAYLAR	900	$1,195,290.66	$1,328.10	0.28%
9	Chronic Inflammatory Disease	STELARA	42	$1,107,790.54	$26,375.97	0.01%
10	HIV-Multiclass Combo	BIKTARVY	243	$999,125.34	$4,111.63	0.08%
11	SGLT-2 Inhibitors & Combos	JARDIANCE	1,432	$839,207.01	$586.04	0.45%
12	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY/UNOREADY**	78	$795,674.03	$10,200.95	0.02%
13	Chronic Inflammatory Disease	**ENBREL/SURECLICK/MINI**	76	$596,292.49	$7,845.95	0.02%
14	Diabetes Monitoring and Testing	**DEXCOM**	1,664	$590,965.26	$355.15	0.52%
15	Anticonvulsants - 2nd Generation	EPIDIOLEX	167	$540,795.20	$3,238.29	0.05%
16	Oral Anticoagulants	**ELIQUIS/STARTER PACK**	939	$526,508.21	$560.71	0.29%
17	Atypical Antipsychotics	**ABILIFY MAINTENA, ASIMTUFII**	151	$512,640.22	$3,394.97	0.05%
18	Metabolic Modifiers	VYKAT XR	14	$500,387.70	$35,741.98	0.00%
19	Atypical Antipsychotics	ARISTADA	160	$467,190.43	$2,919.94	0.05%
20	Chronic Inflammatory Disease	BIMZELX	25	$462,043.82	$18,481.75	0.01%
21	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,294	$456,153.46	$106.23	1.34%
22↑	Antihemophilic Products	NUWIQ	5	$444,664.45	$88,932.89	0.00%
23	Atypical Antipsychotics	REXULTI	306	$409,309.67	$1,337.61	0.10%
24	Chronic Inflammatory Disease	RINVOQ	61	$406,006.16	$6,655.84	0.02%
25↑	Chronic Inflammatory Disease	**TREMFYA/PEN/INDUCTION PACK**	26	$398,755.25	$15,336.74	0.01%
26↑	Hepatitis C	MAVYRET	31	$398,325.28	$12,849.20	0.01%
27	Oncology	KISQALI	27	$393,876.34	$14,588.01	0.01%
28	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	588	$384,738.23	$654.32	0.18%
29	Chronic Inflammatory Disease	TALTZ	49	$379,107.42	$7,736.89	0.02%
30	Movement Disorder Drug Therapy	INGREZZA	45	$363,846.66	$8,085.48	0.01%
31	Atypical Antipsychotics	CAPLYTA	217	$331,822.03	$1,529.13	0.07%
32	Irritable Bowel Syndrome (IBS) Agt	LINZESS	613	$317,226.44	$517.50	0.19%
33	Migraine Products	NURTEC	266	$304,976.52	$1,146.53	0.08%
34	Growth Hormones	NORDITROPIN FLEXPRO	65	$296,501.94	$4,561.57	0.02%
35	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,871	$288,453.41	$49.13	1.83%
36↑	Hepatitis C	SOFOSBUVIR/VELPATASVIR	36	$288,379.80	$8,010.55	0.01%
37	Antihemophilic Products	HEMLIBRA	6	$268,471.02	$44,745.17	0.00%
38	Cystic Fibrosis	PULMOZYME	57	$256,149.44	$4,493.85	0.02%
39	Antihemophilic Products	NOVOSEVEN RT	3	$252,931.65	$84,310.55	0.00%
40	Psychotherapeutic & Neurological	LYBALVI	160	$243,987.56	$1,524.92	0.05%
41	Migraine Products	UBRELVY	234	$243,510.13	$1,040.64	0.07%
42	ADHD & Narcolepsy Medications	JORNAY PM	553	$237,827.41	$430.07	0.17%
43↑	Pulmonary Arterial Hypertension	UPTRAVI	8	$233,448.92	$29,181.12	0.00%
44	ADHD & Narcolepsy Medications	AZSTARYS	558	$223,414.79	$400.38	0.17%
45↓	Anti-Infective Agents - Misc.	XIFAXAN	67	$220,011.26	$3,283.75	0.02%
46↑	Pulmonary Arterial Hypertension	WINREVAIR	11	$208,052.45	$18,913.86	0.00%
47	Anticonvulsants - 2nd Generation	FINTEPLA	20	$204,234.87	$10,211.74	0.01%
48↑	Atypical Antipsychotics	UZEDY	69	$204,195.70	$2,959.36	0.02%
49↑	Asthma	TEZSPIRE	43	$201,485.96	$4,685.72	0.01%
50↑	Misc. Immunomodulators	VYVGART HYTRULO	3	$200,815.65	$66,938.55	0.00%
	Total Top 50 Drugs		**25,216**	**$31,335,348.97**	**$1,242.68**	**7.85%**

Old Business

Non-hormonal drugs for vasomotor symptoms

- Veozah (fezolinetant) and Lynkuet (elinzanetant) for the treatment of moderate to severe vasomotor symptoms due to menopause

Time frame: Year 2024 – 2025

Drug Name	Quarter	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizers	Age Range
VEOZAH 45mg tab 1 tab QD	1Q2024*	19	$10,030.54	$527.92	29.6 per 29.6 days	11	33 – 64
	2Q2024	15	$7,879.80	$525.32	29.4 per 29.4 days	6	36 – 59
	3Q2024*	22	$11,441.69	$520.08	29.7 per 29.7 days	10	47 – 63
	4Q2024	33	$17,654.37	$534.98	29.8 per 29.8 days	13	39 – 63
	1Q2025	42	$23,031.31	$548.36	29.8 per 29.8 days	18	39 – 64
	2Q2025	50	$27,413.15	$548.26	29.8 per 29.8 days	22	31 – 64
	3Q2025	68	$37,338.35	$549.09	29.7 per 29.7 days	25	31 – 64
	4Q2025	60	$32,934.26	$548.90	29.8 per 29.8 days	27	36 – 64
LYNKUET 60mg cap 2 caps HS	4Q2025	0		*~$600*	*60 per 30 days*		

*Reviewed at prior P&T meetings

Potential PA Criteria for Veozah and Lynkuet

State A

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Trial and failure, contraindication, or intolerance to TWO of the following:
   - Gabapentin
   - Menopausal hormone therapy (e.g., estrogen monotherapy or estrogen + progesterone)
   - Oxybutynin
   - SSRI (e.g., paroxetine, escitalopram, citalopram)
   - SNRI (e.g., venlafaxine and desvenlafaxine)

State B

Initial Authorization: 6 months
1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Submission of medical records (e.g., chart notes, paid claims history) documenting trial and failure, contraindication, or intolerance to both of the following (document drug, date, and duration of trial):
   - Menopausal hormone therapy (e.g., Premarin, Bijuva, Estrogel, etc.)
   - Non-hormonal therapy (e.g., paroxetine mesylate, venlafaxine, clonidine, etc.)

Reauthorization – 6 months
1. Documentation of positive clinical response to therapy (e.g., decrease in frequency and severity of vasomotor symptoms from baseline, etc.)

State C

Initial Authorization: 6 months

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Member is 18 years of age or older
3. Member has tried and failed at least 90 days of therapy with ONE of the following, confirmed by claims history or chart documentation: hormonal agent (e.g., oral, injectable, topical, transdermal, or vaginal) OR non-hormonal agent (e.g., gabapentin, paroxetine, venlafaxine, oxybutynin)
4. Prescriber attests to the following for Veozah:
    - Member does not have cirrhosis
    - Member does not have severe renal impairment or end-stage renal disease (ESRD)
    - Member is not currently utilizing a CYP1A2 inhibitor and will not be initiated on CYP1A2 inhibitor therapy while on concomitant Veozah (fezolinetant) therapy

Reauthorization: 6 months

1. History of the requested agent for at least 90 days of the past 120 days, confirmed by claims history or chart documentation
2. One of the following:
    - Member has previously tried and failed at least 90 days of therapy with ONE hormonal agent (e.g., oral, injectable, topical, transdermal, or vaginal), confirmed by claims history or chart documentation
    - Member has contraindication to hormonal therapy and has previously tried and failed at least 90 days of therapy with ONE non-hormonal agent (e.g., gabapentin, paroxetine, venlafaxine, oxybutynin), confirmed by claims history or chart documentation
3. Prescriber attests to the following for Veozah:
    - Member does not have cirrhosis
    - Member does not have severe renal impairment or end-stage renal disease (ESRD)
    - Member is currently not on a CYP1A2 inhibitor and will not be initiated on a CYP1A2 inhibitor while on concomitant Veozah (fezolinetant) therapy

Commercial

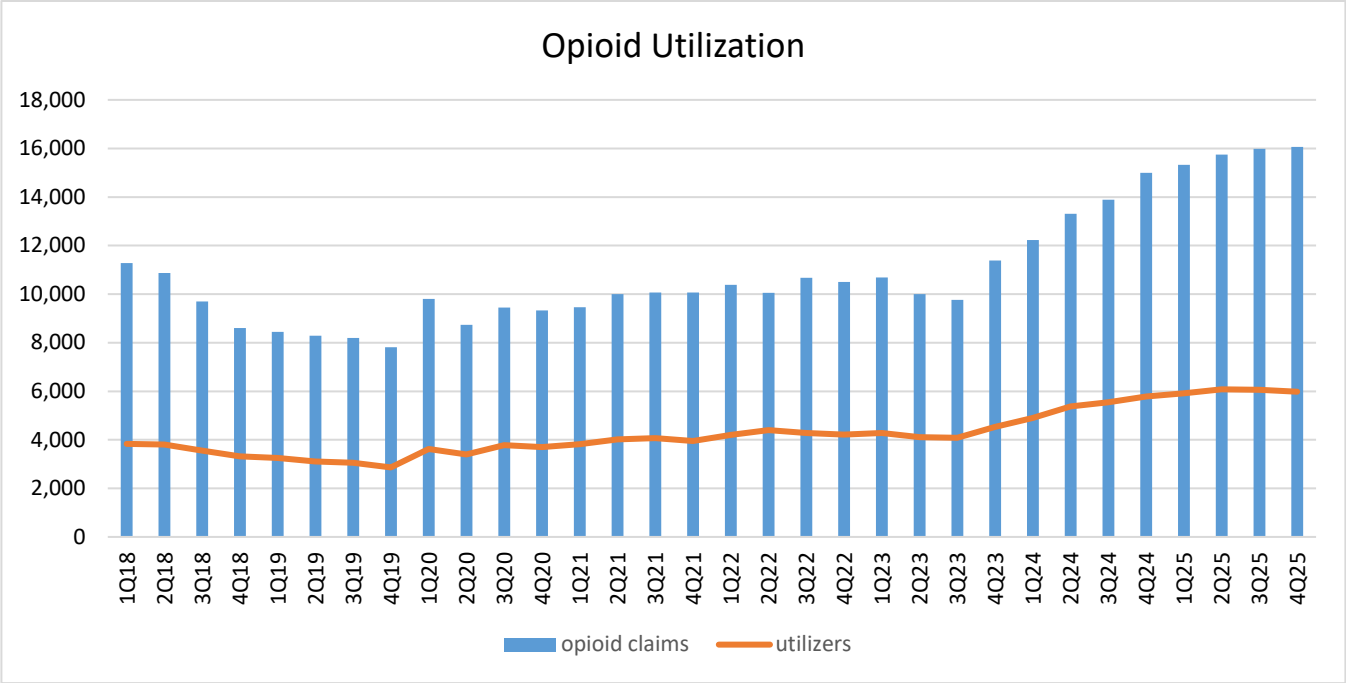
Initial Authorization: 6 months

1. Diagnosis of moderate to severe vasomotor symptoms due to menopause
2. Trial and failure, contraindication, or intolerance to one of the following:
    - Menopausal hormone therapy (e.g., Premarin, Bijuva, Estrogel, etc.)
    - Non-hormonal therapy with a different mechanism of action (e.g. paroxetine, venlafaxine, clonidine, gabapentin, etc.)
3. Prescriber attests that baseline serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) and total bilirubin levels are less than 2 times the upper limit of normal (ULN) prior to initiating requested drug

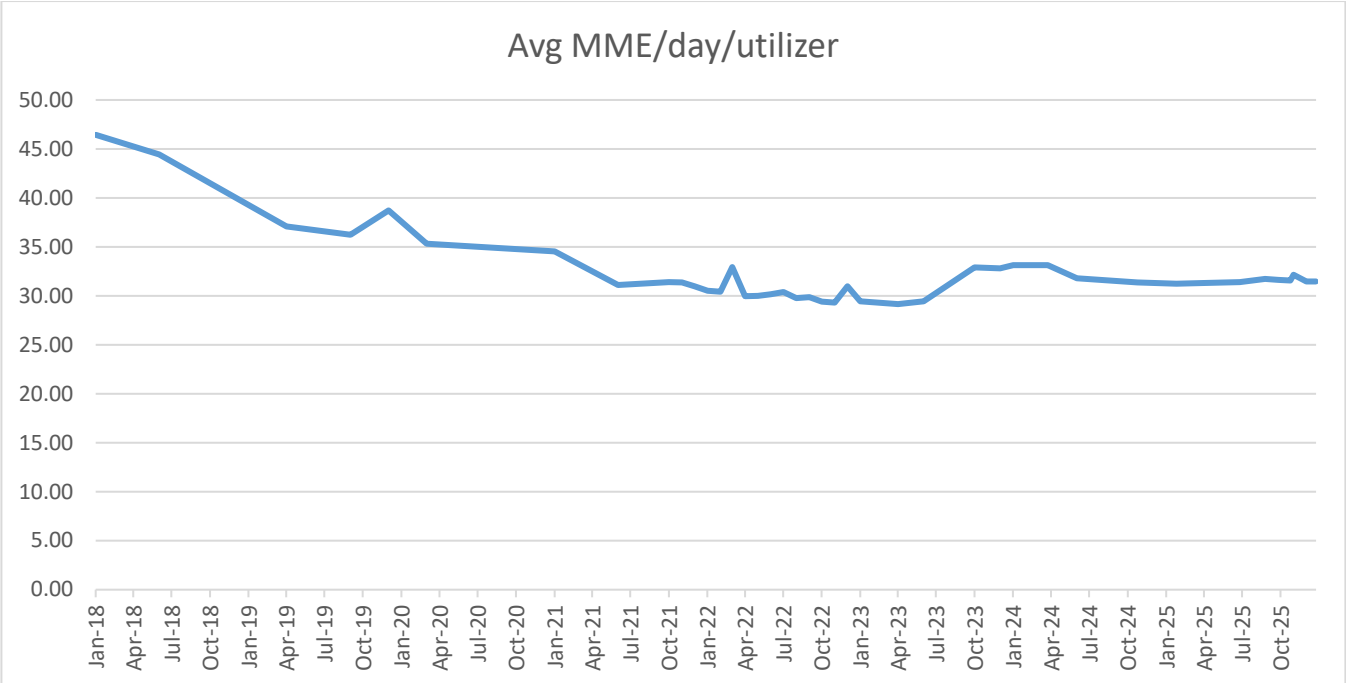
Reauthorization: 6 months

1. Patient demonstrates positive clinical response to therapy (e.g., decrease in frequency and severity of vasomotor symptoms from baseline, etc.)
2. One of the following within the past 3 months:
    - For patients with total bilirubin levels less than or equal to 2 times the ULN, transaminase elevations do not exceed 5 times the ULN
- For patients with total bilirubin levels greater than 2 times the ULN, transaminase elevations do not exceed 3 times the ULN

Opioid Summary



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



Opioid Initiatives:

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

Other Initiatives:

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

Total Eligibles and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%
3Q2023	131,292	26,218	19.9%
4Q2023	134,270	29,320	21.8%
1Q2024	141,162	32,891	23.3%
2Q2024	149,613	32,686	21.8%
3Q2024	159,160	35,263	22.2%
4Q2024	162,163	36,468	22.5%
1Q2025	164,446	38,367	23.3%
2Q2025	161,372	34,446	21.3%
3Q2025	158,250	34,997	22.1%
4Q2025	157,279	37,099	23.6%

SDM 4Q2025
Sep 25 to Dec 25

Opioid Utilization Snapshot

3Q2025
Jun 25 to Sep 25

Opioid Claims **16,058**

3.1% prescription claims filled for an opioid

1.4% higher than Medicaid FFS benchmark

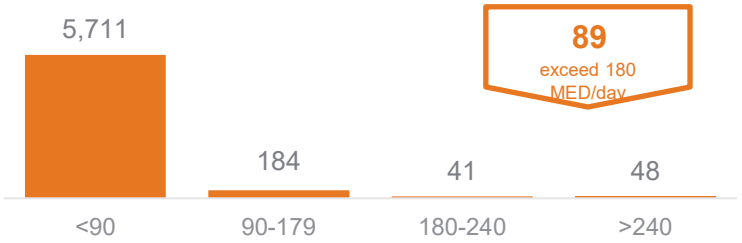
Utilizers **5,984**

33.3% are high utilizers [1]

7.8% 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

98 opioid utilizing members with 3+ pharmacies

608 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

Opioid Claims **15,986**

3.3% prescription claims filled for an opioid

1.6% higher than Medicaid FFS benchmark

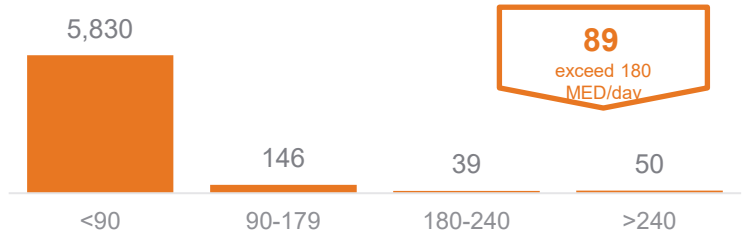
Utilizers **6,065**

32.3% are high utilizers [1]

6.3% 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

93 opioid utilizing members with 3+ pharmacies

646 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 4Q2025
Opportunities date range: Sep - Dec 2025
Benchmark: MEDICAID FEE FOR SERVICE

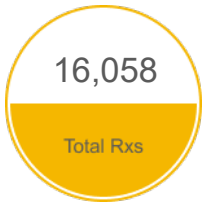
Utilizers: 5,984

3.1% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.1% of all prescriptions this period, which is 1.4% higher than the benchmark
- 1,993 high opioid utilizers were identified this period, which is 7.8% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
11.8%

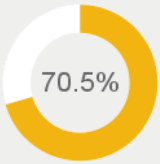
Opioid utilizers

HIGH UTILIZERS
33.3%
1,993 high utilizers

7.8% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

70.5% of all opioid Rxs were filled for short acting opioids. **3,750** Rxs were for medication assisted therapy (MAT) and **125** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

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

Utilizers by cumulative MED

89 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	5,711	184	41	48

MED – view definition

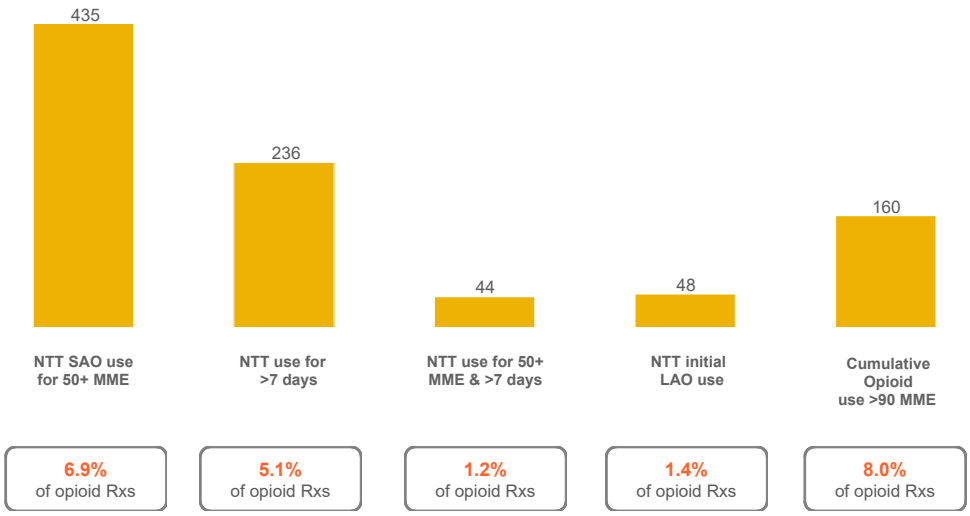
Opioid Opportunity Assessment

SDM 4Q2025
Opportunities date range: Sep - Dec 2025
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.8%

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?

98 opioid utilizing members use 3 or more pharmacies and 608 opioid utilizing members use 3 or more prescribers.

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

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
1,308	820	1,180	720	162

Anticonvulsants –view definition

PAD Biosimilar Agents – Preferred Drug List

Tocilizumab

Estimated Savings: $

PREFERRED AGENT (NO PA REQUIRED)	NON-PREFERRED AGENT (PA REQUIRED)
TYENNE (tocilizumab-aazg)	ACTEMRA (tocilizumab)
	AVTOZMA (tocilizumab-anoh)
	TOFIDENCE (tocilizumab-bavi)

Infliximab

Estimated Savings: $

PREFERRED AGENT (NO PA REQUIRED)	NON-PREFERRED AGENT (PA REQUIRED)
INFLIXIMAB	AVSOLA (infliximab-axxq)
	INFLECTRA (infliximab-dyyb)
	REMICADE (infliximab)
	RENFLEXIS (infliximab-abda)

Pegfilgrastim

Estimated Savings: $$$

PREFERRED AGENT (NO PA REQUIRED)	NON-PREFERRED AGENT (PA REQUIRED)
FULPHILIA (pegfilgrastim-jmdb)	NEULASTA (pegfilgrastim)
	FYLNETRA (pegfilgrastim-pbbk)
	NYVEPRIA (pegfilgrastim-apgf)
	STIMUFEND (pegfilgrastim-fpgk)
	UDENYCA (pegfilgrastim-cbqv)
	ZIEXTNEZO (pegfilgrastim-bmez)

TOTAL ESTIMATED SAVINGS: $2,953,960

** Includes federal shares

New Business

Brinsupri (brensocatib)

- for treatment of non-cystic fibrosis bronchiectasis in adult and pediatric patients 12 years of age and older

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizers	Age Range
Brinsupri tab	0		*~$7,000*	*30 per 30 days*		

Potential PA Criteria

State A

Initial Authorization: 1 year

1. **BOTH** of the following:
   a. Diagnosis of non-cystic fibrosis bronchiectasis (NCFB)
   b. Diagnosis has been confirmed by computed tomographic (CT) scan
2. Diagnostic testing confirms patient does NOT have cystic fibrosis
3. Submission of medical records (e.g., chart notes) confirming patient has a clinical history consistent with non-cystic fibrosis bronchiectasis (e.g., chronic cough or sputum production or recurrent respiratory tract infections)
4. Patient is 12 years of age or older
5. **ONE** of the following:
   a. If patient is 12 to 17 years of age, patient has had at least one (1) documented pulmonary exacerbation requiring treatment with systemic antibiotics in the previous 12 months
   b. If patient is 18 years of age or older, patient has had at least two (2) documented pulmonary exacerbations requiring treatment with systemic antibiotics in the previous 12 months
6. **ONE** of the following:
   a. For patients with co-existing COPD, submission of medical records (e.g., chart notes) or paid claims documenting that the patient is receiving **ONE** of the following therapies:
      - Triple therapy (i.e., an inhaled corticosteroid [ICS] [e.g., budesonide], a long-acting muscarinic antagonist [LAMA] [e.g., tiotropium, umeclidinium], and a long-acting beta agonist [LABA] [e.g., salmeterol, arformoterol, formoterol])
      - If ICS are contraindicated, a LAMA and a LABA
   b. For patients with co-existing asthma, submission of medical records (e.g., chart notes) or paid claims documenting that the patient is currently being treated with **ONE** of the following unless there is a contraindication or intolerance to these medications:
      i. **BOTH** of the following:
         - Inhaled corticosteroid (ICS) (e.g., fluticasone propionate)
         - Additional asthma controller medication (e.g., leukotriene receptor antagonist [LTRA] [e.g., montelukast], long-acting beta-2 agonist [LABA] [e.g., salmeterol], long-acting muscarinic antagonist [LAMA] [e.g., tiotropium])
      ii. One combination ICS/LABA product (e.g., Advair, Breo Ellipta)
7. Prescribed by or in consultation with a pulmonologist

Reauthorization: 1 year

1. Patient demonstrates positive clinical response to therapy (e.g., stabilization or reduction in number of pulmonary exacerbations)

State B

Initial Authorization: 1 year
1. Diagnosis of non-cystic fibrosis bronchiectasis (NCFB)
2. Diagnosis has been confirmed by a documented computed tomography (CT) scan
3. Prescribed by, or in consultation with, a pulmonologist or infectious disease
4. **ONE** of the following:
    a. Patient is 12 to 17 years of age with at least one documented pulmonary exacerbation in the past 12 months requiring systemic antibiotic therapy
    b. Patient is 18 years of age or older with at least two documented pulmonary exacerbations in the past 12 months requiring systemic antibiotic therapy

Reauthorization: 1 year
1. Patient demonstrates positive clinical response to therapy (e.g., stabilization or reduction in number of pulmonary exacerbations, reduced cough or sputum)

Commercial C

Authorization may be granted for the diagnosis of non-cystic fibrosis bronchiectasis (NCFB) in an adult or pediatric patient 12 years of age or older when the following criteria is met:
- The diagnosis was confirmed by a high-resolution computed tomography (HRCT) study of the chest.
- The patient has experienced a pulmonary exacerbation in the last 12 months (e.g., the presence of 3 or more of the following symptoms for at least 48 hours: increased cough; increased sputum production or change in sputum consistency; increased sputum purulence; increased breathlessness, decreased exercise tolerance, or both; fatigue, malaise, or both; or hemoptysis.)

Continuation of therapy

Authorization may be granted for the diagnosis of non-cystic fibrosis bronchiectasis (NCFB) in an adult or pediatric patient 12 years of age or older when the following criteria is met:
- The patient has experienced a positive response to therapy (e.g., reduction in pulmonary exacerbations from baseline)

Coxanto (oxaprozin capsule)

- for the relief of the signs and symptoms of osteoarthritis (OA, 1,200 mg QD), rheumatoid arthritis (RA, 1,200 mg QD), and juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA, 600 mg to 1,200 mg QD)

Time frame: 2024 to current

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizers	Age Range
oxaprozin 600 mg tab	3	$122.83	$49.95	60 per 30 days	1	54
oxaprozin 600 mg cap	0		*$2,850 to $5,245*	*120 per 30 days*		
Coxanto 300 mg cap	0		*$2,850 to $5,245*	*120 per 30 days*		

Potential PA Criteria

Commercial A

1. Submission of medical records (e.g., chart notes) confirming request is for an FDA-approved indication
2. Submission of medical records (e.g., chart notes) (document drug, duration, dose and date of use) confirming history of use of ALL available alternative(s)
3. **BOTH** of the following:
   a. Documentation provided stating the alternative(s) has/have not been effective
   b. Justification/rationale provided explaining how the medication is expected to provide benefit when the alternative product(s) has/have not been shown to be effective despite having the same active ingredient and/or same mechanism of action

Commercial B

1. Intolerance to TWO preferred oral non-steroidal anti-inflammatories (NSAIDs) one of which is oxaprozin 600 mg tablet (generic Daypro)
2. Dose does not exceed FDA approved maximum dose.

MASH Treatments

Indication	Rezdiffra tab	Wegovy inj	Wegovy oral
Treatment of noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults	✔	✔	

Feature	Rezdiffra	Wegovy
Primary Target	Thyroid hormone receptor beta (THR-*B*)	GLP-1 receptor
Mechanism	Activates THR-*B* to enhance liver fat metabolism	Mimics GLP-1 to regulate glucose and appetite
Liver Fat Reductions	Significant (direct action on liver fat metabolism)	Moderate (secondary effect of weight loss)
Weight Loss Effect	Minimal or indirect (via improved liver health)	Significant
Improvement in insulin sensitivity	No direct effect on insulin sensitivity	Yes (via weight loss)
Anti-inflammatory action	Direct (reduces liver inflammation and fibrosis)	Indirect (via weight loss)

*From Fatty Liver Foundation

Time frame: 4Q2025

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizers	Age Range	Gender
Rezdiffra tab (resmetirom)	11	$45,390.95	$4,126.45	30 per 30 days	6	34 – 55	2 ♂, 4 ♀
Wegovy inj (semaglutide)	30	$39,489.09	$1,316.30	2.3 mg per 28 days	10	14 – 60	3 ♂, 7 ♀

*Red font denotes drug is on PA

Rezdiffra PA Criteria update:

Initial Authorization

1. Patient is 18 years or older
2. Diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or metabolic dysfunction associated steatohepatitis (MASH)
3. Submission of medical records (e.g. chart notes or tests such as fibroscan, fibrosis-4 index, MRE, liver biopsy, etc) confirming disease is fibrosis stage F2 or F3.
4. Prescriber attests patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
5. Patient does not have decompensated cirrhosis (Child-Pugh Class B or C)
6. Prescribed by or in consultation with a gastroenterologist or hepatologist *or endocrinologist*
7. *Medication will not be used in combination with Wegovy (semaglutide) for the treatment of MASH*
8. *Trial of Wegovy for XX days first unless patient has had an inadequate response, intolerance, or contraindication OR Paid claims or submission of medical records (e.g., chart notes) confirming a trial and inadequate response, contraindication, or intolerance to Wegovy (semaglutide)*

Renewal Criteria
Must meet all of the following:

1. Prescriber attest patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
2. Submission of medical records (e.g., chart notes) documenting a positive clinical response to therapy (e.g. NASH resolution, fibrosis stage improvements)
3. *Submission of medical records (e.g., chart notes) confirming patient has not progressed to cirrhosis*
4. *Medication will not be used in combination with Wegovy (semaglutide) for the treatment of MASH*

Zepbound (tirzepatide) OSA

- for the treatment of moderate to severe obstructive sleep apnea in adults with obesity

Potential PA Criteria

State A
Initial Authorization: 6 months

1. Patient is 18 years of age or older
2. Diagnosis of moderate to severe Obstructive Sleep Apnea (OSA)
3. Hypersomnolence secondary to another sleep disorder, neurologic disorder, medical condition, or by medicine or substance use has been ruled out
4. Submission of medical records (e.g. chart notes) documenting **BOTH** of the following:
   - Initial body mass index (BMI) of ≥ 30 kg/m2;
   - ≥ 15 respiratory events per hour of sleep confirmed by sleep study
5. Patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
6. Trial and failure (minimum duration 3 months with documented compliance) of Continuous Positive Airway Pressure (CPAP) or BiPAP device, unless contraindicated
7. Patient is not concomitantly using DPP-4 inhibitor therapy
8. Medication is not being co-administered with another GLP-1 receptor agonists
9. Patient does not have personal or immediate family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2)

Reauthorization: 6 months

1. Patient is participating in a supervised comprehensive weight management program that encourages behavioral modification, reduced calorie diet, and increased physical activity
2. Patient is not concomitantly using DPP-4 inhibitor therapy
3. Will not being co-administered with another GLP-1 receptor agonists
4. Submission of medical records (e.g., chart notes) documenting a positive clinical response to therapy (e.g., decrease number of apneas and hypopneas during sleep from baseline)

State B

Initial Authorization: 1 year

A. Must meet all of the following:
   1. Member is 18 years of age or older
   2. Diagnosis of moderate to severe obstructive sleep apnea (OSA) in individuals with obesity AND all of the following:
      a. Member has a documented BMI of ≥ 30 kg/m2 before initiating Zepbound (supported by chart documentation, including baseline weight before initiating Zepbound, obtained within the past 3 months)
      b. **ONE** of the following:
         i. Member has an apnea hypopnea index (AHI) of ≥ 15 events/hour, as measured on polysomnography (PSG) or home sleep apnea test (HSAT) that has been reviewed and interpreted by a sleep medicine-certified physician (supported by submitted documentation from a PSG or HSAT obtained within the past year)
         ii. **BOTH** of the following:
            - Member has had a prior apnea hypopnea index (AHI) of ≥ 15 events/hour, as measured on polysomnography (PSG) or home sleep apnea test (HSAT) that was reviewed and interpreted by a sleep medicine-certified physician (supported by submitted documentation)
            - Prescriber has submitted documentation confirming member has been utilizing positive airway pressure (PAP) therapy (e.g., CPAP, BiPAP) with documented adherence from within the past 90 days (adherence defined as ≥4 hours of use per night for ≥70% of all nights within a 30-day period, supported by submitted PAP therapy report or chart note documentation)
      c. Member does not have a diagnosis of Type 1 or Type 2 diabetes mellitus
      d. Member's HbA1c is less than 6.5% (supported by chart documentation from within the past 3 months)
   3. Prescriber attests to all of the following:
      - Member does not have diagnosis of central or mixed sleep apnea with percent of mixed or central apneas/hypopneas ≥ 50%
      - Member will use Zepbound in combination with reduced calorie diet and increased physical activity
   4. Member will not use Zepbound concurrently with another GLP-1 RA or combination products (including tirzepatide-containing products)*
   5. Dose requested does not exceed 15 mg/week

Reauthorization: 1 year

1. Must meet all of the following:
   a. History of requested agent for at least 84 days within the past 112 days, as confirmed by claims history or chart documentation
   b. On initial reauthorization ONLY (i.e., members who have been on requested therapy for > 1 year and < 2 years), member demonstrates a documented reduction in AHI from baseline study (e.g., PSG or HSAT that was reviewed and interpreted by a sleep medicine-certified physician, CPAP or BiPAP sleep data) obtained within the past 3 months
   c. Member demonstrates a meaningful weight loss from baseline (defined as a weight loss of at least 5% from baseline)
   d. Prescriber attests to all of the following: [PAS note: please include field for attestation for each]
      - Member does not have Type 1 or Type 2 diabetes mellitus
      - Member has not been diagnosed with central or mixed sleep apnea
   e. Member is not utilizing concurrently with another GLP-1 RA or combination product
   f. Dose requested does not exceed 15 mg/week

Commercial D

Initial Authorization: 6 months

1. Diagnosis of obstructive sleep apnea
2. Submission of medical records (e.g., chart notes) confirming disease is moderate to severe as defined by 15 or more obstructive respiratory events (apnea-hypopnea index [AHI]) per hour of sleep confirmed by a sleep study (e.g., polysomnography, home sleep apnea test [HSAT]) [17, 19-20]
3. Patient is 18 years of age or older
4. Submission of medical records (e.g., chart notes) confirming Body Mass Index (BMI) of greater than or equal to 30 kg/m2
5. Submission of medical records (e.g., chart notes) confirming **ONE** of the following:
    a. Patient has been evaluated and counseled on continuous positive airway pressure CPAP therapy as the preferred treatment of choice
    b. Patient is not a candidate for CPAP therapy (e.g., upper airway anatomic abnormalities, etc.)
6. Submission of medical records (e.g., chart notes) confirming medication will be used in combination with a program supporting a reduced calorie diet of at least 500 kcal/day and patient can be active for at least 150 minutes per week
7. Submission of medical records (e.g., chart notes) confirming HbA1c less than 6.5% in the past 12 months
8. **ONE** of the following:
    a. Paid claims or submission of medical records (e.g., chart notes) confirming at least a 3 month trial and inadequate response, contraindication, or intolerance to one non-GLP-1 receptor agonist weight loss medication (e.g., Qsymia)
    b. No formulary alternative is available to treat the patient's condition
9. Submission of medical records (e.g., chart notes) confirming or absence of paid claims medication is not being co-administered with any of the following:
    - Tirzepatide-containing product (e.g., Mounjaro)
    - GLP-1 receptor agonists (e.g., Saxenda, Trulicity, Victoza)
    - Other weight loss agents indicated for short-term weight reduction or chronic weight management (e.g., Qsymia)

Reauthorization: 6 months

1. Paid claims or submission of medical records (e.g., chart notes) confirming patient is currently on a maintenance dose of 10 mg, 12.5mg, or 15 mg once weekly
2. **ONE** of the following:
    a. **BOTH** of the following:
        - Paid claims or submission of medical records (e.g., chart notes) confirming patient has been receiving Zepbound therapy for up to 6 months
        - Submission of medical records (e.g., chart notes) confirming weight loss of greater than or equal to 5% of baseline body weight
    b. **BOTH** of the following:
        - Paid claims or submission of medical records (e.g., chart notes) confirming patient has been receiving Zepbound therapy for greater than 6 months
        - Submission of medical records (e.g., chart notes) confirming patient is continuing to experience or maintain weight loss
3. Submission of medical records (e.g., chart notes) confirming medication will be used in combination with a program supporting a reduced calorie diet of at least 500 kcal/day and patient can be active for at least 150 minutes per week
4. Submission of medical records (e.g., chart notes) confirming HbA1c less than 6.5% in the past 12 months
5. Submission of medical records (e.g., chart notes) confirming or absence of paid claims medication is not being co-administered with any of the following:

- Tirzepatide-containing product (e.g., Mounjaro)
- GLP-1 receptor agonists (e.g., Saxenda, Trulicity, Victoza)
- Other weight loss agents indicated for short-term weight reduction or chronic weight management (e.g., Qsymia)

Health Plan C

Approval Criteria: 6 months

1. Submission of medical records (e.g., chart notes) confirming disease is moderate to severe as evidenced by **BOTH** of the following
   a. Polysomnography (PSG) or home sleep apnea test (HSAT) confirming the apnea-hypopnea index (AHI) greater than or equal to 15 obstructive respiratory events per hour
   b. ALL of the following conditions affecting breathing have been ruled out:
      - Diagnosis of central or mixed sleep apnea
      - Diagnosis of Cheyne-Stokes respiration
      - Diagnosis of obesity hypoventilation syndrome or daytime hypercapnia
      - Presence of significant craniofacial abnormalities
2. Member is 18 years of age or older
3. Submission of medical records (e.g., chart notes) confirming Body Mass Index (BMI) of greater than or equal to 30kg/m2
4. Submission of medical records (e.g., chart notes) confirming **BOTH** of the following:
   a. Member has been evaluated and counseled on continuous positive airway pressure CPAP therapy as the preferred treatment of choice
   b. **ONE** of the following:
      i. Member has not experienced symptom improvement despite demonstrating adherence to CPAP treatment for at least 3 months, with adherence to therapy defined as the use of device at least 4 hours per night on 70% of the nights during a consecutive 30-day period
      ii. Member is not a candidate for CPAP therapy (due to upper airway anatomic abnormalities)
5. SUBMISSION OF MEDICAL RECORDS (E.G., CHART NOTES) CONFIRMING MEDICATION WILL BE USED IN COMBINATION WITH A PROGRAM SUPPORTING A REDUCED CALORIE DIET OF AT LEAST 500 KCAL/DAY AND MEMBER CAN BE ACTIVE FOR AT LEAST 150 MINUTES PER WEEK
6. Submission of medical records (e.g., chart notes) or absence of paid claims confirming medication is not being co-administered with tirzepatide-containing products (e.g., Mounjaro) or GLP-1 receptor agonists (e.g., Ozempic, Rybelsus, Trulicity, Saxenda)
7. Submission of medical records (e.g., chart notes) confirming member has not achieved weight loss of greater than or equal to 5% of initial weight after 6 months enrollment and active participation in a structured weight loss program which addresses all of the following:
   - Dietary modification
   - Lifestyle modifications including attention to physical activity, sleep, stress
   - Behavioral counseling
   - Nutritional counseling
8. Submission of medical records (e.g., chart notes) confirming ALL of the following:
   - HbA1c less than 6.5% in the past 12 months
   - Member does not have diagnosis of Type 1 or Type 2 Diabetes
9. Prescribed by or in consultation with a sleep specialist

Reauthorization: 6 months

1. Paid claims or submission of medical records (e.g., chart notes) confirming member is currently on a maintenance dose of 10mg, or 15mg once weekly
2. Submission of medical records (e.g., chart notes) confirming **ONE** of the following:

- Member has been receiving Zepbound therapy for up to 6 months and has had a weight loss of greater than or equal to 5% of baseline body weight
- Member has been receiving Zepbound therapy for greater than 6 months and is continuing to experience or maintain weight loss

3. Submission of medical records (e.g., chart notes) confirming medication will be used in combination with a program supporting a reduced calorie diet of at least 500 kcal/day and member can be active for at least 150 minutes per week
4. Submission of medical records (e.g., chart notes) or absence of paid claims confirming medication is not being co-administered with tirzepatide-containing products (e.g., Mounjaro) or GLP-1 receptor agonists (e.g., Ozempic, Rybelsus, Trulicity, Saxenda)
5. Submission of medical records (e.g., chart notes) confirming member has experienced improvement in obstructive sleep apnea symptoms (e.g., less daytime sleepiness, fewer nighttime awakenings, fewer partner-reported snoring episodes or pauses in breathing, member no longer requires the use of CPAP)
6. Submission of medical records (e.g., chart notes) confirming ALL of the following:
   - HbA1c less than 6.5% in the past 12 months
   - Member has not developed Type 2 Diabetes
7. Prescribed by or in consultation with a sleep specialist
8. Member remained adherent to treatment as determined by claim history showing member filled at least 140 days' supply (typically five fills of 28 days' supply or two fills of 84 days' supply, or some combination) during the 6 months after the initial approval date

Optum Rx®

New Drug Overview
Brinsupri (brensocatib)
Medispan Class: Respiratory agents, Misc - Dipeptidyl Peptidase 1 (DPP1) Inhibitors

Introduction

Disease background

- Bronchiectasis is a progressive disease of the lung that results from an infection or other circumstances that injures airway walls, and is described as dilated bronchi that is irreversible and bronchial infection and inflammation in the airways (*Tino et al 2025, Barker 2025, National Institutes of Health [NIH] 2023*).
- The development of bronchiectasis is caused by 2 main features, including infectious insult as well as impaired drainage, airway obstruction, or a defect in host defense; diagnosis is based on chronic cough, generation of thick sputum, generally having at least exacerbation per year and the presence of bronchial airway dilatation on chest computed tomographic scans (Barker 2025).
  - In general, bronchiectasis can affect only 1 segment or lobe of the lung (focal) or both lungs may be involved (diffuse) (Tino et al 2025).
  - Bronchiectasis often occurs with cystic fibrosis (NIH 2023), but this topic focuses on non-cystic fibrosis bronchiectasis.
- Per a 2017 retrospective cohort study that included United States healthcare claims data between 2009 and 2013, the prevalence of bronchiectasis was estimated to be 139 per 100,000 adults, with an annual incidence of 29 per 100,000 adults (Tino et al 2025).
  - It is thought to be more frequent in females as well as older adults.
- While the origin for bronchiectasis is not known, it generally results from an infection or condition that harms the airway walls or prevents the airways from allowing the mucous to be removed (NIH 2023).
  - Persistent infections of the lung produce a sequence of lung damage and flare-ups, which are often called exacerbations.
- The most frequently observed symptoms of bronchiectasis include (NIH 2023):
  - A daily cough, occurring over ≥ 8 weeks
  - Daily production of a large amount of sputum
  - Shortness of breath and wheezing
  - Chest pain
  - Fevers and/or chills
  - Fatigue
  - Clubbing
- Patients should be educated on airway clearance techniques. Various treatments that may be used in the management of bronchiectasis include antibiotics for acute exacerbations, muco-active agents, steroids, or NSAIDs.

Pharmacology/usage

- Brinsupri (brensocatib) is a dipeptidyl peptidase 1 (DPP1) inhibitor. It is a competitive, reversible inhibitor of DPP1. DPP1 activates pro-inflammatory neutrophil serine proteases (NSPs) during neutrophil maturation in the bone marrow. Activated NSPs are implicated in the pathogenesis of neutrophil-mediated non-cystic fibrosis bronchiectasis inflammation. In cell-based assays, DPP1 inhibition by brensocatib reduces the activity of NSPs including neutrophil elastase, cathepsin G, and proteinase 3.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Brinsupri (brensocatib)
For the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older.	✔

(Prescribing information: Brinsupri 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Brinsupri (brensocatib)	Film-Coated Tablets	Oral	Once daily, with o without food	• Patients who miss a dose should take the next dose at their regular time the next day. Do not double the dose to make up for the missed dose

See the current prescribing information for full details.

Clinical Efficacy Summary

- The safety and efficacy of Brinsupri was evaluated in 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational trials (ASPEN and WILLOW) (*Chalmers et al 2025a*,
  - ASPEN was a Phase 3, 52-week trial in adult and pediatric patients ≥ 12 years of age (N=1,721) with non-cystic fibrosis bronchiectasis (NCFB; n =1680 adults; n = 41 pediatric patients 12 to 18 years of age). Patients were randomized to Brinsupri 10mg (n = 583), Brinsupri 25mg (n = 575), or placebo (n = 563) administered orally once daily.
  - WILLOW was a 24-week trial in adult patients with NCFB (N=256) who were randomized to Brinsupri 10mg (n = 82), Brinsupri 25mg (n = 87), or placebo (n = 87) administered orally once daily.
  - In both studies, all adult patients had a history of confirmed NCFB by chest computed tomography with at least 2 documented pulmonary exacerbations (PEx) prior to screening in the past 12 months. In the ASPEN study, pediatric patients ≥ 12 years of age had at least 1 PEx in the prior 12 months.
- *In the* ASPEN study, the mean age of included patients was 60 years, while 64% were female, 74% were White, 30% were former smokers, 29% had ≥3 pulmonary exacerbations in the prior 12 months, and 19% were on chronic macrolide therapy. The ppFEV1 post-bronchodilator mean was 74 (*Chalmers et al 2025a).*
  - The primary efficacy endpoint was the annualized rate of PEx over the 52-week treatment period.
    - Pulmonary exacerbations were defined as worsening of 3 or more of the following major symptoms over 48 hours, included increased cough, increased sputum volume or change in sputum consistency, increased sputum purulence, increased breathlessness, decreased exercise tolerance, fatigue and/or malaise, and hemoptysis, resulting in a healthcare provider's decision to prescribe systemic antibiotics.
    - Pulmonary exacerbations were considered severe if requiring treatment with intravenous antibacterial drugs and/or resulted in hospitalization.
  - Treatment with Brinsupri 10mg or 25mg in patients with NCFB demonstrated reductions in the mean rate of PEx over 52 weeks as compared with placebo.
    - The difference for the 10mg dose vs placebo was statistically significantly different (p = 0.004), as well as with the 25mg dose vs placebo (p = 0.005).
  - Results of this primary endpoint and other secondary endpoints are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

Study population	Placebo (N=563)	Brinsupri 10mg (N=583)	Brinsupri 25mg (N=575)
Annualized Rate of PEx	1.29	1.02	1.04
Rate Ratio		0.79	0.81
Median Time to first PEx (weeks)	36.71	49.00	50.71
Hazard Ratio (HR)		0.81	0.83

Study population	Placebo (N=563)	Brinsupri 10mg (N=583)	Brinsupri 25mg (N=575)
Proportion of patients that were PEx Free at week 52, %	40.3%	48.5%	48.5%
Odds Ratio		1.41	1.40
Annualized Rate of Severe PEx	0.19	0.14	0.14
Rate Ratio		0.74	0.74
Least Squares (LS) mean change from baseline in post-bronchodilator FEV1 (ml) at week 52	-62	-50	-24
Difference vs placebo		11	38

- WILLOW was a Phase 2, 24-week trial that included 256 adult patients with NCFB who were randomized to brensocatib 10 mg daily (n = 82), brensocatib 25 mg daily (n = 87), or placebo (n = 87) (*Chalmers et al 2020*).
  - The primary endpoint of time to the first PEx was longer for brensocatib-treated patients vs placebo (10 mg: HR, 0.58; 95% CI, 0.35 to 0.95; 25 mg: 0.62; 95% CI, 0.38 to 0.99, respectively).

Clinical guidelines

- There are no U.S.-based guidelines for the treatment of NCFB, but international guidelines and position statements are available from the European Respiratory Society (ERS), Thoracic Society of Australia and New Zealand (TSANZ) and the British Thoracic Society (BTS) (*Chalmers et al 2025b, Chang et al 2021, Chang et al 2023, Hill et al 2019*).
  - Treatment recommendations include use of antibiotics for the treatment of pulmonary exacerbations for 14 days based upon lower airway culture results, clinical severity, and patient-specific factors. Long-term antibiotic treatment (oral or inhaled) should be considered for patients with frequent pulmonary exacerbations (≥ 3 requiring antibiotics in the preceding 12 months).
  - Other recommended therapies include pulmonary rehabilitation, exercise, and appropriate vaccinations for high-risk patients with chronic lung disease (eg, influenza, pneumococcal).
  - The following are not routinely recommended, but may have a place in therapy based on concomitant disease states (eg, COPD, asthma):
    - Oral/inhaled corticosteroids, inhaled BDs, mucoactive agents (humidification with sterile water or normal saline to facilitate airway clearance may be considered), and alternative treatments such as cough suppressants, homeopathic remedies, and nutritional supplementation.
  - Referral to a multidisciplinary team is recommended if patients are considered candidates for surgery and/or transplant.

- Brensocatib is the first agent that targets NSPs that mediate inflammation as part of NCFB pathophysiology.
  - At the time of when the guidelines were written, brensocatib was not yet FDA approved. The guidelines note that while recommendations on use are not possible, updates to the document will address this new product at some point after it becomes available.

- An Institute for Clinical and Economics (ICER) evidence report on brensocatib for (*Wasfy et al 2025*) assigned a rating of B+ to brensocatib (moderate certainty of a small or substantial net health benefit, with high certainty of at least a comparable net health benefit), based on the results from the ASPEN study.
  - There is residual uncertainty about the efficacy of brensocatib in specific subgroups since there was no benefit demonstrated in some subgroups, such as patients with more advanced symptoms and worse baseline lung function (FEV_1 < 50% or BSI ≥ 9).

- While there is evidence for the efficacy of brensocatib in reducing PEx, the effects are less clear for the residual burden of daily symptoms outside of PEx (eg, fatigue, daily breathlessness, burdens of conventional airway clearance, use of inhaled and oral antibiotics, and other treatments).
- There is strong evidence for a small net health benefit, although larger benefits remain speculative (eg, slower deterioration in lung function as measured by FEV_1); potential benefits may be seen with longer follow-up.

Table 4: Evidence rating for adolescents and adults with NCFB

Treatment	Comparator	Evidence Rating
Brensocatib + usual care	Usual care alone	B+

Safety summary

- **Contraindications:** None.
- **Box Warning:** None.
- Warnings and precautions:
  - Treatment with Brinsupri is associated with an increase in dermatologic adverse reactions, including rash, dry skin, and hyperkeratosis. Monitor patients for development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings.
  - Treatment with Brinsupri is associated with an increase in gingival and periodontal adverse reactions. Refer patients to dental care services for regular dental checkups while taking Brinsupri. Advise patients to perform routine dental hygiene.
  - The concomitant use of Brinsupri and live attenuated vaccines has not been evaluated. It is not known whether administration of live attenuated vaccines during Brinsupri treatment will affect the safety or effectiveness of these vaccines. The use of live attenuated vaccines should be avoided in patients receiving Brinsupri.

- **Common adverse drug reactions**: Listed % incidence for adverse drug reactions= reported % incidence for drug (Brinsupri 10mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  - The most frequently reported adverse events included upper respiratory tract infection (2%), headache (0%), rash (0%), dry skin (2%), hyperkeratosis (0), and hypertension (2%).
- Listed % incidence for adverse drug reactions= reported % incidence for drug (Brinsupri 25mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  - The most frequently reported adverse events included upper respiratory tract infection (4%), headache (2%), rash (2%), dry skin (3%), hyperkeratosis (2%), and hypertension (0%).

- **Drug interactions**: None.

- **Special populations**:
  - There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
  - The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

Conclusion

- Bronchiectasis is a progressive disease of the lung that results from an infection or other circumstances that injures airway walls, and is described as dilated bronchi that is irreversible and bronchial infection and inflammation in the airways. (Tino et al 2025, Barker 2025, NIH 2023).
- Brinsupri is a DPP1 inhibitor indicated for the treatment of NCFB in adult and pediatric patients 12 years of age and older.
- Its efficacy was assessed in two randomized, double-blind, placebo-controlled, parallel-group trials.
  - The ASPEN trial included adults and pediatric patients 12 years of age and older with NCFB.
    - The primary efficacy endpoint was the annualized rate of PEx over the 52-week treatment period.

        - Treatment with Brinsupri 10 or 25mg in patients with NCFB demonstrated reductions in the mean rate of PEx over 52 weeks as compared with placebo.
    - The WILLOW trial included adults patients with NCFB.
        - The primary efficacy endpoint was the time to first PEx over the 24-week treatment period.
            - The time to first PEX was longer for patients receiving Brinsupri 10mg and 25mg as compared to placebo.
- Guidelines for bronchiectasis do not currently include Brinsupri, as they were published before Brinsupri was FDA approved. However, Brinsupri is the first FDA-approved treatment for NCFB, with evidence supporting its efficacy to reduce flares.

References

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Optum Rx®

Therapeutic Class Overview

GLP-1 Receptor Agonists

Introduction

- Obesity is defined as a body mass index (BMI) of ≥ 30 kg/m^2, and a BMI of 25 kg/m^2 to < 30 kg/m^2 falls within the overweight range. The prevalence of obesity in the United States (U.S.) is approximately 40.3% for adults aged 20 and older, and 20% for children and adolescents aged 2 to 19 years. When data are combined, approximately 73.6% of American adults aged 20 and older have overweight or obesity (*Centers for Disease Control [CDC] 2024[a,b]*).
  - In children, BMI interpretation is age- and sex-specific; BMI is calculated as a percentile rather than a cut-off category as used in adults. Overweight is defined as a BMI ≥ 85th percentile and < 95th percentile for children and teens of the same age and sex. Obesity is defined as a BMI ≥ 95th percentile for children and teens of the same age and sex (*Hampl et al 2023*).
- People who have obesity are at increased risk for several serious diseases and health conditions when compared to those with a healthy weight, such as all-cause mortality, hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), coronary heart disease, stroke, gallbladder disease, osteoarthritis, difficulty with physical functioning, obstructive sleep apnea (OSA), many types of cancer, low quality of life, and mental illness (eg, depression and anxiety) (*CDC 2025*).
- The therapeutic approach to managing obesity and achieving and maintaining a healthy weight includes a combination of diet modification, increased physical activity, and behavior therapy/modification (*American Diabetes Association [ADA] 2026, Apovian et al 2015, CDC 2023, Nadolsky et al 2025, Perreault and Reid 2025, Perreault et al 2025*).
  - The goals of obesity treatment, including drug therapy, are to prevent, treat, or reverse the complications of obesity and improve overall health status and quality of life. Health benefits have been reported with a weight loss of 5% to 10% (eg, reduce the development of T2DM in those with prediabetes and reduce blood pressure and risk factors for cardiovascular [CV] disease [CVD] in those with CV risk factors). Historically, many patients with a weight loss goal of ≥ 20% have not been able to achieve this goal without bariatric surgery. Developments in pharmacotherapies, however, such as the glucagon-like peptide 1 receptor agonists (GLP-1 RAs), may ultimately yield weight loss results approaching those seen with bariatric surgery.
- Several medications are Food and Drug Administration (FDA)-approved for the treatment/management of overweight/obesity in conjunction with healthy eating, physical activity, and behavior modification. Contemporary clinical trials evaluating the efficacy of antiobesity medications have demonstrated 5% to > 20% weight loss when added to lifestyle modification; usage of these medications without lifestyle interventions is generally ineffective over the long term (*Perreault and Reid 2025*).
  - Oral medications are available for short-term adjunctive therapy (ie, benzphetamine, diethylpropion hydrochloride [HCl] and diethylpropion HCl extended-release [ER], phendimetrazine tartrate and phendimetrazine tartrate ER, and phentermine HCl), and for longer-term administration (ie, Xenical [orlistat; also available as an authorized generic and over-the-counter in a reduced-dose strength as Alli], Contrave [naltrexone and bupropion], and Qsymia [phentermine and topiramate]) (*Drugs@FDA 2026*). Of note, these agents will not be reviewed within this overview.
- The focus of this overview will include the injectable and oral GLP-1 RA agents for chronic weight management including Saxenda (liraglutide), Wegovy (semaglutide), and the combination glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA Zepbound (tirzepatide) (*Drugs@FDA 2026*).
  - Wegovy subcutaneous injection and liraglutide are both indicated for adults and pediatric patients ≥ 12 years of age for weight reduction in obesity (liraglutide specifies a weight ≥ 60 kg).
  - Wegovy subcutaneous injection is also indicated to reduce the risk of major adverse CV events (MACE) in adults with established CV disease and either overweight or obesity. It is also the only antiobesity medication indicated for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH).
  - Wegovy tablet, an oral formulation of Wegovy subcutaneous injection, was FDA-approved on December 22, 2025, for chronic weight management and for MACE risk reduction. Wegovy is the first orally available GLP-1 RA with these indications (*Novo Nordisk press release 2025*).
  - Tirzepatide is currently the only antiobesity medication that is also indicated to treat moderate to severe OSA in adults with obesity.
- Medispan class: Anti-Obesity Agents; GIP and GLP-1 Receptor Agonists/GLP-1 Receptor Agonists

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)[a]
Saxenda (liraglutide) injection	✔
Wegovy (semaglutide) injection	-
Wegovy (semaglutide) oral tablet	-
Zepbound (tirzepatide) injection	-

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

(*Drugs@FDA 2026, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2026*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Saxenda[a] (liraglutide) injection	Wegovy[b] (semaglutide) injection	Wegovy[b] (semaglutide) tablet	Zepbound[c] (tirzepatide) injection
To reduce excess body weight and maintain weight reduction long term in adult patients with obesity or overweight in the presence of ≥ 1 weight-related comorbid condition (eg, hypertension, T2DM, dyslipidemia, OSA, or CVD)	✔	✔	✔	✔
To reduce excess body weight and maintain weight reduction long term in pediatric patients ≥ 12 years of age	✔ (> 60 kg)	✔		
To reduce the risk of MACE (ie, CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with established CVD and either obesity or overweight		✔	✔	
To treat moderate to severe OSA in adults with obesity				✔
Treatment of noncirrhotic MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults[d]		✔		

Abbreviations: BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; MACE = major adverse cardiovascular events; OSA = obstructive sleep apnea; T2DM = type 2 diabetes mellitus; MASH = metabolic dysfunction-associated steatohepatitis

[a]Limitations of use: Should not be coadministered with other liraglutide-containing products or with any other GLP-1 RAs. The safety and effectiveness in pediatric patients with T2DM have not been established.

[b]Limitations of use: Coadministration with other semaglutide-containing products or with any other GLP-1 RAs is not recommended. Tablets are not approved for use in patients < 18 years of age.

[c]Limitations of use: Coadministration with other tirzepatide-containing products or any other GLP-1 RAs is not recommended. The safety and efficacy of Zepbound in combination with other products intended for weight loss have not been established. Zepbound has not been studied in patients with a history of pancreatitis.

[d]This indication is approved under accelerated approval based on improvements of MASH and fibrosis. Continued approval for this indication may be contingent upon the verification and description of clinical benefit in a confirmatory trial.

(*Prescribing information: Saxenda 2025, Wegovy 2025, Zepbound 2026*)

- 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

Saxenda (liraglutide)

- The FDA approval of Saxenda for management of overweight/obesity was based on the SCALE clinical trial program (*Davies et al 2015, Garvey et al 2020, Pi-Sunyer et al 2015, Saxenda prescribing information , Wadden et al 2013*). The

SCALE trials were 56-week, Phase 3, double-blind (DB), placebo-controlled (PC), parallel group (PG), multicenter (MC), randomized controlled trials (RCT).
  - Adult patients lost an average of 4.9% to 7.4% of baseline bodyweight at 56 weeks with Saxenda. A summary of the SCALE clinical trial program are shown in Table 3 below.
  - Patients receiving Saxenda typically saw greater improvements in measurements of waist circumference (-6.0 to -8.2 cm), lipid profiles (total cholesterol [-1.4 to -3.2 mg/dL], high-density lipoprotein [HDL; +2.3% to +4.8 mg/dL]), blood pressure (systolic blood pressure [SBP; -3.0 to -4.3 mmHg]), hemoglobin A1c [HbA1c] (-0.3% to -1.3%), and other cardiometabolic parameters vs placebo.
  - The most common adverse effects (AEs) were gastrointestinal (GI)-related (eg, nausea, vomiting, diarrhea, constipation).
- The FDA approval of Saxenda for pediatric patients ≥ 12 years of age was based on a 56-week PG RCT in 251 pubertal patients aged 12 to 17 years, with BMI ≥ 30 kg/m^2 or BMI ≥ 95th percentile for age and sex (*Kelly et al 2020, Saxenda prescribing information 2025*).
  - After a 12-week lifestyle run-in period, patients were randomized to Saxenda (n = 125) or placebo (n = 126) once daily. Saxenda was titrated to 3 mg over a 4- to 8-week period based on tolerability. The primary endpoint was change in BMI standard deviation score (SDS).
  - At baseline, the mean BMI SDS for the Saxenda group was 3.14 vs 3.20 in the placebo group. The mean change in BMI SDS from baseline to week 56 in the Saxenda group was -0.23 vs -0.00 in the placebo group (estimated treatment difference [ETD], -0.22 [95% confidence interval (CI), -0.37 to -0.08]; p = 0.0022). A greater proportion of patients receiving Saxenda achieved ≥ 5% and ≥ 10% weight loss vs placebo.

Table 3. Summary of clinical trials with Saxenda (liraglutide) for management of overweight/obesity

Trial[a]	Treatment	Patient population	Proportion of weight lost	Proportion with ≥ 5% lost	Proportion with ≥ 10% lost
SCALE-Obesity + Prediabetes (Study 1)	Liraglutide 3 mg SC daily (n = 2487) Placebo (n = 1244)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	At 56 weeks: Liraglutide: -7.4% Placebo: -3.0% p < 0.001	At 56 weeks: Liraglutide: 62.3% Placebo: 34.4% p < 0.001	At 56 weeks: Liraglutide: 33.9% Placebo: 15.4% p < 0.001
SCALE-Diabetes (Study 2)	Liraglutide 3 mg SC daily (n = 423) Placebo (n = 212)	Adults with BMI ≥ 27 and with T2DM	At 56 weeks: Liraglutide: -5.4% Placebo: -1.7% p < 0.001	At 56 weeks: Liraglutide: 49.0% Placebo: 16.4% p < 0.001	At 56 weeks: Liraglutide: 22.4% Placebo: 5.5% p < 0.001
SCALE-Maintenance (Study 3)[b]	Liraglutide 3 mg SC daily (n = 212) Placebo (n = 210)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	At 56 weeks: Liraglutide: -4.9% Placebo: -0.3% p < 0.001	At 56 weeks: Liraglutide: 44.2% Placebo: 21.7% p < 0.001	At 56 weeks: Liraglutide: 25.4% Placebo: 6.9% p < 0.001

[a] All trials incorporated reduced caloric intake (approximately -500 kcal/day deficit) and increased physical activity (≥ 150 min/week)
[b] All patients were first treated with a low-calorie diet (total energy intake 1200 to 1400 kcal/day) in a run-in period lasting up to 12 weeks. Patients who lost ≥ 5% of their screening body weight after 4 to 12 weeks during the run-in were then randomized, with equal allocation, to receive either liraglutide or placebo for 56 weeks.

NOTE: Discontinuation rates in the 3 clinical trials were 27% for Saxenda vs 35% for placebo; ~10% treated with Saxenda vs 4% with placebo discontinued due to an AE (mostly during the first few months).

Wegovy (semaglutide) injection

- The FDA approval of Wegovy injection for management of overweight/obesity was based on the STEP clinical trial program (*Davies et al 2021, Garvey et al 2022, Rubino et al 2021, Rubino et al 2022, Wadden et al 2021, Wilding et al 2021*). STEP 1 to 5 were all 68-week, Phase 3, DB, MC, PC, RCTs, while STEP 8 was a 68-week Phase 3b, open-label (OL) RCT.

- Patients lost up to 16.0% of their baseline weight at 68 weeks with Wegovy. A summary of the STEP clinical trial program is shown in Table 4.
- Patients receiving Wegovy typically saw greater improvements in measurements of waist circumference (-9.4 to -14.6 cm), lipid profiles (total cholesterol [-1.4 to -3.9 mg/dL]; HDL (+5.2 to +6.9 mg/dL]), blood pressure (SBP [-3.9 to -6.2 mmHg]), HbA1c (-0.4% to -1.6%), and other cardiometabolic parameters as compared to placebo.
- The most common AEs were GI-related, including nausea, vomiting, diarrhea, and constipation.

- The accelerated approval of Wegovy (semaglutide) injection for metabolic-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis [NASH]) in adults with moderate to advanced fibrosis was demonstrated based on the results of a planned interim analysis of the ongoing ESSENCE trial; A Phase 3, DB, MC, PC, RCT. The primary endpoints of the analysis were the resolution of steatohepatitis without worsening of liver fibrosis and the reduction in liver fibrosis without worsening of steatohepatitis at week 72, involving the first 800 patients (semaglutide, n = 534; placebo, n = 266) (*Sanyal et al 2024*).
  - Resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of patients in the semaglutide 2.4 mg group and in 34.3% patients in the placebo group (estimated difference, 28.7%; 95% CI, 21.1 to 36.2; p < 0.001).
  - A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide 2.4 mg group and in 22.4% of those in the placebo group (estimated difference, 14.4%; 95% CI, 7.5 to 21.3; p < 0.001).
- STEP-TEENS was a 68-week RCT that formed the basis of FDA approval of Wegovy injection for adolescent patients ≥ 12 years of age (*Weghuber et al 2022, Wegovy prescribing information 2024*). After a 12-week lifestyle run-in period (including dietary recommendations and physical activity counseling), patients were randomized to Wegovy (n = 125) or placebo (n = 126) once weekly.
  - The mean baseline body weight was 108 kg, and mean BMI was 37 kg/m^2. Patients on Wegovy experienced a -16% change in BMI vs a +0.6% change for those on placebo. A total of 77.1% and 65.1% of patients on Wegovy experienced a ≥ 5% or ≥ 10% reduction in baseline BMI, respectively, vs 19.7% and 7.7% of patients on placebo. Patients on Wegovy had greater improvements in cardiometabolic parameters than those on placebo.

Table 4. Summary of clinical trials with Wegovy (semaglutide) for management of overweight/obesity

Trial	Treatment	Patient population	Proportion of weight lost	Proportion with ≥ 5% lost	Proportion with ≥ 10% lost
STEP 1[a]	Semaglutide 2.4 mg SC weekly (n = 1306) Placebo (n = 655)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Baseline to 68 weeks: Semaglutide: -14.9% Placebo: -2.4% p < 0.001	Baseline to 68 weeks: Semaglutide: 83.5% Placebo: 31.1% p < 0.001	Baseline to 68 weeks: Semaglutide: 66.1% Placebo: 12.0% p < 0.001
STEP 2[a]	Semaglutide 2.4 mg SC weekly (n = 404) Placebo (n = 403)	Adults with BMI ≥ 27 and with T2DM	Baseline to 68 weeks: Semaglutide: -9.6% Placebo: -3.4% p < 0.001	Baseline to 68 weeks: Semaglutide: 67.4% Placebo: 30.2% p < 0.001	Baseline to 68 weeks: Semaglutide: 44.5% Placebo: 10.2% p < 0.001
STEP 3[b]	Semaglutide 2.4 mg SC weekly (n = 407) Placebo (n = 204)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Baseline to 68 weeks: Semaglutide: -16.0% Placebo: -5.7% p < 0.001	Baseline to 68 weeks: Semaglutide: 84.8% Placebo: 47.8% p < 0.001	Baseline to 68 weeks: Semaglutide: 73.0% Placebo: 27.1% p < 0.001
STEP 4[a,c]	Semaglutide 2.4 mg SC weekly (n = 535) Placebo (n = 268)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Week 20 to week 68: Semaglutide: -7.9% Placebo: +6.9% p < 0.001	--	--

STEP 5[a]	Semaglutide 2.4 mg SC weekly (n = 152) Placebo (n = 152)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Baseline to 104 weeks: Semaglutide: -15.2% Placebo: -2.6% p < 0.001	Baseline to 104 weeks: Semaglutide: 77.1% Placebo: 34.4% p < 0.001	Baseline to 104 weeks: Semaglutide: 61.8% Placebo: 13.3% p < 0.001
STEP 8[a]	Semaglutide 2.4 mg SC weekly (n = 126) Liraglutide 3 mg SC daily (n = 127) Placebo (n = 85)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Baseline to 68 weeks: Semaglutide: -15.8% Liraglutide: -6.4% Placebo: -1.9% p < 0.001[d]	--	Baseline to 68 weeks: Semaglutide: 70.9% Liraglutide: 25.6% Placebo: 15.4% p < 0.001[d]
Abbreviations: BL = baseline; BMI = body mass index; SC = subcutaneous; T2DM = Type 2 diabetes mellitus					

[a] Trial incorporated reduced caloric intake (-500 kcal/day deficit) and increased physical activity (≥ 150 min/week)
[b] Trial incorporated an intense hypocaloric diet (ie, weeks 1 to 8: 1000-1200 kcal/day provided as meal replacements [eg, liquid shakes, meal bars, portion-controlled meals] and subsequent transition to 1200 to 1800 kcal/day of conventional food through week 68 based on randomization body weight) and intense physical activity (ie, at randomization, patients were prescribed 100 minutes of physical activity per week [spread across 4-5 days], which increased by 25 minutes every 4 weeks, to reach 200min/week)
[c] All patients were dose escalated on semaglutide during a 20-week run-in period; those who reached the 2.4 mg weekly dose at the end of the run-in period were then randomized to either continue on Wegovy or to placebo for 48 weeks; data are from week 20 to week 68. The week 0 weight was 107 kg and the week 0 BMI was 38 kg/m^2.
[d] For difference between semaglutide vs liraglutide
NOTE: Discontinuation rates ranged from 6 to 16% for Wegovy vs 3 to 19% for placebo; ~7% treated with Wegovy vs 3% with placebo discontinued due to an AE. Baseline weight ranged from 96 to 106 kg and baseline BMI from 34 to 38 kg/m^2.

- SELECT was a Phase 3 RCT (event-driven superiority trial) (N = 17,604) that investigated whether the addition of Wegovy injection to standard care would be superior to placebo in reducing the risk of MACE among patients with overweight/obesity and preexisting CVD who did not have diabetes (*Lincoff et al 2023, Ryan et al 2020*). Patients were followed for a mean of 39.8 months.
  - The primary endpoint was the composite of death from CV causes, nonfatal MI, or nonfatal stroke (assessed in a time-to-first-event analysis). A primary CV endpoint event occurred in 569/8803 (6.5%) patients receiving Wegovy vs 701/8801 (8.0%) receiving placebo (hazard ratio [HR], 0.80; 95% CI, 0.72 to 0.90; p < 0.001); the trial achieved its primary endpoint by demonstrating a statistically significant and superior reduction in MACE of 20% for people treated with semaglutide 2.4 mg vs placebo.
  - Changes in body weight and waist circumference over the course of the trial were additional supportive secondary endpoints. At 104 weeks, the mean change in body weight was -9.39% with Wegovy vs -0.88% with placebo (treatment difference, -8.51%; 95% CI, -8.75 to -8.27); the mean change in waist circumference was -7.56 cm with Wegovy vs -1.03 cm with placebo (treatment difference, -6.53; 95% CI, -6.79 to -6.27). Treatment differences for other measurements of health favored Wegovy.
    - A prespecified analysis of the SELECT trial on the relationships between baseline adiposity measures, treatment-induced adiposity changes, and subsequent MACE risk found that the cardioprotective effects of semaglutide were independent of baseline adiposity and weight loss and had only a small association with waist circumference, suggesting some mechanisms for benefit beyond adiposity reduction (*Deanfield et al 2025*).

Wegovy (semaglutide) oral tablet

- The efficacy of oral Wegovy 25 mg was evaluated in the Phase 3, OASIS-4 trial. Patients with obesity or with overweight and ≥ 1 weight-related comorbidity (except T2DM) were randomized 2:1 (N = 307) to receive oral Wegovy 25 mg (n = 205) or placebo (n = 102) for 64 weeks; dose escalation occurred over the first 12 weeks, and maintenance dosing was administered for 52 weeks. The primary endpoints included the percent change in body weight and the proportion of participants with ≥ 5% body weight loss (*ClinicalTrials.gov [NCT05564117], Wharton et al 2025*).
  - Secondary endpoints evaluated the proportion of patients with ≥ 10%, ≥ 15%, and ≥ 20% body weight loss and quality of life (QOL) measures.
- A total of 81.5% of participants enrolled in the oral Wegovy group (167/205) and 74.5% of enrolled in the placebo group (76/102) completed the full 64 weeks of treatment. Data presented follow the intent-to-treat (ITT) principle.

- At 64 weeks, the estimated change in body weight with oral Wegovy was -13.6% vs -2.2% with placebo (ETD, -11.4%; 95% CI, -13.9 to -9.0; p < 0.001). The proportion of patients achieving ≥ 5% weight loss was 79.2% (n = 152) with oral Wegovy vs 31.1% (n = 28) with placebo.

- Results from secondary endpoints demonstrated:
  - The proportion of patient achieving ≥ 10%, ≥ 15%, and ≥ 20% weight loss was significantly higher in with semaglutide compared to placebo (63% vs 14.4%, 50% vs 5.6%, 29.7% vs 3.3%, respectively; p < 0.001 for all).
  - A significant improvement in the Change in the Impact of Weight on QOL-Lite-Clinical Trials (IWQOL-Lite-CT) Physical Function score; with a baseline score of 56.8 points, the observed mean changes from baseline were 16.2 points (Wegovy) vs 8.4 points (placebo) (p < 0.001)

- The approval of Wegovy tablet for MACE risk reduction was based upon data from the SELECT trial, in which Wegovy subcutaneous injection was evaluated against placebo (*Wegovy prescribing information 2025*).
  - Pharmacokinetic data show similar serum semaglutide concentrations with both dosage forms. In patients with overweight/obesity without T2DM, semaglutide concentrations following once-daily administration of oral Wegovy 25 mg tablet are predicted to be comparable to Wegovy 2.4 mg once-weekly injection, with higher variability in semaglutide concentrations compared to subcutaneous administration (90% of patients had average concentrations between 27 and 186 nmol/L with Wegovy 25 mg tablet vs 51 and 110 nmol/L with Wegovy 2.4 mg once-weekly injection) (*Wegovy prescribing information 2026*).

Zepbound (tirzepatide)

- The FDA-approval of Zepbound for management of overweight/obesity was based on the SURMOUNT clinical trial program (*Aronne et al 2024, Garvey et al 2023, Jastreboff et al 2022, Wadden et al 2023, Zepbound prescribing information 2026*). SURMOUNT-1, -2, and -3 were 72-week, Phase 3, DB, PC, MC, RCTs, while SURMOUNT-4 was a Phase 3 randomized withdrawal trial evaluating patients from weeks 36 to 88. The Phase 3b SURMOUNT-5 trial directly compared tirzepatide and semaglutide for obesity management in people without diabetes (*Aronne et al 2025*).
  - In SURMOUNT-1, -2, and -3, patients lost an average of 12.8% to 20.9% of baseline bodyweight at 72 weeks with Zepbound 5, 10, or 15 mg, with the greatest percentage of weight loss seen in patients who reached maximum tolerated doses of 10 to 15 mg. A summary of the SURMOUNT clinical program is shown in Table 5.
  - Patients receiving tirzepatide up to 72 weeks typically saw greater improvements in measurements of waist circumference (-10.8 to -18.5 cm), lipid profiles (total cholesterol [-1.0 to -6.3 mg/dL]; HDL [+6.9% to +9.7% mg/dL]), blood pressure (SBP [-5.6 to -7.7 mmHg]), HbA1c (-0.4% to -2.1%), and other cardiometabolic parameters as compared to placebo.
  - The most common AEs were GI-related, including nausea, vomiting, diarrhea, decreased appetite, and constipation.

Table 5. Summary of clinical trials with tirzepatide for management of overweight/obesity

Trial[a]	Treatment	Patient population	Proportion of weight lost	Proportion with ≥ 5% lost	Proportion with ≥ 10% lost
SURMOUNT-1	Tirzepatide 5 mg SC weekly (n = 630) Tirzepatide 10 mg SC weekly (n = 636) Tirzepatide 15 mg SC weekly (n = 630) Placebo (n = 643)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	BL to 72 weeks: Tirzepatide 5 mg: 15.0%[b] Tirzepatide 10 mg: 19.5% Tirzepatide 15 mg: 20.9% Placebo: 3.1% p < 0.001[c]	BL to 72 weeks: Tirzepatide 5 mg: 85.1%[b] Tirzepatide 10 mg: 88.9% Tirzepatide 15 mg: 90.9% Placebo: 34.5% p < 0.001[c]	BL to 72 weeks: Tirzepatide 5 mg: 68.5% Tirzepatide 10 mg: 78.1% Tirzepatide 15 mg: 83.5% Placebo: 18.8% p < 0.001[c]
SURMOUNT-2	Tirzepatide 10 mg SC weekly (n = 312)	Adults with BMI ≥ 27 and with T2DM	BL to 72 weeks: Tirzepatide MTD: 12.8%	BL to 72 weeks: Tirzepatide 10 mg: 79%	BL to 72 weeks: Tirzepatide 10 mg: 61%

	Tirzepatide 15 mg SC weekly (n = 311) Placebo (n = 315)		Tirzepatide 15 mg: 14.7% Placebo: 3.2% p < 0.001 [c]	Tirzepatide 15 mg: 83% Placebo: 32% p < 0.001 [c]	Tirzepatide 15 mg: 65% Placebo: 9% p < 0.001 [c]
SURMOUNT-3[d]	Tirzepatide MTD SC weekly (n = 287) Placebo (n = 292)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	BL to 72 weeks: Tirzepatide MTD: 18.4% Placebo: 2.5% p < 0.001	BL to 72 weeks: Tirzepatide MTD: 87.5% Placebo: 16.5% p < 0.001	BL to 72 weeks: Tirzepatide MTD: 76.7% Placebo: 8.9% p < 0.001
SURMOUNT-4[e]	Tirzepatide MTD SC weekly (n = 335) Placebo (n = 335)	Adults with BMI ≥ 30 or ≥ 27 + comorbidity except T2DM	Weeks 36 to 88: Tirzepatide MTD: 5.5% Placebo: 14.0% (gained) p < 0.001	Weeks 36 to 88: Tirzepatide MTD: 97.3% Placebo: 70.3% p < 0.001	Weeks 36 to 88: Tirzepatide MTD: 92.1% Placebo: 16.2% p < 0.001
SURMOUNT-5	Tirzepatide MTD (10 or 15 mg) SC weekly (n = 374) Semaglutide MTD (1.7 mg or 2.4 mg) SC weekly (n = 376) 72 weeks	Adults with BMI ≥ 30 or ≥ 27 + ≥ 1 prespecified obesity related comorbidity[f]	Mean % change in body weight from BL to week 72: Tirzepatide MTD: 20.2% Semaglutide MTD: 13.7% p < 0.001	More patients treated with tirzepatide compared to semaglutide had reductions in body weight of ≥ 10%, 15%, 20%, and 25% from baseline (p < 0.001)[g]	
Abbreviations: BL = baseline; BMI = body mass index; MTD = maximum tolerated dose (10 or 15 mg tirzepatide); SC = subcutaneous; T2DM = Type 2 diabetes mellitus					

[a] Trial included lifestyle intervention (regular counseling sessions with a dietician or qualified health professional, deficit of 500 kcal/day, and ≥ 150 minutes of physical activity/week)
[b] The change in body weight in the tirzepatide 5 mg group was not a primary end point and was analyzed as a key secondary end point
[c] p < 0.001 for all comparisons vs placebo
[d] Patients randomized if achieved ≥ 5% loss of baseline weight during a 12-week lead-in period providing intensive lifestyle intervention (~ 72%)
[e] All patients were dose escalated on tirzepatide during a 36-week lead-in period; those who reached the MTD or tirzepatide (10 or 15 mg) at the end of the run-in period were then randomized to either continue on tirzepatide or to placebo for 52 weeks; data are from week 36 to week 88. During the 36-week lead-in, mean weight reduction was -20.9% and BMI reduction was -8.0%. The week 0 weight was 107.3 kg, and the week 0 BMI was 38.4 kg/m^2. Patients maintaining ≥ 80% of weight lost at week 88 from week 36 were 89.5% and 16.6% of patients in the tirzepatide vs placebo groups, respectively.
[f] Including hypertension, dyslipidemia, OSA, or CVD, but excluding patients with T2DM.
[g] Analyzed as a key secondary end points.
NOTE: Discontinuation rates for SURMOUNT-1, -2, -3, and -4 ranged from 5% to 12% for Zepbound vs 11% to 23% for placebo; 4 to 11% treated with Zepbound vs ~3% administered placebo discontinued due to an AE. Baseline weight ranged from 101 to 110 kg and baseline BMI from 36 to 39 kg/m^2.

- The FDA approval of Zepbound for the management of OSA was based on the SURMOUNT-OSA trials: two, Phase 3, DB, PC, RCTs in 469 individuals with moderate to severe OSA and obesity. Study 1 enrolled patients unable or unwilling to use continuous positive airway pressure (CPAP) therapy, and Study 2 enrolled patients on CPAP therapy at baseline. Participants were assigned to receive either tirzepatide or placebo for 52 weeks. The primary end point was the change in the apnea–hypopnea index (AHI, the average number of apneas and hypopneas per hour of sleep) from baseline (mean AHI, 51.5 events [study 1] and 49.5 events [study 2]) (*Malhotra et al 2024*).
  - In trial 1, the mean change in AHI at week 52 was -25.3 events per hour with tirzepatide and -5.3 events per hour with placebo (treatment difference, -20.0 events per hour; 95% CI, -25.8 to -14.2; p < 0.001).
  - In trial 2, the mean change in AHI at week 52 was -29.3 events per hour with tirzepatide and −5.5 events per hour with placebo (treatment difference, -23.8 events per hour; 95% CI, -29.6 to -17.9; p < 0.001).

- Statistically significant improvements in key secondary endpoints were also demonstrated in the tirzepatide group including the percent change in bodyweight and in AHI, changes in high-sensitivity C-reactive protein (hsCRP) concentration, hypoxic burden, SBP, and in patient reported sleep impairment and disturbance ($p < 0.001$ for all except hsCRP in study 1 [$p = 0.004$], and SBP in study 2 [$p = 0.02$]).
- The most commonly reported adverse events with tirzepatide were GI-related, and mostly mild to moderate in severity.

Systemic reviews/Meta-analyses and Comparative Reviews

Liraglutide/Saxenda in pediatric patients (*Ryan et al 2021*)

- The objective of this systemic review was to determine the weight, BMI, cardiometabolic effects, and GI effects of GLP-1 RAs in children with obesity. RCTs published through January 1, 2021 were included that explored the use of GLP-1 RAs in children and adolescents < 18 years of age at the time of randomization, with obesity, with or without a diagnosis of T2DM.
  - Of the 9 trials included in the review, 3 trials evaluated exenatide (approved for management of T2DM and not overweight/obesity) and 6 evaluated liraglutide at doses ranging from 1.2 to 3.0 mg (dosing used as Victoza or Saxenda); 8 of the studies were PG RCTs and 1 study used a crossover design. All studies reported the use of a volume-matched placebo injection pen, and 3 of the studies reported concurrent lifestyle interventions. The trials enrolled a total of 574 children and adolescents, 302 of whom were administered a GLP-1 RA. All studies included children with obesity or severe obesity, and 3 of the studies exclusively included participants with T2DM or prediabetes, although diagnosis of T2DM was not an exclusion criterion for the remainder of studies.
  - The mean age across all included participants was 14.15 years, with a slight female (53.3%) majority. Mean weights of participants at baseline ranged from 71.5 kg to 124 kg, with BMIs ranging from 33.9 to 43 kg/m^2 and BMI z-scores ranging from 2.9 to 3.9.
- The primary outcomes for the quantitative meta-analysis included reductions in body weight/BMI/z score, HbA1c, fasting plasma glucose, lipid profile (triglycerides, total cholesterol, LDL), and blood pressure.
  - Use of GLP-1 receptor agonists caused modest reductions in body weight, with a mean difference of -1.50 kg (95% CI, -2.50 to -0.50), BMI (mean difference of -1.24 kg/m^2 [95% CI, -1.71 to -0.77]) and BMI z-score (mean difference of -0.14 [95% CI, -0.23 to -0.06]). Subsequent subgroup analyses by the specific medication revealed no discernable difference in the body weight, BMI, or BMI z-score reducing effects of exenatide when compared with Saxenda.
  - A sensitivity analysis exploring the effect of concurrent lifestyle intervention, provided to both control and intervention arms, on weight and BMI outcomes revealed the adjunctive therapy to be highly complementary to GLP-1 receptor agonist treatment.
  - Among the 6 studies that reported HbA1c, GLP-1 receptor agonists only had an effect on populations which were exclusively composed of children with insulin resistance (ie, T2DM or prediabetes; mean difference, -1.05 % [95% CI, -1.93 to -0.18]). No effect on fasting plasma glucose was noted for either population.
  - In the 3 studies that explored lipid profiles, no improvements in total cholesterol, LDL, or triglycerides were noted. Among the 4 studies reporting blood pressure, treatment had no effect on diastolic blood pressure and produced a modest decrease in SBP (mean difference, -2.30 mmHg [95% CI, -4.11 to -0.49]).
  - Of the studies where liraglutide/Saxenda was used, the most commonly reported treatment-emergent AEs were GI-related, skin and SC tissue-related (6.3 to 14.3 per 100 participants), neurologic (18.8 to 50 per 100 participants), endocrine-related, and hepatobiliary. The most common endocrine AE was hypoglycemia (14.3 to 25 per 100 participants), and the singular hepatobiliary AE was elevated transaminases (0 to 7.1 per 100 participants).
- The authors concluded that GLP-1 RAs are safe and effective in modestly reducing weight, BMI, HbA1c, and SBP in children and adolescents with obesity in a clinical setting, albeit with increased rates of nausea.

Saxenda (*Zhang et al 2019*)

- A systemic review/meta-analysis assessed the efficacy and safety of Saxenda in obese, non-diabetic individuals. Five RCTs (published up to and including May 2018) that evaluated a total of 4754 patients who received Saxenda (n = 2996) or placebo (n = 1758) were included. The duration of treatment ranged from 14 to 56 weeks. No heterogeneity was found among the trials.
  - The analysis showed that patients who received Saxenda showed significantly greater mean weight loss vs placebo (mean difference, -5.52; 95% CI, -5.93 to -5.51; $p < 0.00001$).

- Four RCTs included the proportion of patients who lost ≥ 5% of initial body weight. The analysis suggested that a greater proportion of patients lost ≥ 5% of initial body weight with Saxenda (n = 2816) vs placebo (n = 1579) (OR, 5.46 [95% CI, 3.57 to 8.34]; p < 0.00001).
- Five RCTs included an analysis of SBP differences from baseline to study end, and it was determined that patients receiving Saxenda had significantly greater decreases vs those receiving placebo (mean difference, -2.56 [95% CI, -3.28 to -1.84]; p < 0.00001).
- Four RCTs included the proportion of patients who withdrew from the trial due to an AE. Rates of withdrawal were similar for those treated with Saxenda (n = 2972) vs those on placebo (n = 1731) (OR, 2.85 [95% CI, 0.84 to 9.62]; p = 0.09). Additionally, nausea was more common among those treated with Saxenda than placebo (OR, 5.04 [95% CI, 3.34 to 7.6]; p < 0.00001).
- The authors concluded that liraglutide is an effective and safe treatment for obese, non-diabetic individuals.

- A systematic review of 26 RCTs (N = 15,491) evaluated the efficacy and safety of GLP-1RAs and co-agonists (3 commercially available agents [liraglutide, semaglutide injection, tirzepatide] and 9 premarket agents) for the long-term weight management in adults with overweight or obesity, but without T2DM(72% female, mean age 34 to 57 years old). The median treatment duration was 43 weeks (range, 16 to 104 weeks). Compared to placebo, tirzepatide 15 mg weekly resulted in the greatest weight loss of up to 17.8% (72 weeks of treatment), followed by semaglutide 2.4 mg weekly with up to 13.9% weight loss (68 weeks of treatment), and liraglutide 3 mg daily with up to 5.8% weight loss (26 weeks of treatment). AEs were frequent, and the majority were GI-related including nausea, vomiting, diarrhea and constipation (*Moiz et al 2025*).
- An Institute for Clinical and Economic Review (ICER) report evaluated the clinical effectiveness of Wegovy (semaglutide 2.4 mg injection and 25 mg oral tablet) and tirzepatide 15 mg, compared to lifestyle modifications alone or no specific intervention for obesity. The population included adults with obesity or with overweight and ≥ 1 weight-related comorbid condition, who are actively seeking medical management for weight loss; adults with established diabetes were not included. Evidence ratings were as follows (*ICER 2025*):
  - Because treatment with all 3 drugs results in substantial weight loss and improvement in metabolic risk factors, there is high certainty that all 3 drugs have substantial net health benefit over lifestyle modifications alone (**A**).
    - An "A" rating is a "superior" rating in which there is a high certainty of a substantial (moderate to large) net health benefit.
  - There is less certainty about the relative effects of the drugs to each other, particularly for outcomes beyond weight loss (eg, CV outcomes), and thus the comparison between tirzepatide and semaglutide (oral or injection) is "promising but inconclusive" (**P/I**).
    - A "P/I" rating conveys a moderate certainty of a small or substantial net health benefit, with high certainty of at least a comparable net health benefit.
  - Treatment with oral Wegovy results in slightly lower amounts of weight loss compared with Wegovy injection, with uncertainty about the degree of CV benefit, and thus oral Wegovy was judged to be "comparable or worse" than Wegovy injection (**C-**).
    - A "C-" rating conveys a moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit.

Clinical Guidelines

- Several organizations and medical associations have developed guidelines for managing obesity as a chronic disease and to improve morbidity and mortality associated with obesity (*ADA 2026, Apovian et al 2015, Garvey et al 2016, Grunvald et al 2022, Haml et al 2023, Jensen et al 2014, Nadolsky et al 2025, Styne et al 2017, VA/DoD 2025, WHO 2025*) .
  - In general, treatment approaches for obesity should be individualized, and a combination approach may be considered when appropriate. Several guidelines provide recommendations regarding pharmacotherapy, which should be used as an adjunct to behavioral modification when the BMI is ≥ 27 kg/m^2 with a comorbidity (eg, T2DM) or when the BMI is > 30 kg/m^2, though guidelines have also suggested that BMI should not be relied on as the sole diagnostic staging tool for overweight/obesity.
    - Antiobesity medications generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient (eg, comorbidities [eg, T2DM], patients' preferences, and access to the therapy).
    - Short-term treatment (3 to 6 months) using weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended based on scientific evidence.

- If weight loss or health outcome goals are not achieved with current treatment, the clinician can consider intensification of behavioral treatment, the addition or reevaluation of obesity pharmacotherapy, and/or referral for evaluation for bariatric surgery in patients otherwise meeting BMI and comorbidity criteria.

- **American Diabetes Association (ADA) Standards of Care in Diabetes 2026: Obesity and Weight Management for the Prevention and Treatment of T2DM (*ADA 2026*)**
  - To support the diagnosis of obesity, BMI should be calculated; additional measurements of body fat distribution (eg, waist circumference, waist-to-hip ratio, and/or waist-to-height ratio) should be performed.
  - In those with T2DM and overweight/obesity, agents with both glucose-lowering and weight loss effects are preferred; the preferred pharmacotherapy should be a GLP-1 RA or dual GIP/GLP-1 RA with greater weight loss efficacy (ie, semaglutide or tirzepatide), especially considering their added weight-independent benefits. Weight management pharmacotherapy indicated for chronic use should be continued beyond reaching weight loss goals to maintain the health benefits, as sudden discontinuation often results in weight gain and worsening or reemergence of cardiometabolic risk factors. In those with T2DM not reaching weight treatment goals, modifying or intensifying treatment with additional approaches (eg, structured lifestyle management programs, metabolic surgery, additional/alternative pharmacologic agents) is recommended.
    - Weight management treatment should aim for any magnitude of weight loss, and includes interventions that focus on nutrition, physical activity, and behavioral therapy. Weight loss of 5% to 7% improves glycemia and other intermediate CV risk factors. A sustained loss of > 10% usually confers greater benefits, including disease-modifying effects and possible remission of T2DM, and may improve long-term CV outcomes and mortality.
  - Those who achieve ≥ 5% weight loss after 3 months' use should continue the medication long term. When early weight loss results are modest (typically < 5% weight loss after 3 months' use) the benefits of ongoing treatment need to be balanced in the context of the glycemic response, the availability of other potential treatment options, treatment tolerance, and overall treatment burden. For those not reaching or maintaining weight-related treatment goals, weight management therapies should be reevaluated, and treatment intensified with additional approaches (eg, metabolic surgery, additional pharmacologic agents, structured lifestyle management programs).

- **VA/DoD 2025: Clinical Practice Guideline for the Management of Adult Overweight and Obesity (*VA/DoD 2025*)**
  - This guideline is an update to the 2020 VA/DoD clinical practice guideline for the management of adult overweight and obesity and is based on clinical evidence related to information published from April 1, 2019 to January 6, 2025. The guideline is intended to improve the quality of care and clinical outcomes and is not intended to define a standard of care (ie, mandated or strictly required).
  - The guideline is designed to assist providers in managing or comanaging patients with overweight and/or obesity.
  - Overall, the guideline recommends semaglutide or tirzepatide for both weight loss and to maintain weight loss, in conjunction with a comprehensive lifestyle intervention, in patients with a BMI ≥ 27 kg/m^2 who also have an obesity-associated condition; and those who have a BMI ≥ 30 kg/m^2. (Strength: Strong for)
    - The guideline suggests phentermine/topiramate ER or liraglutide for both weight loss and to maintain weight loss, in conjunction with a comprehensive lifestyle intervention, in patients with a BMI ≥ 27 kg/m^2 who also have an obesity-associated condition and those who have a BMI ≥ 30 kg/m^2. (Strength: Weak for)
    - This guideline suggests naltrexone/bupropion ER for weight loss, in conjunction with a comprehensive lifestyle intervention, in patients with a BMI ≥ 27 kg/m^2 who also have an obesity-associated condition; and those who have a BMI ≥ 30 kg/m^2. (Strength: Weak for)
    - There is insufficient evidence to recommend either for or against:
      - Orlistat, metformin, sodium glucose cotransporter type 2 inhibitors, or pramlintide for weight loss. (Strength: Neither for nor against)
      - Phentermine monotherapy, benzphetamine, diethylpropion, or phendimetrazine, for weight maintenance. (Strength: Neither for nor against)
    - The guideline suggests against using dietary supplements or nutraceuticals for clinically meaningful weight management. (Strength: Weak against)

- **American Association of Clinical Endocrinology (AACE) Consensus Statement: Algorithm for the evaluation and treatment of adults with obesity/adiposity-based chronic disease—2025 update (*Nadolsky et al 2025*)**

- This Consensus Statement update provides an evidence-based guidance to assist health care professionals and adults with obesity and adiposity-based chronic disease (ABCD) in shared decision making to improve care and achieve health goals; it serves as an update to the 2016 AACE algorithm for the medical care of patients with obesity.
  - ABCD is a complex, chronic disease that necessitates long-term treatment and care. Emphasis is placed on optimizing health rather than just weight reduction and achieving clinical goals other than a singular focus on BMI. Choice of interventions and intensity of treatment should be individualized, taking disease severity or stage into account. Equality of care and reducing weight bias and stigma through a biopsychosocial chronic care model are also important.
  - Lifestyle interventions remain an important component for optimizing health in individuals with ABCD. This includes personalized medical nutrition therapy, prescribed physical activity, and behavioral interventions to help optimize healthful eating and integrate movement into daily life. It is key that individuals with ABCD incorporate these lifestyle and behavioral efforts alongside initiation and continuation of pharmacotherapeutic interventions for improvement of overall health.
- Hierarchies of preferred medications for complication-centric care of people with ABCD
  - Hierarchies are based on clinical trial data. Drugs are not listed when relevant data are not available. However, weight loss regardless of treatment modality may provide benefit.
  - In general, first-line pharmacologic options for cardiometabolic (ie, prediabetes, metabolic syndrome, diabetes prevention,T2DM, MACE prevention, blood pressure lowering, MASH, chronic kidney disease, heart failure with preserved ejection fraction) and biomechanical conditions (ie, osteoarthritis and OSA) consistently prioritize the use of GLP-1RAs, semaglutide and tirzepatide.
    - Phentermine/topiramate is also considered first-line in select situations, specifically for blood pressure lowering and OSA.
- Treatment may be adjusted over time; the optimal dose to maintain long-term weight loss need not be the maximum dose.
- A first-generation medication (ie, phentermine, orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide) may be trialed to maintain long-term weight loss after initial treatment using a second-generation medication (ie, semaglutide, tirzepatide).

- **World Health Organization (WHO) guideline on the use of GLP-1 therapies for the treatment of obesity in adults** (*Celletti 2025*)
  - This guideline is the first clinical guidance from the WHO on the pharmacological treatment of obesity in adults. The guideline offers evidence-informed recommendations on the use of GIP/GLP-1 (tirzepatide) and GLP-1 (liraglutide, semaglutide) RAs.
  - The guidelines recognize obesity as a chronic, relapsing disease requiring lifelong care and emphasize early diagnosis and integrated, person-centered approaches combining behavioral, medical, surgical, and other interventions alongside prevention and management of comorbidities.
  - Conditional treatment recommendations include:
    - In adults living with obesity, GIP/GLP-1 or GLP-1 RAs may be used as long-term (≥ 6 months of continuous use) treatment for obesity in people with BMI ≥ 30 kg/m^2.
    - In adults living with obesity who are prescribed GIP/GLP-1 or GLP-1 RAs, intensive behavioral therapy may be provided as a cointervention within a comprehensive multimodal clinical algorithm.

- **American Academy of Pediatrics (AAP): Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity (*Hampl et al 2023*)**
  - Children with obesity commonly become adolescents and adults with obesity. BMI levels strongly track throughout childhood and adolescence and are predictive of high adult BMI.
  - Children with overweight and obesity benefit from health behavior and lifestyle treatment, which is a child-focused, family-centered, coordinated approach to care, coordinated by a patient-centered medical home, and may involve pediatricians, other pediatric health care providers (such as registered dietitian nutritionists, psychologists, nurses, exercise specialists, and social workers), families, schools, communities, and health policy.
  - There is substantial evidence to support concurrent treatment of obesity and comorbidities to achieve weight loss, avoid further weight gain, and improve obesity-related comorbidities.

    - The majority of studies on comorbidities demonstrate an association between overweight/obesity, severity of obesity, and higher prevalence of comorbidities. Studies also report improvement in comorbidities with intensive lifestyle treatment, weight loss medication, and/or bariatric surgery.
    - Cardiometabolic markers improved significantly in children with obesity who underwent intensive pediatric obesity treatment of 3 to 6 months, which provides an opportunity for clinicians to emphasize health outcomes of lifestyle management. Decreases in BMI can lead to clinically meaningful improvements in comorbidities.
  - Intensive health behavior and lifestyle treatment (IHBLT) is the foundational approach to achieve body mass reduction/attenuation of excessive weight gain in children. The most consistently effective IHBLT programs deliver ≥ 26 hours of face-to-face family-based counseling on nutrition and physical activity over ≥ 3 to 12 months for children aged ≥ 6 years. Interventions that delivered ≥ 52 hours of contact over the same duration demonstrated the most consistent and significant reduction in BMI and cardiometabolic comorbidity improvement.
    - Some behavior strategies may include (but are not limited to): reduction of sugar-sweetened beverages, incorporating 60 minutes of moderate to vigorous physical activity daily, reducing sedentary behaviors (eg, screen time), and getting an appropriate amount of sleep.
  - Pediatricians and other health care professionals may offer children aged ≥ 8 years with obesity weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.

- **American Gastroenterological Association (AGA) Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity (*Grunvald et al 2022*)**
  - *Of note, Zepbound was not FDA-approved at the time of guideline publication; thus, recommendations only include liraglutide and semaglutide.*
  - All recommendations have a conditional strength of recommendation with a moderate quality of evidence unless otherwise noted.
  - In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the addition of pharmacological agents to lifestyle interventions is recommended by the AGA over continuing lifestyle interventions alone (strong).
    - Implementation considerations: Anti-obesity medications (AOM) generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient (eg, comorbidities, patients' preferences, costs, and access to the therapy).
  - In adults with obesity/overweight with weight-related complications, the AGA suggests using liraglutide 3 mg or semaglutide 2.4 mg (and select oral agents indicated for weight management) in combination with lifestyle modifications, as opposed to the use of lifestyle modifications alone.
    - Due to its significant net benefit compared to other approved medications, semaglutide 2.4 mg may be prioritized for the long-term treatment of obesity for most patients.
    - Glucoregulatory benefits and approval for the treatment of T2DM are associated with the GLP-1 RAs.
    - Gastric emptying may be delayed by GLP-1 RAs, with AEs of nausea and vomiting. These AEs may be mitigated by gradual dose titration.
    - GLP-1 RAs have been associated with an increased risk of pancreatitis and gallbladder disease.

Other indications

- **The 2023 AASLD guideline on the clinical assessment and management of nonalcoholic fatty liver disease (NAFLD)** indicates that diet, exercise, and weight loss are key lifestyle interventions to promote CV and liver heath and improve metabolic comorbidities (*Rinella et al 2023*).
  - Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose dependent manner. All patients should be encouraged to increase activity level as much as possible; individualized prescriptive exercise may increase sustainability. Bariatric surgery can be considered in patients who meet criteria, as it effectively resolves NAFLD/NASH in most patients without cirrhosis and reduces mortality from CVD and malignancy.
  - At the time of guideline development (2023) there were no FDA approved medications for the treatment of NAFLD at the time of guideline development. However, drugs approved to treat associated comorbidities may be considered in the appropriate clinical setting. In November 2025, the AASLD published an update to their guidance for the use of semaglutide injection for MASH. The update indicates that candidates for semaglutide therapy include those patients with MASH and stage 2 to 3 fibrosis, identified using noninvasive tests. Lifestyle modifications remains the cornerstone

of MASH management alongside semaglutide. Additionally, combination use with resmetirom (Rezdiffra) has not been studied and is not currently recommended (*Bansal et al 2025*).

- The 2018 American Thoracic Society guideline for the role of weight management in the treatment of OSA makes a strong recommendation for patients who have overweight or obesity be treated with comprehensive lifestyle intervention consisting of a reduced-calorie diet, exercise or increased physical activity, and behavioral guidance. In patients with OSA with a BMI ≥ 27 kg/m^2 whose weight has not improved despite a comprehensive lifestyle program, an evaluation for antiobesity pharmacotherapy is suggested (*Hudgel et al 2018*).

Safety Summary

- Safety profiles for each of the agents as seen in their respective clinical trials are included below. In January 2026, the FDA released an updated drug safety communication requesting the manufacturers of GLP-1 RAs for weight loss (Saxenda, Wegovy, Zepbound) to remove language regarding the risk of suicidal ideation and behavior from labeling. This action follows an FDA review that found no increase in the risk of suicidal ideation and behavior with the use of these drugs (*FDA drug safety communication 2026*).
  - GLP-1 RAs are also currently being investigated for the need for regulatory action following reports of potential signals of a serious risk or new safety information for aspiration and alopecia. Of note, patients should not stop taking these medications without consulting a provider and should report severe side effects (*FDA Averse Event Reporting System [FAERS] 2024*).

Contraindications:

- Saxenda, Wegovy, Zepbound
  - Personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
  - Hypersensitivity to individual agents or their excipients
- Saxenda
  - Pregnancy

Boxed warnings:

- Saxenda, Wegovy, Zepbound: Risk of thyroid C-cell tumors
  - Personal or family history of MTC or in patients with MEN 2; patients should be counseled regarding the potential risk of MTC and the symptoms of thyroid tumors.
  - Risk of thyroid C-cell tumors; it is unknown whether Saxenda, Wegovy, or Zepbound causes thyroid C-cell tumors, including MTC, in humans.

Warnings and precautions:

- Saxenda
  - Thyroid C-cell tumors: See Boxed Warning section above
  - Acute pancreatitis: Saxenda should be promptly discontinued if pancreatitis is suspected, and not restarted if pancreatitis is confirmed.
  - Acute gallbladder disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated.
  - Hypoglycemia: When Saxenda is used concomitantly with insulin secretagogue (eg, a sulfonylurea) or insulin, hypoglycemia may occur. The risk may be lowered by a reduction in the dose of insulin secretagogues or insulin. In the pediatric clinical trial, patients did not have T2DM; hypoglycemia occurred in Saxenda-treated pediatric patients. Patients should be informed of the risk of hypoglycemia and educated on the signs and symptoms of hypoglycemia.
  - Heart rate increase: Heart rate should be monitored at regular intervals.
  - Renal impairment: Renal impairment has been reported in postmarketing documents, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Caution should be employed when initiating or escalating doses of Saxenda in patients with renal impairment.
  - Hypersensitivity reactions: There have been postmarketing reports of serious hypersensitivity reactions (eg, anaphylactic reactions and angioedema). Saxenda and other suspect medications should be discontinued, and prompt medical advice should be sought.
  - Suicidal behavior and ideation: Patients should be monitored for depression or suicidal thoughts, and Saxenda discontinued if symptoms develop.

- Pulmonary aspiration during general anesthesia or deep sedation.
- Severe GI adverse reactions; not recommended in patients with severe gastroparesis.

- Wegovy
  - Thyroid C-cell tumors: See Boxed Warning section above
  - Acute pancreatitis: Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with Wegovy in clinical trials. Wegovy should be promptly discontinued if pancreatitis is suspected and should not be restarted if pancreatitis is confirmed.
  - Acute gallbladder disease: Cholecystitis/cholelithiasis has occurred in clinical trials. Substantial or rapid weight loss can increase the risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated.
    - The incidence of cholelithiasis and cholecystitis was higher in Wegovy-treated pediatric patients ≥ 12 years of age than adults.
  - Hypoglycemia: Wegovy lowers blood glucose and can cause hypoglycemia. Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of insulin secretagogue or insulin may be necessary. Patients should be informed of the risk of hypoglycemia and educated on the signs and symptoms of hypoglycemia. When initiating Wegovy, reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin should be considered to reduce the risk of hypoglycemia.
  - Acute kidney injury due to volume depletion, especially in patients who experienced GI side effects leading to dehydration such as nausea, vomiting, or diarrhea.
  - Hypersensitivity: Serious hypersensitivity reactions (eg, anaphylaxis, angioedema) have been reported. If hypersensitivity reactions occur, patients should discontinue use, be treated promptly per standard of care, and should be monitored until signs and symptoms resolve. Anaphylaxis and angioedema have been reported with other GLP-1 RAs. Wegovy should be used with caution in patients with a history of anaphylaxis or angioedema with another GLP-1 RA because it is unknown whether such patients will be predisposed to these reactions with Wegovy.
  - Diabetic retinopathy complications in patients with T2DM: Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy and has been reported in trials with semaglutide. Patients with a history of diabetic retinopathy should be monitored.
  - Heart rate increase: Treatment has been associated with increases in resting heart rate. Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should be instructed to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during treatment. If patients experience a sustained increase in resting heart rate, Wegovy should be discontinued.
  - Suicidal behavior and ideation: Patients should be monitored for depression or suicidal thoughts, and Wegovy discontinued if symptoms develop.
  - Pulmonary aspiration during general anesthesia or deep sedation.
  - Severe GI adverse reaction, with a higher incidence in Wegovy-treated patients (4.1%) compared to placebo (0.9%).

- Zepbound
  - Severe GI disease: Use has been associated with GI AEs, sometimes severe. Tirzepatide has not been studied in patients with severe GI disease, including severe gastroparesis, and is not recommended in these patients.
  - Acute kidney injury: Renal function should be monitored in patients reporting adverse reactions that could lead to volume depletion (eg, dehydration due to nausea, vomiting, diarrhea).
  - Acute gallbladder disease: Acute gallbladder disease has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow-up are indicated.
  - Acute pancreatitis: Acute pancreatitis has been reported in clinical trials. Tirzepatide should be discontinued promptly if pancreatitis is suspected and should not be restarted if pancreatitis is confirmed.
  - Hypersensitivity reactions: Serious hypersensitivity reactions (eg, anaphylaxis, angioedema) have been reported postmarketing with tirzepatide. If a hypersensitivity reaction is suspected, patients should be advised to promptly seek medical attention and discontinue tirzepatide.
  - Hypoglycemia: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing the dose of the insulin secretagogue or insulin may be necessary. Patients should be informed of the risk of hypoglycemia and educated on the signs and symptoms of hypoglycemia.
  - Diabetic retinopathy complications in patients with T2DM: Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression.

- Suicidal behavior and ideation: Patients should be monitored for depression or suicidal thoughts. Tirzepatide should be discontinued if symptoms develop.

Adverse effects

- Saxenda
  - The most common AEs (≥ 5%) in adult patients were nausea (39.3%), diarrhea (20.9%), constipation (19.4%), vomiting (15.7%), injection site reactions (13.9%), headache (13.6%), hypoglycemia in T2DM (12.6%), dyspepsia (9.6%), fatigue (7.5%), dizziness (6.9%), abdominal pain (5.4%), increased lipase (5.3%), and upper abdominal pain (5.1%).
  - The most common AEs (≥ 5%) in pediatric patients were nausea (42.4%), vomiting (34.4%), diarrhea (22.4%), hypoglycemia (15.2%), gastroenteritis (12.8%), dizziness (10.4%), and pyrexia (8.0%).
- Wegovy injection
  - The most common AEs (≥ 5%) in adult patients were nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), abdominal pain (20%), headache (14%), fatigue (11%), dyspepsia (9%), dizziness (8%), abdominal distension (7%), eructation (7%), hypoglycemia in patients with T2DM (6%), flatulence (6%), gastroenteritis (6%), and gastroesophageal reflux disease (5%).
  - The most common AEs (≥ 5%) in pediatric patients were nausea (42%), vomiting (36%), diarrhea (22%), headache (17%), abdominal pain (15%), nasopharyngitis (12%), dizziness (8%), gastroenteritis (7%), and constipation (6%).
  - The following AEs have been reported during post approval use of semaglutide, the active ingredient of Wegovy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
    - GI disorders: Acute pancreatitis and necrotizing pancreatitis, sometimes resulting in death
    - Hypersensitivity: Anaphylaxis, angioedema, rash, and urticaria
    - Renal and urinary disorders: Acute kidney injury
- Wegovy tablet
  - The most common (incidence ≥ 15%) AEs with Wegovy tablet were nausea, vomiting, nasopharyngitis, corona virus disease 2019, constipation, dyspepsia, and diarrhea (all in similar percentages as Wegovy injection).
  -
- Zepbound
  - AEs that occurred more commonly with tirzepatide than with placebo and in ≥ 2% of patients treated with tirzepatide include nausea (25 to 28%), diarrhea (19 to 23%), vomiting (8 to 13%), constipation (11 to 17%), abdominal pain (9 to 10%), dyspepsia (9 to 10%), injection site reactions (6 to 8%), fatigue (5 to 7%), hypersensitivity reactions (5%), eructation (4 to 5%), hair loss (4 to 5%), gastroesophageal reflux disease (4 to 5%), flatulence (3 to 4%), abdominal distension (3 to 4%), dizziness (4 to 5%), and hypotension (1 to 2%).
  - The following AEs have been reported during post approval use of tirzepatide, the active ingredient of Zepbound. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
    - GI disorders: Ileus
    - Hypersensitivity: Anaphylaxis, angioedema

Key Drug Interactions

- Saxenda, Wegovy, Zepbound
  - Oral medications: GLP-1 RAs and GIP/GLP-1 RAs delay gastric emptying and thus have the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with these agents.
- Wegovy, Zepbound
  - Concomitant use with an insulin secretagogue (eg, sulfonylurea) or insulin: Wegovy and Zepbound lowers blood glucose and can cause hypoglycemia. The addition of Wegovy in patients treated with insulin has not been evaluated. When initiating Wegovy or Zepbound, a dose reduction of concomitantly administered insulin secretagogue or insulin should be considered to reduce the risk of hypoglycemia.
- Zepbound
  - Patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (eg, warfarin) should be monitored when concomitantly administered with tirzepatide.

- Patients using oral hormonal contraceptives should be advised to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation and for 4 weeks after each dose escalation of tirzepatide. Hormonal contraceptives that are not administered orally should not be affected.

Specific populations

- Saxenda, Wegovy, Zepbound
  - May cause fetal harm; discontinue treatment when pregnancy is recognized
- Wegovy
  - For patients with MASH, use during pregnancy only if the potential benefit justifies the potential risk to the fetus.
  - Lactation: Breastfeeding not recommended during treatment with Wegovy tablets.
  - Females and males of reproductive potential: For patients receiving treatment where the potential risk outweighs the potential benefit, discontinue treatment at least 2 months before a planned pregnancy because of the long half-life of semaglutide.
- Zepbound
  - May cause fetal harm; discontinue treatment when pregnancy is recognized
  - Females and males of reproductive potential: Advise females using oral contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation.

Dosing and Administration

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Frequency	Comments
Saxenda (liraglutide)	Injection	SC	Daily	• Prior to initiation, patients should be trained on proper injection techniques • Saxenda should be injected in the abdomen, thigh, or upper arm once daily at any time of day, without regard to the timing of meals • The initial dose should be 0.6 mg once weekly with weekly dose escalation, as tolerated, up to 3 mg • In pediatric patients who do not tolerate an increased dose during dose escalation, the dose may also be lowered to the previous dose; dose escalation for pediatric patients may take up to 8 weeks • For pediatric patients < 12 years old who do not tolerate 3 mg daily, the dose may be reduced to 2.4 mg daily • Saxenda should be discontinued in adult patients who do not tolerate the 3 mg dose, and in pediatric patients who do not tolerate the 2.4 mg dose • Adults: Evaluate after 16 weeks; if < 4% of initial weight is lost, treatment should be discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment • Pediatric patients: Evaluate after 12 weeks; if there is < 1% change in BMI from baseline, treatment should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment • If a dose is missed, the once-daily regimen should be resumed at the prescribed dose; if > 3 days have elapsed since the last dose, it should be reinitiated at 0.6 mg daily to reduce the risk of GI AEs

Drug	Available Formulations	Route	Frequency	Comments
				• Saxenda should be used with caution in patients with mild, moderate, and severe renal impairment, including end-stage renal disease • Saxenda should be used with caution in mild, moderate, or severe hepatic impairment
Wegovy (semaglutide)	Injection	SC	Once weekly	• Prior to initiation, patients should be trained on proper injection techniques • Wegovy should be administered once on the same day each week, at any time of day, with or without meals, into the abdomen, thigh, or upper arm • The dose should be initiated at 0.25 mg once weekly for 4 weeks, with titration every 4 weeks, as tolerated, to the recommended maintenance dose ○ The maintenance dose in adults is either 2.4 mg (recommended) or 1.7 mg weekly; treatment response and tolerability should be considered when selecting a maintenance dose ○ The maintenance dose in pediatric patients is 2.4 mg once weekly; patients unable to tolerate this dose may reduce the dose to 1.7 mg once weekly • In patients who cannot tolerate the 1.7 mg weekly dose, treatment should be discontinued as the 0.25 mg, 0.5 mg, and 1 mg doses are not approved for chronic weight management • If 1 dose is missed and the next scheduled dose is > 2 days away, administer as soon as possible; if the next scheduled dose is < 2 days away, resume dosing on the regularly scheduled day of the week; if ≥ 2 consecutive doses are missed, the dosing may resume as scheduled or Wegovy may be reinitiated following the dose escalation schedule, which may reduce GI symptomsPatients taking Wegovy 2.4 mg injection may switch to the 25 mg tablet (1 week after stopping injection) • In patients with diabetes, blood glucose should be monitored prior to starting and during treatment
Wegovy (semaglutide)	Tablet	PO	Daily	• The dose should be taken orally once daily on an empty stomach in the morning with ≤ 4 ounces of water. • Wegovy tablets should not be taken with other liquids besides water. • After taking a Wegovy tablet, patients should wait ≥ 30 minutes before eating food, drinking beverages, or taking other oral medications. • More than 1 tablet per day should not be taken. • Tablets should be swallowed whole, and should not be split, crushed, chewed, or dissolved in any solution. • If patients do not tolerate a dose during dosage escalation, a delay in escalation may be considered. • The dose should be initiated at 1.5 mg daily for 30 days, with titration every 30 days until maintenance dose of 25 mg once daily is reached; if patients cannot tolerate this dose,

Drug	Available Formulations	Route	Frequency	Comments
				switching to Wegovy injection 1.7 mg once weekly may be considered. • Patients may switch from one dosage form to another. Patients taking Wegovy 2.4 mg injection may switch to the 25 mg tablet (1 week after stopping injection); patients taking the 25 mg tablet may switch to the 2.4 mg injection (day after stopping tablet). • In patients with diabetes, blood glucose should be monitored prior to starting and during treatment
	Injection	SC	Once weekly	• Prior to initiation, patients should be trained on proper injection techniques • Zepbound should be administered once weekly at any time, with or without meals into the abdomen, thigh, or upper arm • The starting dosage should be injected subcutaneously once weekly beginning at 2.5 mg, with dose titration every 4 weeks, as tolerated to the maintenance dose. • The recommended maintenance dosages in adults include 5 mg, 10 mg, or 15 mg (maximum dose) once weekly; treatment response and tolerability should be considered in selecting a maintenance dose • If a dose is missed, administer as soon as possible within 4 days (96 hours) after the missed dose; if > 4 days have passed, the missed dose may be skipped and administered on the regularly scheduled day at the regular once weekly dosing schedule • The day of the weekly administration may be changed, if necessary, as long as the time between doses is ≥ 3 days (72 hours)

See the current prescribing information for full details.

Conclusion

- Patients who have obesity or overweight are at increased risk for comorbidities and all-cause mortality when compared to those without obesity or overweight.
- The goals of obesity treatment are to prevent, treat, or reverse the complications of obesity and improve overall health status, achieved through weight loss and maintenance of weight loss.
  - Guideline-recommended weight loss of 5% to 10% can reduce obesity-related medical conditions and CV disease risk factors in many patients; however, some patients may benefit from additional weight loss if health outcome goals were not achieved with their current treatment.
- The GLP-1 RAs (Saxenda and Wegovy [injection and tablet]) and the combination GIP/GLP-1RA (Zepbound), combined with lifestyle modification, may result in weight loss that approaches results historically only seen with bariatric surgery (≥ 20%). All 4 agents are FDA-approved for weight management in patients with obesity or overweight with ≥ 1 weight-related comorbidity. Wegovy (injection and tablet) is also indicated to reduce the risk of MACE in adults with established CVD and either overweight or obesity. Saxenda and Wegovy injection also have indications for pediatric populations. In clinical trials:
  - Patients on Saxenda lost 5% to 7% of baseline body weight at week 56
  - Patients on Wegovy injection lost 10% to 19% of baseline body weight at week 68; weight loss at 2 years was approximately 15%.
  - The estimated change in body weight with oral Wegovy was -13.6% vs -2.2% with placebo at week 64.
  - Patients on Zepbound lost 13% to 21% of baseline body weight at week 72; weight loss at 88 weeks was approximately 25%.

- Beyond weight loss indications, Zepbound is also FDA approval for OSA, while Wegovy holds an accelerated approval for MASH (continued approval for accelerated indications is contingent upon the verification and description of clinical benefit in a confirmatory trial).
- Overall, guidelines recommend comprehensive lifestyle intervention/modification, with pharmacologic therapy recommended as an adjunct to behavior modification; in patients with T2DM and obesity or overweight, GLP-1 RAs or the GIP/GLP-1 RA are recommended therapies due to concomitant effects on blood glucose management. Certain guidelines suggest prioritizing Wegovy and Zepbound over Saxenda due to the magnitude of net benefit;
  - For the management of OSA and MASH, weight loss/comprehensive lifestyle interventions continue to be the mainstay of treatment. The AASLD indicates that candidates for semaglutide therapy include patients with MASH and stage 2 to 3 fibrosis.
- Contraindications for all agents include personal or family history of MTC or in patients with MEN 2; boxed warnings include personal or family history of MTC or in patients with MEN 2 and the risk of thyroid C-cell tumors.
- Treatment approaches for obesity should be individualized based on patient risk factors, concomitant disease states, and prior attempts at weight loss. GLP-1 RAs and GIP/GLP-1RA agents have demonstrated efficacy when used in conjunction with lifestyle modification. The decision to initiate drug therapy should be made after consideration of risks and benefits and after consideration of all treatment options (eg, lifestyle, pharmacologic, device, surgical).

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