South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 18, 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

September 18, 2026
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/meet/27732316951577?p=2WdDY6Iv2DMHIH3uS5
Meeting ID: 277 323 169 515 77
Passcode: L54p94Kf

Join with a Video Conferencing Device
teams@optum.onpexip.com
Video ID: 112 659 050 72

Join by Phone
+1 952-222-7450
Phone Conference ID: 112 292 38#

Call to Order

Approval of Previous Meeting Minutes

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

Old business
- **Opioid Update**
- **Brand SSRI utilization**
- **Zyrtec chew vs cetirizine chew**

New business
- **Open Meetings Acknowledgement**
- **Ranitidine**
- **Tyenne**
- **GLP-1 review**
- **PA reviews**
- **Exdensur**
- **Nereus**

Public input accepted after individual topic discussion
Next meeting date December 11, 2026 (tentative) & adjournment

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

Friday, June 26, 2026
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Van Gilder called the meeting to order at 1:01 pm. The minutes of the March meeting were presented for review. Wilson moved to approve the minutes, and Oehlke seconded the motion. The motion carried unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report for the period of January 1, 2026, through March 31, 2026. During this period, a total of 6,564 PAs were reviewed. Of these, 159 requests (2.46%) were received by telephone, 106 requests (1.61%) were received by fax, 3,096 requests (47.2) were reviewed electronically, and 3,203 requests (47.8%) submitted 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 from January 1, 2026, to March 31, 2026. The top five therapeutic classes based on paid amount were immunomodulator agents, atypical antipsychotics, incretin mimetics, tumor necrosis factor inhibitors, and interleukin-mediated agents. These top 15 therapeutic classes comprise 16.77% of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid constitute 7.95% of total claims. Van Gilder asked if there were any public comments; none were offered.

Old Business

Opioid update

The committee reviewed opioid outcomes compared to the previous quarter. There was a slight increase in opioid utilization during 1Q2026. The average MME/day/utilizer remained steady.

H. Pylori Review

The committee reviewed utilization of medications used in the treatment of *H. pylori* infection. Van Gilder noted utilization was concentrated primarily among lower-cost treatment options and indicated no significant concerns warranting PA. Jockheck suggested ongoing monitoring of utilization trends and suggested revisiting the topic in few years. Van Gilder asked if there were any public comments; none were offered.

New Business

Prescription drug utilization report
Jockheck presented a prescription utilization report. In response to a question from McGill regarding whether rebates are primarily associated with brand-name drugs, Jockheck explained that rebates are received for both brand and generic drugs, including supplemental rebates. Van Gilder asked if there were any public comments; none were offered.

PA reviews
The committee reviewed PA requests and utilization for medications to treat rosacea and topical acne medications. Following discussion of rosacea therapies, Baack moved to remove the PA requirement for azelaic gel. Oehlke seconded the motion. The motion carried unanimously. Following discussion of the topical acne medications, Van Gilder recommended removing the PA for adapalene-benzoyl gel and implementing PA to select high-cost clindamycin products. Baack made the motion and McGill seconded the motion. The motion carried unanimously. Van Gilder called for public comments; none were offered.

The committee reviewed PA requests and utilization of oral allergen medications. Following discussion, Baack moved to discontinue the Oral Allergen PA criteria. Wilson seconded the motion. The motion carried unanimously.

The committee reviewed PA requests and utilization of Altabax and Xepi. After review, committee recommended no changes to the current PA criteria. Van Gilder called for public comments; none were offered.

The committee reviewed PA requests and utilization of angiotensin receptor blocker (ARB) medications. After review, committee recommended no changes to the current PA criteria. Van Gilder called for public comments; none were offered.

The committee reviewed PA requests and utilization of antidepressants. Following discussion, Van Gilder recommended removing fluoxetine solution and mirtazapine ODT. Baack made the motion and Oehlke seconded the motion. The motion carried unanimously. Wilson requested more information on patients utilizing branded antidepressants when generics are available.

The committee reviewed PA requests and utilization of Auvelity and Exxua. After review, committee recommended no changes to the current PA criteria. E. Van Gilder called for public comments; none were offered.

The committee reviewed PA requests and utilization of antiemetics. Baack requested to review Nereus at the next meeting. Van Gilder recommended removing PA from granisetron and doxylamine-pyridoxine. McGill made the motion. Oehlke seconded the motion. The motion carried unanimously.

The committee reviewed PA requests and utilization of non-sedating antihistamines. Following review, Baack moved to remove PA on desloratadine ODT, cetirizine ODT, and loratadine ODT. McGill seconded the motion. The motion carried unanimously. McGill noted that cetirizine chewable tablets appeared to be more expensive than Zyrtec chewable tablets and questioned package size differences could be the contribution to the cost discrepancy. An in-depth review was requested.

Nurtec ODT
The committee reviewed the proposed updates to the PA criteria for Nurtec ODT. Van Gilder commented that requiring trial and failure of injectable CGRP therapies is standard practice on commercial health plans. Van Gilder called for public comments; none were offered. Preuss moved to approve the recommended criteria as presented, and Wilson seconded the motion. The motion carried unanimously.

Tonmya
Clinical information for Tonmya was presented for review. Van Gilder called for public comments; none were offered. Following discussion, Baack motioned to adopt the PA criteria from State A with a requirement for 60-day trial and failure of cyclobenzaprine within the previous 120 days. Oehlke seconded the motion. The motion carried unanimously.

Icotyde
Clinical information for Icotyde was presented for review. During the discussion, Jockheck clarified the state is seeking to require step through preferred injectable products. The committee requested that the criteria be streamlined and brought back for further review at the next meeting. Van Gilder called for public comments; none were offered.

Adjournment
The next meeting is scheduled for September 18, 2026. The December meeting is tentatively scheduled for December 11, 2026. All motioned and were in favor of adjourning the meeting. The meeting adjourned at 2:06 pm CT.

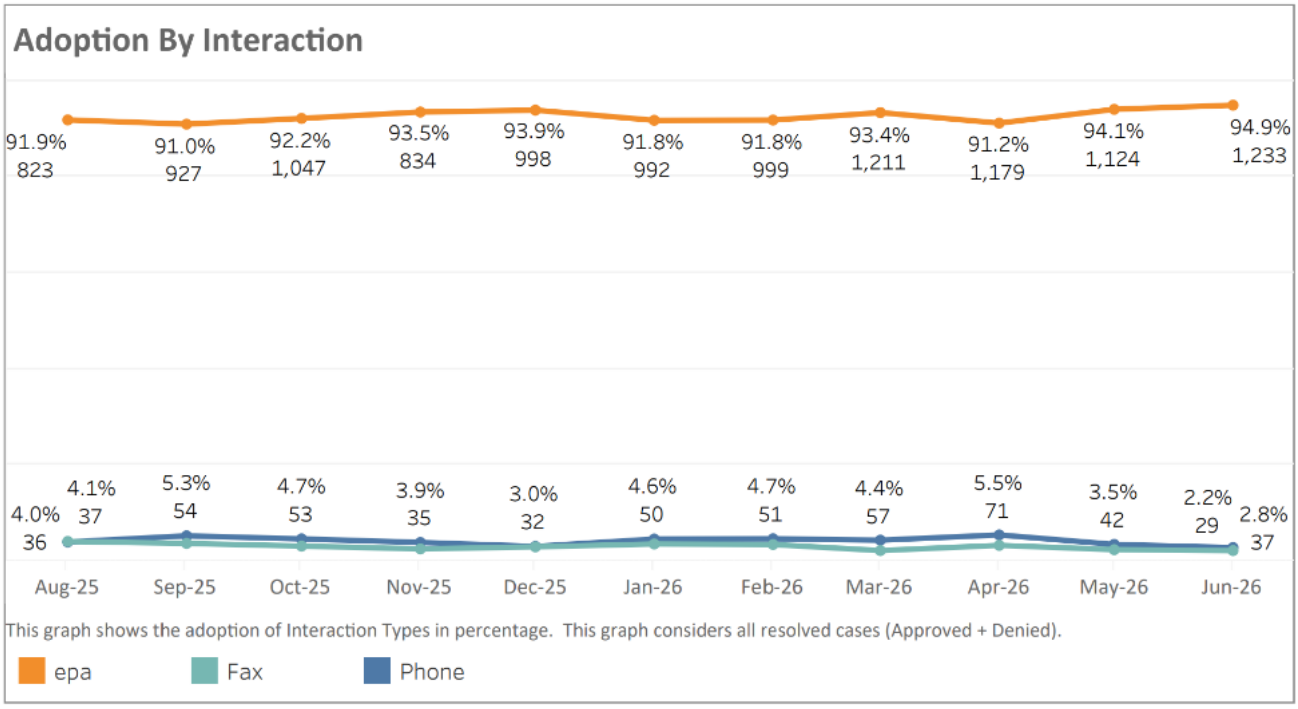
PA Report
4/1/2026 – 6/30/2026

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	5,958	5,958	0	100%	0.00%
Urgent	712	712	0	100%	0.00%
Grand Total	**6,670**	**6,670**	**0**		

Priority	Standard	Urgent
ePA	2,861	675
Fax	92	9
Phone	125	28
Real-Time	2,880	

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**6,670**	**153**	**2.3%**	**101**	**1.5%**	**2,880**	**43.2%**	**3,536**	**53%**



PA Initial Requests Summary

Month	Approved	Denied	Total
April-26	1,959	349	2,307
May-26	1,791	281	2,072
June-26	1,916	374	2,290
2Q26	**5,667**	**1,004**	6,670
Percent of Total	**84.95%**	**15.05%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIPSYCHOTICS/ANTIMANIC	1,893	41	1,934	97.88%	28.99%	, ARIPIPRAZOLE
ANTIDIABETICS	883	80	963	91.69%	14.44%	, OZEMPIC
ADHD/ANTI-NARCOLEPSY/ ANTI-OBESITY/ANOREX	456	279	735	62.04%	11.02%	, WEGOVY
MEDICAL DEVICES & SUPPLIES	422	164	586	72.01%	8.78%	, FREESTYLE
ANALGESICS - OPIOID	320	35	355	90.14%	5.32%	HYDROCODONE/ APAP
OTHERS -	1,693	405	2098	80.70%	31.45%	
2Q26	**5,667**	**1,004**	**6,671**	**84.95%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
April-26	25	62.50%	15	37.50%	40
May-26	19	82.61%	4	17.39%	23
June-26	19	51.35%	18	48.65%	37
2Q26	**63**	**63.00%**	**37**	**37.00%**	**100**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS	1,893	41	1,934	97.88%
27 – ANTIDIABETICS	883	80	963	91.69%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	456	279	735	62.04%
97 - MEDICAL DEVICES AND SUPPLIES	422	164	586	72.01%
65 - ANALGESICS – OPIOID	320	35	355	90.14%
67 - MIGRAINE PRODUCTS	266	57	323	82.35%
90 – DERMATOLOGICALS	275	43	318	86.48%
58 – ANTIDEPRESSANTS	210	36	246	85.37%
52 - GASTROINTESTINAL AGENTS - MISC.	212	30	242	87.60%
49 - ULCER/ANTISPASMODICS/ANTICHOLINERG	139	13	152	91.45%
66 - ANALGESICS - ANTI-INFLAMMATORY	110	29	139	79.14%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.	51	14	65	78.46%
12 - ANTIVIRALS	50	14	64	78.13%
41 - ANTIHISTAMINES	35	18	53	66.04%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGT	45	8	53	84.91%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGT	42	6	48	87.50%
54 - URINARY ANTISPASMODICS	40	7	47	85.11%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	20	13	33	60.61%
39 - ANTIHYPERLIPIDEMICS	22	7	29	75.86%
72 - ANTICONVULSANTS	24	4	28	85.71%
75 - MUSCULOSKELETAL THERAPY AGENTS	12	13	25	48.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	23	1	24	95.83%
50 - ANTIEMETICS	14	8	22	63.64%
28 - THYROID AGENTS	15	6	21	71.43%
83 - ANTICOAGULANTS	13	6	19	68.42%
94 - DIAGNOSTIC PRODUCTS	7	11	18	38.89%
33 - BETA BLOCKERS	6	11	17	35.29%
34 - CALCIUM CHANNEL BLOCKERS	8	7	15	53.33%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL	6	7	13	46.15%
40 - CARDIOVASCULAR AGENTS - MISC.	12	0	12	100.00%
36 - ANTIHYPERTENSIVES	4	6	10	40.00%
64 - ANALGESICS - NONNARCOTIC	1	9	10	10.00%
38 - VASOPRESSORS	1	7	8	12.50%
74 - NEUROMUSCULAR AGENTS	4	3	7	57.14%
82 - HEMATOPOIETIC AGENTS	3	2	5	60.00%
85 - HEMATOLOGICAL AGENTS - MISC.	4	1	5	80.00%
01 - PENICILLINS	4	0	4	100.00%
45 - RESPIRATORY AGENTS - MISC.	4	0	4	100.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES	4	0	4	100.00%
03 - MACROLIDES	1	2	3	33.33%
16 - ANTI-INFECTIVE AGENTS - MISC.	1	1	2	50.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS	2	0	2	100.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC	1	1	2	50.00%
24 - ESTROGENS	1	1	2	50.00%
86 - OPHTHALMIC AGENTS	0	2	2	0.00%
15 - ANTHELMINTICS	1	0	1	100.00%
32 - ANTIANGINAL AGENTS	0	1	1	0.00%
2Q26	**5,667**	**1,004**	**6,671**	
Percent of Total	**84.95%**	**15.05%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
ZEPBOUND	4	9	13	30.77%
WEGOVY	3	8	11	27.27%
LINZESS	4	3	7	57.14%
DEXCOM	5	3	8	62.5%
ARIPIPRAZOLE	3	0	3	100%
DUPIXENT	3	0	3	100%
HYDROCODONE/APAP	3	0	3	100%
AJOVY	2	0	2	100%
BIMZELX	0	2	2	0%
DEXMETHYLPHENIDATE ER	0	2	2	0%
FREESTYLE LIBRE	3	1	4	75%
QELBREE	1	1	2	50%
SYNTHROID	2	0	2	100%
TRAMADOL	1	1	2	50%
ALLERGY RELIEF	1	0	1	100%
CONTOUR NEXT BLOOD GLUCOSE TEST	0	1	1	0%
EBGLYSS	1	0	1	100%
ELTROMBOPAG	1	0	1	100%
EMGALITY	0	1	1	0%
EVERSENSE	0	1	1	0%
EXDENSUR	1	0	1	100%
FEXOFENADINE	1	0	1	100%
FIDAXOMICIN	1	0	1	100%
GENOTROPIN/MINIQUICK	2	0	2	100%
HUMIRA PEN	1	0	1	100%
ICATIBANT	1	0	1	100%
KINERET	1	0	1	100%
LANSOPRAZOLE ODT	1	0	1	100%
LINEZOLID	1	0	1	100%
LYBALVI	1	0	1	100%
MALATHION	1	0	1	100%
MAVYRET	1	0	1	100%
MEKINIST	1	0	1	100%
MIRTAZAPINE	1	0	1	100%
MODAFINIL	1	0	1	100%
MOUNJARO	1	0	1	100%
MYRBETRIQ	0	1	1	0%
NURTEC	1	0	1	100%
OLANZAPINE	1	0	1	100%
OMNITROPE	1	0	1	100%
REPATHA SURECLICK	0	1	1	0%
RINVOQ	1	0	1	100%
RISPERIDONE	1	0	1	100%
SKYRIZI	0	1	1	0%
SKYTROFA	1	0	1	100%
STEQEYMA	1	0	1	100%
TEZSPIRE	1	0	1	100%
TREMFYA	0	1	1	0%
XELJANZ	1	0	1	100%
2Q26	**63**	**37**	**100**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2026 – 6/30/2026					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITOR	19,763	258,510.13	$13.08	6.03%
2	ATYPICAL ANTIPSYCHOTICS	13,327	5,632,822.33	$422.66	4.07%
3	RESPIRATORY AND CNS STIMULANTS	10,636	1,190,116.26	$111.90	3.25%
4	PROTON-PUMP INHIBITORS	10,354	251,521.38	$24.29	3.16%
5	AMPHETAMINES	10,199	676,161.7	$66.30	3.11%
6	GABA-MEDIATED ANTICONVULSANTS	9,098	224,822.25	$24.71	2.78%
7	SELECTIVE BETA-2-ADRENERGICS	8,981	465,825.6	$51.87	2.74%
8	SECOND GENERATION ANTIHISTAMINES	8,741	94,598.23	$10.82	2.67%
9	OPIOID AGONISTS	8,574	261,065.91	$30.45	2.62%
10	SEROTONIN MODULATORS	8,439	237,346.07	$28.12	2.58%
11	ADRENALS	8,177	1,165,611.04	$142.55	2.50%
12	ANTICONVULSANTS, MISC	7,801	1,021,847.12	$130.99	2.38%
13	HMG-COA REDUCTASE INHIBITORS	7,483	86,718.78	$11.59	2.28%
14	BETA-ADRENERGIC BLOCKING	6,812	100,482.81	$14.75	2.08%
15	AMINOPENICILLIN ANTIBIOTICS	6,613	98,931.41	$14.96	2.02%
Total		**144,998**	**11,766,381.02**	**$81.15**	**44.26%**

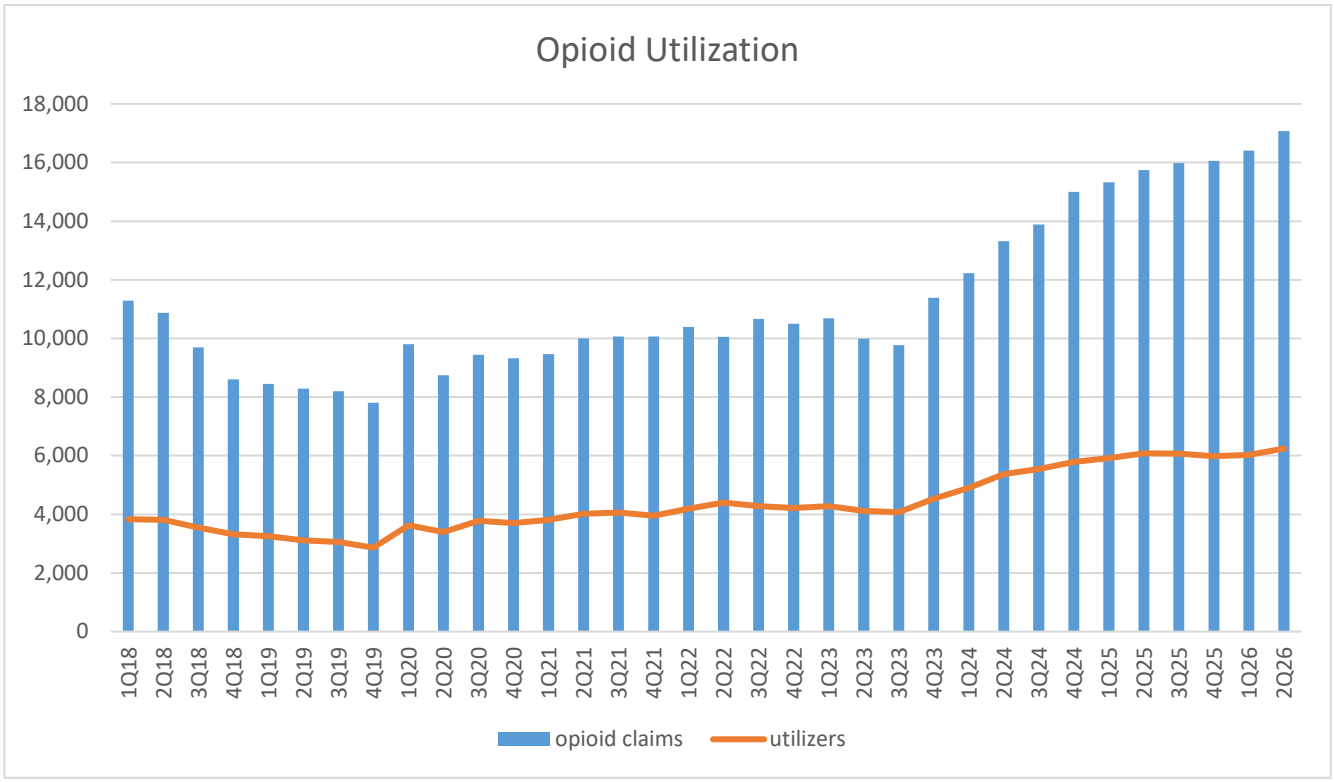
TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2026 – 6/30/2026					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	IMMUNOMODULATORY AGENTS	1,159	5,658,247.3	$4,882.01	0.35%
2	ATYPICAL ANTIPSYCHOTICS	13,327	5,632,822.33	$422.66	4.07%
3	INCRETIN MIMETICS	4,582	4,755,644.84	$1,037.90	1.40%
4	TUMOR NECROSIS FACTOR INHIBITOR	396	3,296,684.47	$8,324.96	0.12%
5	ANTINEOPLASTIC AGENTS	473	2,618,369.68	$5,535.67	0.14%
6	INTERLEUKIN-MEDIATED AGENTS	245	2,318,207.06	$9,462.07	0.07%
7	CYSTIC FIBROSIS (CFTR) CO	64	1,649,054.67	$25,766.48	0.02%
8	HEMOSTATICS	68	1,547,232.45	$22,753.42	0.02%
9	HIV INTEGRASE INHIBITOR A	347	1,347,576.75	$3,883.51	0.11%
10	CALCITONIN GENE-RELATED PEPTIDE	1,248	1,239,197.79	$992.95	0.38%
11	RESPIRATORY AND CNS STIMULANT	10,636	1,190,116.26	$111.90	3.25%
12	ADRENALS	8,177	1,165,611.04	$142.55	2.50%
13	ANTICONVULSANTS, MISC	7,801	1,021,847.12	$130.99	2.38%
14	OTHER MISCELLANEOUS THERAPY	167	876,162.88	$5,246.48	0.05%
15	DEVICES	4,602	838,344.34	$182.17	1.40%
Total		53,292	35,155,118.98	$659.67	16.27%

Total Rx Claims from 4/1/2026 – 6/30/2026	**327,587**

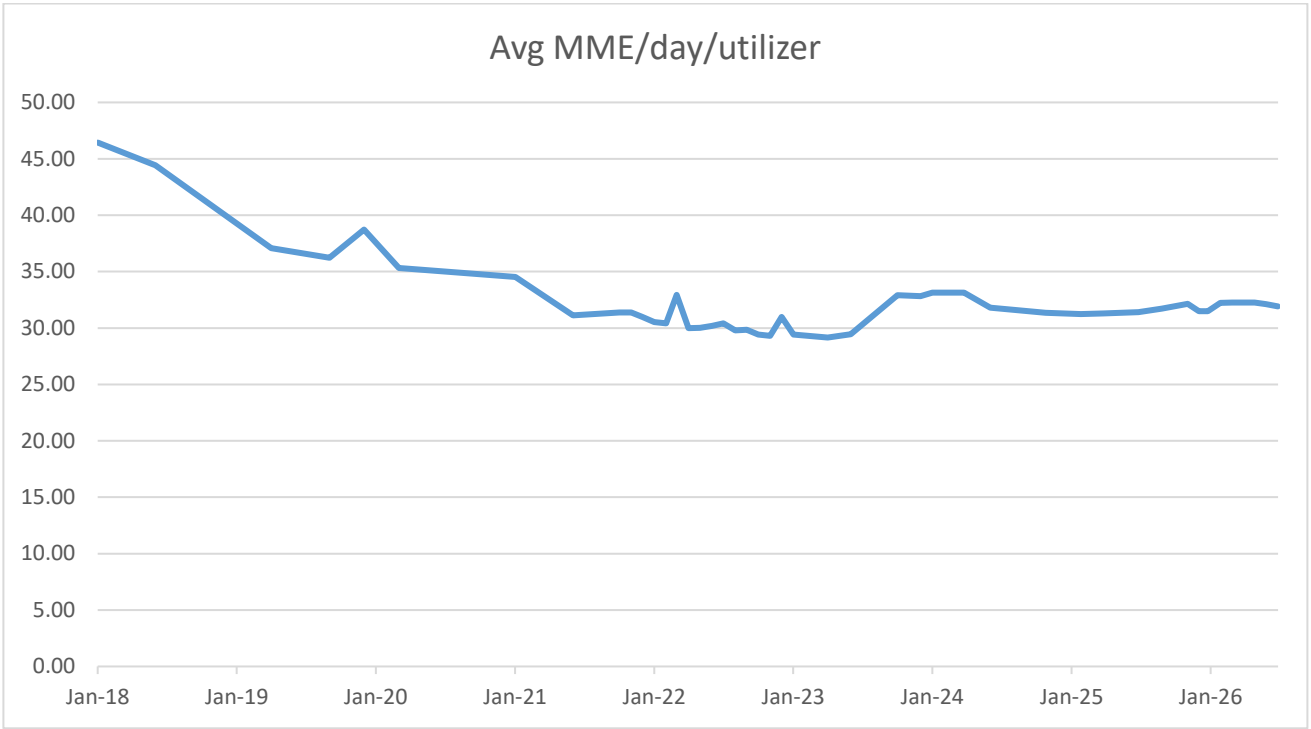
TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2026 – 6/30/2026						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Antidepressants	FLUOXETINE	6,737	83,747.06	$12.43	2.06%
2	Antidepressants	**SERTRALINE**	6,120	79,166.98	$12.94	1.87%
3	Anticonvulsants - 2nd Generation	GABAPENTIN	6,092	88,546.48	$14.53	1.86%
4	Antidepressants	TRAZODONE	5,814	68,235.89	$11.74	1.77%
5	Proton Pump Inhibitors	**OMEPRAZOLE**	5,780	67,750.14	$11.72	1.76%
6	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,734	269,709.5	$47.04	1.75%
7	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	5,510	159,696.47	$28.98	1.68%
8	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMPH	5,278	156,350.5	$29.62	1.61%
9	Antidepressants	ESCITALOPRAM	5,211	65,370.17	$12.54	1.59%
10	Thyroid Hormones	LEVOTHYROXINE	5,011	55,658.74	$11.11	1.53%
11	Antidepressants	BUPROPION	4,914	72,561.74	$14.77	1.50%
12	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,530	422,504.67	$93.27	1.38%
13	Statins & Combos	ATORVASTATIN	4,240	49,469.83	$11.67	1.29%
14↓	Penicillins	AMOXICILLIN	4,222	56,286.43	$13.33	1.29%
15	Antihistamines	CETIRIZINE	4,138	39,891.8	$9.64	1.26%
16	Biguanides & Combos	METFORMIN	4,085	48,923.85	$11.98	1.25%
17	ACE Inhibitors & Combos	LISINOPRIL	3,716	37,911.35	$10.20	1.13%
18	Antianxiety Agents	**HYDROXYZINE**	3,687	46,942.3	$12.73	1.13%
19	Antidepressants	DULOXETINE	3,560	56,244.89	$15.80	1.09%
20	ADHD & Narcolepsy Medications	GUANFACINE	3,354	51,667.5	$15.40	1.02%
21	Antiadrenergic Antihypertensives	CLONIDINE	3,218	32,443.7	$10.08	0.98%
22	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	3,095	35,106.38	$11.34	0.94%
23	Opioid Agonists & Combos	HYDROCODONE/AC	3,090	54,327.47	$17.58	0.94%
24	Antiemetics	ONDANSETRON ODT	2,899	39,380.81	$13.58	0.88%
25	Leukotriene Modulators	MONTELUKAST	2,878	35,866.5	$12.46	0.88%
26	Calcium Channel Blockers	AMLODIPINE	2,829	29,876.56	$10.56	0.86%
27	Antianxiety Agents	BUSPIRONE	2,726	36,452.3	$13.37	0.83%
28	GLP-1 Receptor Agonists	MOUNJARO	2,681	2,870,343.19	$1,070.62	0.82%
29	Atypical Antipsychotics	ARIPIPRAZOLE	2,606	35,974.74	$13.80	0.80%
30	Statins & Combos	ROSUVASTATIN	2,601	29,276.98	$11.26	0.79%
31	Proton Pump Inhibitors	PANTOPRAZOLE	2,593	33,224.88	$12.81	0.79%
32	Atypical Antipsychotics	QUETIAPINE	2,540	34,141.94	$13.44	0.78%
33	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,527	33,881.56	$13.41	0.77%
34	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,473	25,972.5	$10.50	0.75%
35	Beta Blockers & Combos	METOPROLOL ER	2,391	29,897.41	$12.50	0.73%
36	Penicillins	AMOXICILLIN/CLAVULANATE	2,390	41,794.61	$17.49	0.73%
37↓	Glucocorticosteroids	PREDNISONE	2,324	23,062.9	$9.92	0.71%
38	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,170	30,636.52	$14.12	0.66%
39	Opioid Agonists & Combos	**OXYCODONE**	2,147	32,128.6	$14.96	0.66%
40	Anticonvulsants - 2nd Generation	CLONAZEPAM	2,046	23,210.84	$11.34	0.62%
41	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	2,027	20,763.94	$10.24	0.62%
42	Antidepressants	MIRTAZAPINE	1,974	27,227.33	$13.79	0.60%
43	Cephalosporins	CEPHALEXIN	1,958	29,060.2	$14.84	0.60%
44	Diuretics & Combos	SPIRONOLACTONE	1,949	27,814.72	$14.27	0.59%
45	Antidepressants	**VENLAFAXINE**	1,914	28,226.52	$14.75	0.58%
46	Nasal Steroids	FLUTICASONE	1,897	32,446.81	$17.10	0.58%
47	Atypical Antipsychotics	RISPERIDONE	1,850	24,759.5	$13.38	0.56%
48	H-2 Antagonists	FAMOTIDINE	1,832	23,152.89	$12.64	0.56%
49	Beta Blockers & Combos	**PROPRANOLOL**	1,823	27,141.69	$14.89	0.56%
50	Vitamins & Supplements	FOLIC ACID	1,800	15,754.08	$8.75	0.55%
	Total Top 50 Drugs		**168,981**	**5,739,984.36**	**$33.97**	**51.58%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2026 – 6/30/2026						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	DUPIXENT	763	3,260,033.68	$4,272.65	0.23%
2	GLP-1 Receptor Agonists	MOUNJARO	2,681	2,870,343.19	$1,070.62	0.82%
3	Chronic Inflammatory Disease	**HUMIRA/PEN**	228	2,089,444.14	$9,164.23	0.07%
4	Atypical Antipsychotics	**INVEGA/SUSTENNA/HAFYERA**	470	1,585,916.78	$3,374.29	0.14%
5	Chronic Inflammatory Disease	SKYRIZI/PEN	68	1,559,285.12	$22,930.66	0.02%
6	GLP-1 Receptor Agonists	OZEMPIC	1,478	1,475,422.82	$998.26	0.45%
7	Cystic Fibrosis	TRIKAFTA	54	1,364,906.97	$25,276.06	0.02%
8	Atypical Antipsychotics	VRAYLAR	874	1,250,975.09	$1,431.32	0.27%
9	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY/UNOREADY**	81	1,016,996.81	$12,555.52	0.02%
10	HIV-Multiclass Combo	BIKTARVY	244	1,002,397.76	$4,108.19	0.07%
11	Chronic Inflammatory Disease	**ENBREL/SURECLICK/MINI**	107	859,467.51	$8,032.41	0.03%
12	Chronic Inflammatory Disease	TALTZ	70	630,140.05	$9,002.00	0.02%
13↑	Atypical Antipsychotics	CAPLYTA	354	571,096.59	$1,613.27	0.11%
14	Anticonvulsants - 2nd Generation	EPIDIOLEX	171	559,390.41	$3,271.29	0.05%
15	Metabolic Modifiers	VYKAT XR	18	548,973.9	$30,498.55	0.01%
16	Atypical Antipsychotics	**ABILIFY MAINTENA/ASIMTUFII**	162	542,294.41	$3,347.50	0.05%
17	Atypical Antipsychotics	**ARISTADA/INITIO**	176	521,176	$2,961.23	0.05%
18	SGLT-2 Inhibitors & Combos	JARDIANCE	1,546	514,729.87	$332.94	0.47%
19	Oncology	KISQALI	36	508,839.05	$14,134.42	0.01%
20	Diabetes Monitoring and Testing S	**DEXCOM**	1,771	505,601.11	$285.49	0.54%
21	Chronic Inflammatory Disease	RINVOQ	63	465,947.96	$7,396.00	0.02%
22	Movement Disorder Drug Therapy	INGREZZA	55	440,872.21	$8,015.86	0.02%
23	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,530	422,504.67	$93.27	1.38%
24	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	622	421,070.34	$676.96	0.19%
25↑	Antihemophilic Products	ALPROLIX	6	407,489.22	$67,914.87	0.00%
26↑	Muscular Dystrophy Agents	DUVYZAT	7	398,341.85	$56,905.98	0.00%
27	Atypical Antipsychotics	REXULTI	290	396,189.67	$1,366.17	0.09%
28	Chronic Inflammatory Disease	TREMFYA	26	383,610.34	$14,754.24	0.01%
29↑	Asthma	TEZSPIRE	74	363,720	$4,915.14	0.02%
30	Migraine Products	NURTEC	300	362,644.61	$1,208.82	0.09%
31	Oral Anticoagulants	**ELIQUIS/STARTER PACK**	1,102	359,264.33	$326.01	0.34%
32	Chronic Inflammatory Disease	BIMZELX	23	354,920.98	$15,431.35	0.01%
33↓	Chronic Inflammatory Disease	STELARA	11	327,859.34	$29,805.39	0.00%
34	Antihemophilic Products	HEMLIBRA	6	318,452.88	$53,075.48	0.00%
35↑	Pulmonary Arterial Hypertension	WINREVAIR	14	306,111.3	$21,865.09	0.00%
36↑	Metabolic Modifiers	SEPHIENCE	6	300,063.3	$50,010.55	0.00%
37↑	Asthma	XOLAIR	86	297,676.23	$3,461.35	0.03%
38	Oncology	JAKAFI	14	296,644.71	$21,188.91	0.00%
39↑	Cystic Fibrosis	ALYFTREK	10	284,147.7	$28,414.77	0.00%
40↑	Chronic Inflammatory Disease	EBGLYSS	40	281,852.38	$7,046.31	0.01%
41↓	Growth Hormones	NORDITROPIN FLEXPRO	68	275,363.34	$4,049.46	0.02%
42	Multiple Sclerosis	KESIMPTA	29	274,235.62	$9,456.40	0.01%
43	Hepatitis C	MAVYRET	21	270,030.46	$12,858.59	0.01%
44↓	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,734	269,709.5	$47.04	1.75%
45	ADHD & Narcolepsy Medications	JORNAY PM	590	265,587.68	$450.15	0.18%
46	Antihemophilic Products	NOVOSEVEN RT	3	265,531.65	$88,510.55	0.00%
47↓	Cystic Fibrosis	PULMOZYME	55	265,472.87	$4,826.78	0.02%
48	Atypical Antipsychotics	UZEDY	90	264,928.02	$2,943.64	0.03%
49↓	Migraine Products	UBRELVY	240	261,530.13	$1,089.71	0.07%
50	Psychotherapeutic-Neurological	LYBALVI	156	245,386.28	$1,572.99	0.05%
	Total Top 50 Drugs		**25,623**	**33,084,590.97**	**$1,291.21**	**7.82%**

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%
1Q2026	157,180	37,968	24.2%
2Q2026	158,529	35,929	22.7%

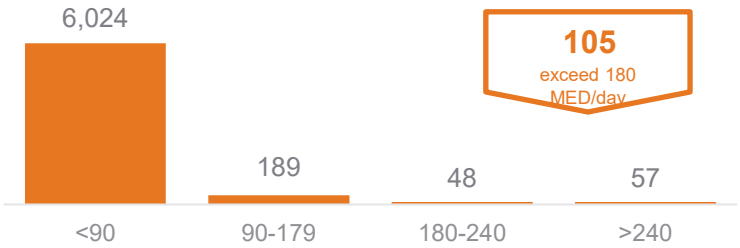
Opioid Utilization Snapshot

SDM 2Q2026
Mar 26 to Jun 26

Opioid Claims **17,078**
3.3% prescription claims filled for an opioid
1.6% higher than Medicaid FFS benchmark

Utilizers **6,245**
35.3% are high utilizers [1]
9.6% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]
Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



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

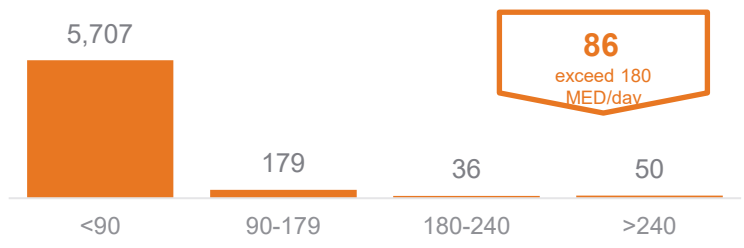
666 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

1Q2026
Dec 26 to Mar 26

Opioid Claims **16,404**
3.1% prescription claims filled for an opioid
1.5% higher than Medicaid FFS benchmark

Utilizers **6,024**
34.6% are high utilizers [1]
8.2% 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
74 opioid utilizing members with 3+ pharmacies

631 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 2Q2026
Opportunities date range: Mar - Jun 2026
Benchmark: MEDICAID FEE FOR SERVICE

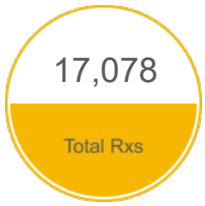
Utilizers: 6,245

3.3% 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.

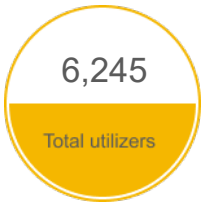
- Opioid prescriptions account for 3.3% of all prescriptions this period, which is 1.6% higher than the benchmark
- 2,202 high opioid utilizers were identified this period, which is 9.6% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
11.9%

Opioid utilizers

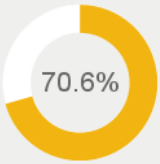


HIGH UTILIZERS
35.3%
2,202 high utilizers

9.6% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

70.6% of all opioid Rxs were filled for short acting opioids. **3,948** Rxs were for medication assisted therapy (MAT) and **203** 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

105 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	6,024	189	48	57

MED – view definition

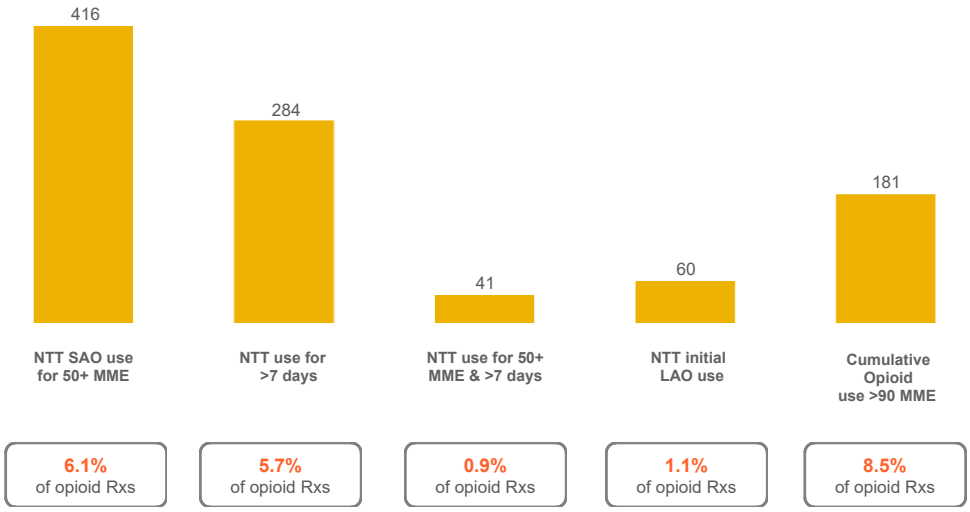
Opioid Opportunity Assessment

SDM 2Q2026
Opportunities date range: Mar - Jun 2026
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.9%

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?

77 opioid utilizing members use 3 or more pharmacies and 666 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
1,405	873	1,256	815	157

Anticonvulsants –view definition

Old Business

Brand SSRI review

Dispense As Written (DAW) PA
Brand name drugs with available generics will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. One of the following:
   1.1. Patient has had a trial and failure with the generic product **OR**
   1.2. Patient has had a trial with the generic product and experienced an adverse reaction (a MedWatch form must be completed) **OR**
   1.3. Patient has a contraindication to the generic product **OR**
   1.4. The generic product is unavailable
   1.5. NTI drugs are not excluded from DAW PA effective 7/1/2023

Member A (55 year old female) – on Lexapro 10mg since 2010

Drug Label Name	Date Filled	QTY	Days Supply	Paid/Rx
LEXAPRO TAB 10MG	Jan 31, 2010	30	30	$88.71
LEXAPRO TAB 10MG	Jan 30, 2011	30	30	$100.25
LEXAPRO TAB 10MG	Feb 27, 2013	30	30	$150.07
LEXAPRO TAB 10MG	Jan 20, 2014	30	30	$178.21
LEXAPRO TAB 10MG	Jan 29, 2015	30	30	$211.52
LEXAPRO TAB 10MG	Jan 23, 2016	30	30	$6.29
LEXAPRO TAB 10MG	Jan 16, 2017	30	30	$276.05
LEXAPRO TAB 10MG	Jan 16, 2018	30	30	$329.27
LEXAPRO TAB 10MG	Jan 11, 2019	30	30	$310.70
LEXAPRO TAB 10MG	Jan 3, 2020	30	30	$339.02
LEXAPRO TAB 10MG	Jan 18, 2021	30	30	$373.56
LEXAPRO TAB 10MG	Jan 15, 2022	30	30	$373.61
LEXAPRO TAB 10MG	Jan 24, 2023	30	30	$406.79
LEXAPRO TAB 10MG	Jan 23, 2024	30	30	$426.77
LEXAPRO TAB 10MG	Jan 10, 2025	30	30	$432.03
LEXAPRO TAB 10MG	Jan 21, 2026	30	30	$473.57
LEXAPRO TAB 10MG	Feb 27, 2026	30	30	$473.57
LEXAPRO TAB 10MG	Mar 24, 2026	30	30	$473.57
LEXAPRO TAB 10MG	Apr 23, 2026	30	30	$473.57
LEXAPRO TAB 10MG	May 18, 2026	30	30	$473.57
LEXAPRO TAB 10MG	Jun 16, 2026	30	30	$473.88
LEXAPRO TAB 10MG	Jul 11, 2026	30	30	$473.10
LEXAPRO TAB 10MG	Aug 10, 2026	30	30	$473.21

Member B (64 year old female) – Lexapro 20mg, tried generic 3 times

Drug Label Name	Date Filled	QTY	Days Supply	Paid/Rx
LEXAPRO TAB 20MG	Jul 16, 2021	30	30	$388.04
LEXAPRO TAB 20MG	Aug 23, 2021	30	30	$388.04
escitalopram tab 20MG	Sep 24, 2021	30	30	$12.21
escitalopram tab 20MG	Oct 20, 2021	30	30	$12.20
LEXAPRO TAB 10MG	Nov 17, 2021	30	30	$373.61
LEXAPRO TAB 20MG	Dec 17, 2021	30	30	$387.56
Ongoing LEXAPRO utilization 2021 to 2026				
LEXAPRO TAB 20MG	Jan 11, 2026	30	30	$470.91
LEXAPRO TAB 20MG	Mar 29, 2026	30	30	$493.93
LEXAPRO TAB 20MG	Apr 30, 2026	30	30	$493.93
LEXAPRO TAB 20MG	May 27, 2026	30	30	$493.70
LEXAPRO TAB 20MG	Jul 3, 2026	30	30	$494.41
LEXAPRO TAB 20MG	Aug 6, 2026	30	30	$494.19

Member C (56 year old female) – Zoloft 50mg

Drug Label Name	Date Filled	QTY	Days Supply	Paid/Rx
sertraline tab 50MG	Feb 5, 2020	22	30	$10.43
sertraline tab 50MG	Mar 2, 2020	30	30	$10.78
sertraline tab 50MG	Mar 28, 2020	22	30	$10.42
sertraline tab 50MG	Apr 24, 2020	16	21	$10.17
sertraline tab B 50MG	May 20, 2020	30	30	$10.80
fluoxetine tab 20MG	Oct 22, 2020	60	60	$41.16
sertraline tab 25MG	Aug 9, 2024	30	30	$11.51
ZOLOFT TAB 50MG	Feb 25, 2026	30	30	$458.32

Member D (62 year old female) – Remeron 15mg

Drug Label Name	Date Filled	Total QTY	Total Days Supply	Pharmacy Due Amount
mirtazapine tab 15MG	Oct 13, 2025	30	30	$12.69
mirtazapine tab 15MG	Nov 10, 2025	30	30	$12.70
REMERON TAB 15MG	Dec 8, 2025	30	30	$196.09
REMERON TAB 15MG	Jan 4, 2026	30	30	$196.03
REMERON TAB 15MG	Feb 8, 2026	30	30	$205.31
REMERON TAB 15MG	Mar 9, 2026	30	30	$205.31
REMERON TAB 15MG	Apr 13, 2026	30	30	$205.31
REMERON TAB 15MG	May 15, 2026	15	30	$107.93
REMERON TAB 15MG	Jun 18, 2026	15	30	$107.93
REMERON TAB 15MG	Jul 17, 2026	15	30	$105.99
REMERON TAB 15MG	Aug 14, 2026	15	30	$105.99

Zyrtec vs cetirizine chewable review

Time Frame: 1Q2026 vs 2Q2026

	1Q2026					2Q2026				
Drug Name	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Mbr**	**Age**	**Total Rx**	**Paid Amount**	**Paid/ Rx**	**Mbr**	**Age**
cetirizine 5mg CHEW NDC 00781-5283-64	3	$234.63	$78.21	3	9, 10, 57	4	$285.73	$71.43	4	4, 10
cetirizine 10mg CHEW NDC 00781-5284-64	4	$260.33	$65.08	2	4, 10	0				
Zyrtec 10mg CHEW NDC 50580-0791-01	3	$95.43	$31.81	1	6	3	$95.43	$31.81	1	6

*Red font denotes drug is on PA/St; Excludes IHS

NDC	Manufacturer Name	Drug Name and Strength	Strength	Brand Generic*	OTC Rx	AWP per tab
00045-0239-12	KENVUE	ZYRTEC CHILD CHW ALLERGY	2.5	B	OTC	$0.98
00045-0239-24	KENVUE	ZYRTEC CHILD CHW ALLERGY	2.5	B	OTC	$0.85
50580-0790-01	KENVUE	ZYRTEC CHILD CHW ALLERGY	2.5	B	OTC	$0.98
50580-0790-02	KENVUE	ZYRTEC CHILD CHW ALLERGY	2.5	B	OTC	$0.85
00045-0241-24	KENVUE	ZYRTEC CHILD CHW 10MG	10	G	OTC	$0.85
00045-0241-28	KENVUE	ZYRTEC CHILD CHW 10MG	10	G	OTC	$0.54
00045-0250-24	KENVUE	ZYRTEC CHW 10MG	10	G	OTC	$0.85
50580-0753-24	KENVUE	ZYRTEC CHW 10MG	10	G	OTC	$0.85
50580-0791-01	**KENVUE**	**ZYRTEC CHILD CHW 10MG**	**10**	G	OTC	**$0.85**
50580-0791-72	KENVUE	ZYRTEC CHILD CHW 10MG	10	G	OTC	$0.54
00781-5283-64	**SANDOZ**	**CETIRIZINE CHW 5MG**	**5**	G	OTC	**$5.36**
00781-5284-06	SANDOZ	CETIRIZINE CHW 10MG (blister)	10	G	OTC	$5.36
00781-5284-64	**SANDOZ**	**CETIRIZINE CHW 10MG**	**10**	G	OTC	**$5.36**
47335-0343-83	SUN PHARMA	CETIRIZINE CHW 5MG	5	G	OTC	$2.47
47335-0344-83	SUN PHARMA	CETIRIZINE CHW 10MG	10	G	OTC	$2.47
00363-0579-73	WALGREENS	WAL-ZYR CHW 5MG	5	G	OTC	$1.40
11917-0097-06	WALGREENS	WAL-ZYR CHW 5MG	5	G	OTC	$1.40
00363-0578-02	WALGREENS	WAL-ZYR CHW 10MG	10	G	OTC	$1.00
11917-0097-07	WALGREENS	WAL-ZYR CHW 10MG	10	G	OTC	$1.00
49035-0652-24	WALMART	CETIRIZINE CHW 10MG	10	G	OTC	$0.46
81131-0156-93	WALMART	CETIRIZINE CHW 10MG	10	G	OTC	$0.46

*B - Brand; G - generic

New Business

Open Meeting Acknowledgement

Ranitidine

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range
ranitidine tab	0		~$423.00			
nizatidine cap	0		~$48.00			
cimetidine sol	4	$278.60	$69.65	2	297 per 22 days	11, 16
cimetidine tab	17	$437.58	$25.74	10	51 per 30 days	5 – 64
famotidine susp	395	$7,468.36	$18.91	225	62 per 27 days	0 – 51
famotidine tab	1,437	$15,684.53	$10.91	703	43 per 29 days	5 – 78

*Excludes IHS

PA criteria for consideration

State A

Approval Criteria

1. One of the following:
    1.1. The patient has experienced therapeutic failure to 2 preferred medications (please specify) OR
    1.2. Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications.

PA criteria for consideration:

1. One of the following:
    1.1. The patient has 6-month trial and failure of BOTH cimetidine and famotidine OR
    1.2. Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with both cimetidine and famotidine

Tyenne

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Mbr	Age Range	Net Price
ACTEMRA INJ 162/0.9	0						$$
ACTEMRA INJ ACTPEN	21	$79,651.06	$3,792.91	3 per 26 days	7	40 – 62	$$
TYENNE INJ 162/0.9	1	$1,489.63	$1,489.63	1.8 per 28 days	1	48	$
TYENNE AUTOINJECTOR	0						$

*Red font denotes drug is on PA/St; Excludes IHS

Key Similarities

- **Medicine**: Same tocilizumab dose and formulation.
- **Route**: Both are subcutaneous (SC) injections. Single-dose prefilled syringe with a needle vs single-dose prefilled pen-like autoinjector with a shielded needle tip
- **Frequency**: Typically once weekly or every two weeks, based on weight and response.
- **Side effects**: Both carry the same risks, including serious allergic reactions and infections.

SQ Formulation

Therapy Indication	TYENNE tocilizumab-aazg	AVTOZMA tocilizumab-anoh	ACTEMRA tocilizumab	TOFIDENCE tocilizumab-bavi
Giant cell arteritis	18+	Not available	18+	Not available
Interstitial lung disease, systemic sclerosis associated	Not indicated	Not available	18+	Not available
Polyarticular Juvenile Idiopathic Arthritis	2+	Not available	2+	Not available
Rheumatoid arthritis	18+	Not available	18+	Not available
Systemic Juvenile Idiopathic Arthritis	2+	Not available	2+	Not available

Glucagon-like peptide-1 (GLP-1) receptor agonist review

Time Frame: 2Q2026

Drug Class	Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbrs	Avg Qty/DS	Age Range
liraglutide	liraglutide inj	37	$11,040.93	$298.40	16	7 per 28 days	13 – 63
dulaglutide	Trulicity INJ	168	$165,609.71	$985.77	73	2 per 28 days	19 – 65
semaglutide	Ozempic ING	1,624	$1,465,042.22	$902.12	624	3 per 25 days	8 – 66
	Ozempic TAB	10	$10,38060	$1,038.06	7	30 per 30 days	16 – 61
	Rybelsus TAB	103	$102,157.79	$991.82	49	30 per 30 days	16 – 64
	Wegovy INJ	39	$51,370.71	$1,317.20	15	2.6 per 28 days	15 – 61
tirzepatide	Mounjaro INJ	2,681	$2,870,343.19	$1,070.62	1,035	2 per 28 days	12 – 70
	Zepbound INJ	76	$79,699.69	$1,048.68	50	2 per 28 days	19 – 64

*Red font denotes drug is on PA/St; Excludes IHS

Drug Class	Drug Name	Tota l Rx	Paid Amount	Paid/Rx	Mbrs	Avg Qty/DS	Age Range
liraglutide	liraglutide inj 18mg/3ml	37	$11,040.93	$298.40	16	7 per 28 DS	13 – 63
dulaglutide	Trulicity INJ 0.75mg/0.5ml	25	$24,649.75	$985.99	15	2 per 28 DS	28 – 63
	Trulicity INJ 1.5mg/0.5ml	51	$50,273.17	$985.75	26	2 per 28 DS	19 – 64
	Trulicity INJ 3mg/0.5ml	46	$45,345.39	$985.77	21	2 per 28 DS	19 – 64
	Trulicity INJ 4.5mg/0.5ml	46	$45,341.40	$985.68	20	2 per 28 DS	46 – 65
semaglutide	Ozempic INJ 2mg/3ml	492	$496,517.39	$1,009.18	263	3 per 29 DS	8 – 64
	Ozempic INJ 4mg/3ml	418	$416,264.93	$995.85	202	3 per 28 DS	13 – 64
	Ozempic INJ 8mg/3ml	558	$552,259.90	$989.71	232	3 per 28 DS	15 – 66
	Ozempic TAB 1.5mg	5	$5,190.30	$1,038.06	5	30 per 30 DS	27 – 61
	Ozempic TAB 4mg	4	$4,152.24	$1,038.06	3	30 per 30 DS	33 – 61
	Ozempic TAB 9mg	1	$1,038.06	$1,038.06	1	30 per 30 DS	16
	Rybelsus TAB 3mg	22	$22,118.43	$1,005.38	19	30 per 30 DS	37 – 63
	Rybelsus TAB 7mg	50	$48,869.13	$977.38	23	30 per 30 DS	16 – 64
	Rybelsus TAB 14mg	31	$31,170.23	$1,005.49	15	30 per 30 DS	22 – 59
	Wegovy INJ 0.25mg	5	$6,585.88	$1,317.18	4	2 per 28 DS	30 – 57
	Wegovy INJ 0.5mg	3	$3,952.48	$1,317.49	3	2 per 28 DS	30 – 51
	Wegovy INJ 1.7mg	10	$13,172.12	$1,317.21	6	3 per 28 DS	15 – 61
	Wegovy INJ 1mg	10	$13,174.84	$1,317.48	5	2 per 28 DS	38 – 61
	Wegovy INJ 2.4mg	11	$14,485.39	$1,316.85	6	3 per 28 DS	15 – 60
tirzepatide	Mounjaro INJ 2.5mg/0.5ml	326	$353,129.90	$1,083.22	226	2 per 28 DS	13 – 64
	Mounjaro INJ 5mg/0.5ml	611	$651,498.68	$1,066.28	318	2 per 28 DS	13 – 64
	Mounjaro INJ 7.5mg/0.5ml	543	$582,758.47	$1,073.22	271	2 per 28 DS	14 – 66
	Mounjaro INJ 10mg/0.5ml	439	$469,149.61	$1,068.68	221	2 per 28 DS	17 – 70
	Mounjaro INJ 12.5mg/0.5ml	246	$267,682.45	$1,088.14	125	2 per 28 DS	12 – 64
	Mounjaro INJ 15mg/0.5ml	516	$546,124.08	$1,058.38	198	2 per 28 DS	16 – 65
	Zepbound INJ 2.5mg/0.5ml	48	$51,023.00	$1,062.98	40	2 per 28 DS	19 – 64
	Zepbound INJ 5mg/0.5ml	19	$20,194.46	$1,062.87	16	2 per 28 DS	19 – 56
	Zepbound INJ 7.5mg/0.5ml	3	$3,187.38	$1,062.46	3	2 per 28 DS	19 – 53
	Zepbound INJ 10mg/0.5ml	1	$1,062.59	$1,062.59	1	2 per 28 DS	35
	Zepbound INJ 12.5mg/0.5ml	3	$2,659.86	$886.62	2	2 per 28 DS	24, 35
	Zepbound INJ 15mg/0.5ml	1	$1,062.85	$1,062.85	1	2 per 28 DS	33
	Zepbound KWP INJ 2.5mg/0.6ml	1	$509.55	$509.55	1	2.4 per 28 DS	40

*Red font denotes drug is on PA/St; Excludes IHS

PA Reviews

Brisdelle/paroxetine mesylate 7.5mg capsule

- for the treatment of moderate to severe vasomotor symptoms (VMS) (hot flashes) associated with menopause

PA Review

Time Frame: 2Q2026

Drug Name	Approvals	Denials	Total	Utilizers
Brisdelle			0	
paroxetine mesylate 7.5mg			0	
paroxetine ER tab 25mg	3	0	3	3
paroxetine ER tab 37.5mg	1	0	1	1
paroxetine tab 30mg (QL 1 per day)	0	1	1	1

Utilization

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbr	Avg Qty	Age Range
Brisdelle 7.5mg	0					
paroxetine mesylate 7.5mg	4	$369.18	$92.30	2	30 per 30 days	41, 56 F
paroxetine ER tab 12.5mg	1	$17.45	$17.45	1	14 per 14 days	31
paroxetine ER tab 25mg	17	$431.99	$25.41	7	37 per 30 days	30 – 56
paroxetine ER tab 37.5mg	14	$377.40	$26.96	5	40 per 33 days	23 - 59
paroxetine susp 10mg/5ml	3	$1,153.81	$384.60	1	900ml per 30 days	36
paroxetine tab 10mg	100	$1,084.89	$10.85	54	33 per 33 days	11 – 77
paroxetine tab 20mg	199	$1,947.03	$9.78	101	32 per 32 days	13 – 77
paroxetine tab 30mg	85	$1,140.73	$13.42	43	32 per 30 days	13 – 77
paroxetine tab 40mg	161	$2,228.98	$13.84	66	33 per 32 days	13 – 64

*Red font denotes drug is on PA; Excludes IHS

Brisdelle/paroxetine mesylate 7.5mg cap PA Criteria

1. Patient has had a 60-day trial and failure of paroxetine oral tablets within the past 6 months

Antidepressant PA Criteria for paroxetine ER and suspension

1. Patient is already stabilized on therapy with the requested medication
2. Patient has had a trial with a first-tier agent in the past 12 months
3. Patient is less than 13 years of age **or** has a diagnosis which confirms a difficulty in swallowing

Cambia, Lofena, Zipsor PA Reviews

- diclofenac potassium – NSAIDs

Time Frame: 2Q2026

Drug Name	Approvals	Denials	Total	Utilizers
Cambia powder 50mg packet			0	
Lofena 25mg tablet			0	
Zipsor 25mg capsule			0	

Diclofenac Utilization

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbr	Avg Qty/Days	Age Range
Cambia powder 50mg packet (diclofenac potassium)	0		*~$3,000*		*50mg QD x 30 DS*	
Lofena 25mg TAB (diclofenac potassium)	0		*~$3,000*		*120 per 30 days*	
diclofenac potassium 25mg TAB	1	$456.52	$456.52	1	120 per 30 days	64
Zipsor 25mg CAP (diclofenac potassium)	0		*~$2,000*		*120 per 30 days*	
diclofenac potassium 50mg tab	20	$349.13	$17.46	13	68 per 30 days	19 – 62
diclofenac sodium 25mg DR tab	2	$66.78	$33.39	2	31 per 12 days	45, 54
diclofenac sodium 50mg DR tab	51	$705.64	$13.84	32	52 per 28 days	18 – 63
diclofenac sodium 75mg DR tab	215	$2,926.09	$13.61	127	56 per 28 days	13 – 64
diclofenac sodium 100mg ER tab	3	$158.75	$52.92	1	60 per 30 days	53
diclofenac epolamine DIS 1.3% (Flector or Licart Patch)	4	$1,620.44	$405.11	2	45 per 30 days	36, 61
diclofenac sodium GEL 1%	7	$268.85	$38.41	5	185 per 15 days	48 – 63
diclofenac sodium GEL 3%	31	$1,495.47	$48.24	24	103 per 25 days	33 – 68
diclofenac sodium SOL 2%	6	$336.81	$56.14	3	112 per 29 days	51 – 62

*Red font denotes drug is on PA; Excludes IHS

PA Criteria

1. The patient must have a documented 30-day trial of a diclofenac product within the last 120 days.

Chronic Constipation Agents

Time Frame: 2Q2026

Drug Name	Approvals	Denials	Total	Utilizers	Limits
AMITIZA (lubiprostone)			0		
lubiprostone	36	2	38	36	
IBSRELA (tenapanor)	1	0	0	1	
LINZESS (linaclotide)	41	21	62	56	
MOTEGRITY (prucalopride)	2	0	2	1	
MOVANTIK (naloxegol)	5	0	5	5	
SYMPROIC (naldemedine)	1	1	2	2	
TRULANCE (plecanatide)	0	2	2	1	

Time Frame: 2Q2026

Mechanism of Action	Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbrs	Avg Qty/DS	Age Range
5-HT3 serotonin receptor antagonist	alosetron	1	$133.81	$133.81	1		
chloride ion channel (CIC) activator	Amitiza (lubiprostone)	0					
	lubiprostone	142	$6,640.89	$46.77	71	55 per 29 DS	11 – 64
sodium-hydrogen exchanger (NHE) inh	Ibsrela (tenapanor)	24	$47,160.50	$1,965.02	12	60 per 30 DS	18 – 60
guanylate cyclase stimulants	Linzess (linaclotide)	693	$183,649.68	$265.01	319	30 per 30 DS	6 – 64
	Trulance (plecanatide)	10	$6,492.20	$649.22		30 per 30 DS	22 – 59
5-HT4 serotonin receptor agonist	Motegrity (prucalopride)	1	*IHS claim*	*$600.00*	1	30 per 30 DS	54
peripheral opioid receptor antagonist	Movantik (naloxegol)	8	$7,634.42	$954.30	6	30 per 30 DS	35 – 61
	Symproic (naldemedine)	4	$1,994.66	$498.67	2	30 per 30 DS	45, 65

*Red font denotes drug is on PA; Excludes IHS except Motegrity claim

Amitiza/lubiprostone PA criteria

1. Patient is 18 years of age or older
2. One of the following:
   - 2.1. Diagnosis of chronic idiopathic constipation
   - 2.2. One of the following:
     - 2.2.1. Both of the following:
       - Diagnosis of irritable bowel syndrome with constipation (IBS-C)
       - Patient is female
     - 2.2.2. Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain
     - 2.2.3. Diagnosis of opioid-induced constipation in patients with chronic pain related to prior cancer or its treatment who do not require frequently (e.g. weekly) opioid dosage escalation

Ibsrela PA Criteria

1. Patient is 18 years of age or older
2. Diagnosis of irritable bowel syndrome with constipation (IBS-C)

Linzess PA Criteria

1. Patient is 18 years of age or older
2. One of the following:
   2.1. Diagnosis of chronic idiopathic constipation
   2.2. Diagnosis of irritable bowel syndrome with constipation (IBS-C)
3. For Linzess 72mcg requests ONLY
   3.1. Patient is 2 –17 years of age
   3.2. Diagnosis of functional constipation

Movantik PA Criteria

1. Patient is 18 years of age or older
2. One of the following:
   2.1. Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain
   2.2. Diagnosis of opioid-induced constipation in patients with chronic pain related to prior cancer or its treatment who do not require frequently (e.g. weekly) opioid dosage escalation

Motegrity PA Criteria

1. Patient is 18 years of age or older
2. Diagnosis of chronic idiopathic constipation

Symproic PA Criteria

1. Patient is 18 years of age or older
2. One of the following:
   2.1. Diagnosis of opioid-induced constipation in an adult patient with chronic, non-cancer pain
   2.2. Diagnosis of opioid-induced constipation in patients with chronic pain related to prior cancer or its treatment who do not require frequently (e.g. weekly) opioid dosage escalation

Trulance PA Criteria

1. Patient is 18 years of age or older
2. One of the following:
   2.1. Diagnosis of chronic idiopathic constipation
   2.2. Diagnosis of irritable bowel syndrome with constipation (IBS-C)

Dificid (fidaxomicin) – oral macrolide antibiotic

- for the treatment of pseudomembranous colitis due to C. difficile infection

Time Frame: 2Q2026

Drug Name	Approvals	Denials	Total	Utilizers
Dificid			0	
fidaxomicin	1	2	3	3

Utilization

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Dificid	0				
fidaxomicin 200mg	2	$5,095.23	$2,547.62	2	29, 53

*Red font denotes drug is on PA/ST; Excludes IHS

PA criteria

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

Note: oral metronidazole and compounded oral vancomycin are covered without prior authorization

2017 IDSA/SHEA Clinical Practice Guidelines (Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America) (published in early 2018) – These guidelines replaced metronidazole as the preferred first-line treatment for an initial episode of non-severe C. difficile infection and instead recommended: vancomycin 125 mg PO QID x 10 days OR fidaxomicin 200 mg PO BID x 10 days

State A PA Criteria

1. Diagnosis of clostridium difficile infection (CDI)
2. Member is 6 months of age or older
3. One of the following:
   3.1. Member has an initial episode of CDI and one of the following:
      - Member is at increased risk of CDI recurrence (see Table 1)
      - Provider has submitted documentation supporting diagnosis of vancomycin-resistant pseudomembraneous colitis
   3.2. Member has a recurrent episode of CDI

State B PA Criteria

1. Diagnosis of Clostridioides difficile-associated diarrhea (CDAD) [previously known as Clostridium difficile- associated diarrhea]
2. BOTH of the following:
   2.1. One of the following:
      - History of failure, contraindication, or intolerance to generic vancomycin oral solution
      - For continuation of prior Dificid therapy
   2.2. Trial and failure, or intolerance to Brand Dificid tablets (applies to requests for generic fidaxomicin and Brand Dificid suspension only)

State C PA Criteria

Brand Dificid

1. Diagnosis of diarrhea due to C. Difficile (C. Diff)
2. Patient started therapy in the hospital and request is to complete the course

Generic fidamoxicin tablet

1. Patient started therapy in the hospital and request is to complete the course
2. Both of the following:
   2.1. Diagnosis of diarrhea due to C. Difficile (C. Diff)
   2.2. Clinically valid reason why Brand Dificid cannot be used

Dupixent, Fasenra, Nucala, Tezspire, Xolair

Time Frame: 2Q2026

Drug Name	Approvals	Denials	Total	Utilizers
Dupixent (dupliumab) INJ	132	8	140	130
Fasenra (benralizumab) INJ	5	0	5	5
Nucala (mepolizumab) INJ	9	0	9	6
Tezspire (tezepelumab-EKKO) INJ	13	3	16	16
Xolair (omalizumab) INJ	14	2	16	16

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty/DS	Age Range
Dupixent	763	$3,260,033.68	$4,272.65	345	3.9 per 32.7 DS	0 – 63
Fasenra	16	$92,627.42	$5,789.21	11	1 per 47 DS	20 – 52
Nucala	42	$184,826.43	$4,400.63	16	1.1 per 27 DS	9 – 64
Tezspire	74	$363,720.00	$4,915.14	27	1.9 per 28 DS	18 – 63
Xolair	86	$297,676.23	$3,461.35	30	2.2 per 28 DS	6 – 64

*Red font denotes drug is on PA/ST; Excludes IHS

Dupixent PA Indications

- Moderate to Severe Asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
- Moderate to Severe Atopic Dermatitis
- Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)
- Eosinophilic Esophagitis
- Prurigo Nodularis
- Chronic Obstructive Pulmonary Disease (COPD)
- Chronic Spontaneous Urticaria (CSU)
- Bullous Pemphigoid (BP)
- Allergic Fungal Rhinosinusitis (AFRS)

Fasenra PA Indications

- Severe Asthma with eosinophilic phenotype
- Eosinophilic Granulomatosis with Polyangiitis – **review criteria**
- Hypereosinophilic syndrome (HES) – **review criteria**

Nucala PA Indications

- Severe Asthma (eosinophilic phenotype)
- Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
- Chronic Obstructive Pulmonary Disease
- Eosinophilic Granulomatosis with Polyangiitis – **review criteria**
- Hyperesoinophilic syndrome – **review criteria**

Tezspire PA Indications

- Moderate to Severe Asthma
- Rhinosinusitis with Nasal Polyposis (CRSwNP)

Xolair PA Indications

- Moderate to Severe Asthma
- Chronic Idiopathic Urticaria
- Chronic Rhinosinusitis, with Nasal polyps with inadequate response to nasal corticosteroids
- IgE-Mediated Food Allergy

Current PA Criteria

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

1. Patient is 18 years of age or older
2. Diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
3. Prescribed by or in consultation with a rheumatologist, pulmonologist, allergist, or immunologist.

Hyperesoinophilic syndrome

1. Patient is 12 years of age or older
2. Diagnosis of hypereosinophilic syndrome
3. Prescribed by or in consultation with a rheumatologist, pulmonologist, allergist, immunologist, or hematologist.

Other PA Criteria

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

1. Diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)
2. Patient's disease has relapsed or is refractory to standard of care therapy (i.e., corticosteroid treatment with or without immunosuppressive therapy)
3. Patient is currently receiving corticosteroid therapy (e.g., prednisolone, prednisone) unless there is a contraindication or intolerance to corticosteroid therapy
4. Prescribed by or in consultation with one of the following: Pulmonologist, Rheumatologist, Allergist/Immunologist

Reauthorization

Patient demonstrates positive clinical response to therapy (e.g., increase in remission time)

Hypereosinophilic Syndrome (HES)

1. Diagnosis of hypereosinophilic syndrome (HES)
2. Patient is 12 years of age or older
3. Patient has been diagnosed for at least 6 months
4. Verification that other non-hematologic secondary causes have been ruled out (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy)
5. Patient is Fip1-like1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA)-negative
6. Patient has uncontrolled HES defined as both of the following:
   - History of 2 or more flares within the past 12 months
   - Pre-treatment blood eosinophil count greater than or equal to 1000 cells/microliter
7. Trial and failure, contraindication, or intolerance to one of the following:
   - Corticosteroid therapy (e.g., prednisone)
   - Cytotoxic/immunosuppressive therapy (e.g., hydroxyurea, cyclosporine, imatinib)
8. Prescribed by or in consultation with one of the following: Allergist/Immunologist, Hematologist

Reauthorization

1. Patient demonstrates positive clinical response to therapy (e.g., reduction in flares, decreased blood eosinophil count, reduction in corticosteroid dose)

Exdensur (depemokimab) – for the add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype

Time Frame: 2Q2026

Mechanism of Action	Drug Name	Total Rx	Paid Amount	Paid/Rx low/high	Avg Qty/DS	Mbr	Age Range
Interleukin 4 receptor (IL-4R) antagonist	Dupixent INJ (dupilumab)	730	$3,260.033.68	$4,055.76 $4,046.36 $8,083.93	2.28 per 35 DS 4 per 33 DS 8 per 29 DS	330	0 – 63
Interleukin 5 receptor (IL-5R) antagonist	Fasenra INJ (benralizumab)	15	$90,495.30	$6,033.02	1 per 47 DS	11	20 – 52
Interleukin 5 (IL-5) antagonist	**Exdensur INJ (depemokimab)**	**1**	**$26,010.55**	**$26,010.55**	**1 per 30 DS**	**1**	**19**
	Nucala INJ (mepolizumab)	42	$184,826.43	$1,606.96 $4,001.53 $11,983.49	0.4 per 28 DS 1 per 28 DS 3 per 28 DS	16	9 – 64
Thymic stromal lymphopoietin (TSLP) inhibitor	Tezspire INJ (tezepelumab)	74	$363,720.00	$4,919.48	1.91 per 28 DS	27	18 – 63
Anti-IgE antibody	Xolair INJ (omalizumab)	86	$297,676.23	$1,564.31 $3,118.08 $4,671.83 $6,225.61	1 per 28 DS 2 per 28 DS 3 per 28 DS 4 per 28 DS	30	6 – 64

*Red font denotes drug is on PA/ST; Excludes IHS; removed claims with primary insurance

PA Criteria for Consideration

- Trial of two preferred products: Dupixent, Fasenra, Nucala, Tezspire, Xolair

Nereus (tradipitant) – neurokinin-1 (NK1) receptor antagonist

- for the prevention of vomiting due to motion sickness

Time Frame: 2Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty/DS	Age Range
meclizine 12.5mg TAB	11	$130.01	$11.82	6	38 per 10 DS	23 – 59
meclizine 25mg TAB	144	$1,869.43	$12.98	94	41 per 16 DS	17 – 64
scopolamine DIS	112	$4,206.91	$37.56	55	6 per 18 DS	2 – 63
Nereus 85mg CAP (tradipitant)	0		*~$300.00*		*Qty 1*	

* Excludes IHS

State A PA Criteria

1. Used for the short-term prevention of vomiting induced by motion
2. Patient is 18 years of age or older
3. Dosing frequency will be limited to once daily dosing
4. Submission of medical records (e.g., chart notes) or verification of paid claims confirming trial and failure, contraindication, or intolerance to two conventional motion sickness therapies including but not limited to the following:
   - environmental modification
   - transdermal scopolamine
   - antihistamines (e.g., dimenhydrinate, meclizine)
5. Requested drug is not being prescribed for off-label use (e.g., drug induced nausea and vomiting, morning sickness, vertigo)

Optum Rx®

Therapeutic Class Overview

Respiratory and allergy biologics

Introduction

- The respiratory and allergy biologics (ie, antiasthmatic monoclonal antibodies) include the interleukin-5 (IL-5) antagonists Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Exdensur (depemokimab-ulaa); the immunoglobulin E (IgE) inhibitors Xolair (omalizumab) and Omlyclo (omalizumab-igec); the interleukin-4 (IL-4) inhibitor Dupixent (dupilumab); and the thymic stromal lymphopoietin (TSLP) blocker Tezspire (tezepelumab-ekko).
  - Respiratory and allergy biologics are a mainstay of treatment for severe asthma; in addition, various agents in this class are also indicated for use in chronic spontaneous urticaria (CSU), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyposis (CRSwNP), allergic fungal rhinosinusitis, hypereosinophilic syndromes (HES), eosinophilic esophagitis (EoE), IgE-mediated food allergy, and chronic obstructive pulmonary disease (COPD).
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In 2023, asthma affected an estimated 23 million adults and 4.8 million children in the United States (U.S.). The exact cause(s) of asthma are unknown. A combination of factors, such as genetics, certain respiratory infections during childhood, and contact with airborne allergens, can contribute to its development. Most patients with asthma also have allergies (*Centers for Disease Control and Prevention [CDC] Web site 2026, National Heart, Lung, and Blood Institute [NHLBI] Web site 2024*).
- Pharmacologic options for asthma management are categorized as: (1) controller medications to achieve and maintain control of persistent asthma or prevent exacerbations (also referred to as maintenance treatment, as appropriate), and (2) reliever medications for symptom relief and before exercise to prevent exercise-induced asthma symptoms (also referred to as rescue inhalers) (*Cloutier et al 2020, NHLBI 2007, Global Initiative for Asthma [GINA] 2026*).
  - Controller medications include:
    - Corticosteroids (inhaled corticosteroids [ICS], or oral corticosteroids (OCS) for severe exacerbations or severely uncontrolled asthma)
    - Long-acting beta$_2$-agonists (LABAs) in combination with ICS (ICS/LABA)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and depemokimab) in patients with severe asthma
    - Add-on tiotropium
    - Add-on azithromycin
  - Reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs)
      - The GINA report no longer recommends treatment of asthma in adults and adolescents with a SABA alone. All adults and adolescents with asthma should receive ICS-containing reliever treatment (referred to by GINA as an anti-inflammatory reliever [AIR] therapy) to reduce the risk of serious exacerbations and to control symptoms.
    - AIR therapy contains both a low-dose ICS and a rapid-acting bronchodilator, including ICS (ie, budesonide)/formoterol and ICS/albuterol combinations.
    - Short-acting muscarinic antagonists (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA (these agents have a slower onset of action vs SABA)
- Approximately 17% of patients have difficult-to-treat asthma and 3.7% have severe disease. Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce exacerbations. Severe asthma is a subset of difficult-to-treat asthma; it is defined as asthma that is uncontrolled despite adherence with maximally optimized high-dose ICS/LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased (*GINA 2025*).
  - GINA guidelines recommend considering several patient-specific factors when making treatment decisions for patients with asthma, including the patient's phenotypic characteristics (including biomarkers), comorbidities, patient views, and practical issues. For those with severe or difficult-to-treat asthma, GINA recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide levels, and allergic triggers to asthma (*GINA 2025*).

- CSU (also referred to as chronic idiopathic urticaria [CIU] in the literature) is defined by the presence of hives on most days of the week for 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CSU (*Khan 2026, Saini 2026*).
  - CSU affects up to 1% of the general population in the U.S., and the prevalence is believed to be similar in other countries. The condition is more common in adults than in children and typically begins in the third to fifth decades of life. CSU is a self-limited disorder in most patients, although the condition generally has a prolonged duration of 2 years to 5 years (*Saini 2026*).
  - Non-sedating H1-antihistamines are the cornerstone of therapy for CSU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H1-antihistamines include the use of H2-antihistamines, leukotriene modifiers, cyclosporine, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, dapsone, and omalizumab (*Bernstein et al 2014, Khan 2025, Maurer et al 2013, Zuberbier et al 2022*).
  - Biologic agents in this review FDA-approved for CSU include dupilumab, omalizumab, and omalizumab-igec.
- EGPA, previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Chung et al 2021, Connelly-Smith et al 2023, Groh et al 2015).*
  - EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
  - Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, mepolizumab, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered (*Emmi et al 2023, Chung et al 2021, Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
  - Biologic agents in this review that are FDA-approved for EGPA include benralizumab and mepolizumab.
- CRSwNP has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact the quality of life. Most cases are idiopathic but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and interleukin-13 (IL-13) (*Hopkins 2019*).
  - Common treatment options for CRSwNP include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms (*Hopkins 2019)*. Biologic agents in this review that are FDA-approved for CRSwNP include dupilumab, mepolizumab, omalizumab, omalizumab-igec, and tezepelumab-ekko.
  - Allergic fungal rhinosinusitis is a subtype of CRSwNP that arises as a result of a localized allergic reaction to noninvasive fungal growth in areas of compromised mucus drainage. Patients with this condition are typically immunocompetent but have evidence of allergy to one or more fungi. Treatment involves a combination of medical management, typically with systemic or topical corticosteroids, and surgery (*Schlosser 2025*). Dupilumab is also FDA-approved for the treatment of allergic fungal rhinosinusitis in those with a history of sino-nasal surgery.
- HES are disorders characterized by the overproduction of eosinophils, which causes organ damage (*Roufosse et al 2025*). Treatment for idiopathic HES may include systemic glucocorticoids, imatinib, hydroxyurea, interferon alfa, alemtuzumab, Janus kinase inhibitors (eg, tofacitinib and ruxolitinib), and IL-5 antagonists (eg, benzralizumab, mepolizumab).
- EoE is a chronic allergic inflammatory disease in which eosinophils build up in the lining of the esophagus (*Hirano et al 2020a*). The presence of eosinophils causes inflammation in the esophagus, which may cause the following symptoms: vomiting, stomach or chest pain, failure to thrive (particularly in children), and difficulty swallowing. Front-line treatments for EoE include proton pump inhibitors and topical glucocorticoids (*Dellon et al 2025*). Dupilumab is also FDA-approved for EoE.
- IgE-mediated food allergy is a leading cause of anaphylaxis (*Fleischer et al 2021, Sampson et al 2014*). Common food allergens include cow's milk, egg, peanut, tree nuts, fish/shellfish, wheat, sesame seed, and soy. Food-related reactions are associated with a broad range of signs and symptoms that can involve the skin, gastrointestinal tract, respiratory tract, and the cardiovascular system. Omalizumab and omalizumab-igec are FDA-approved for IgE-mediated food allergy in adults and children ≥ 1 year of age for the reduction of allergic reactions with accidental exposure (*Omlyclo*

Prescribing Information 2025, Xolair Prescribing Information 2025). Guidance on the use of omalizumab for food allergies is available from national and European guidelines (*Anagnostou et al 2025, Santos et al 2025).*

- COPD is a heterogeneous condition characterized by chronic respiratory symptoms resulting from persistent (often progressive) airflow limitation due to airway and/or alveolar abnormalities. These abnormalities are usually caused by genetic risk factors and/or environmental exposures (such as tobacco smoking and inhalation of toxic particles or gases) that occur over the lifetime of a person with COPD. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2026*). In 2023, the age-adjusted prevalence of COPD among adults in the U.S. was 3.8%. At that time, COPD was one of the top 5 causes of death, with 141,733 deaths occurring due to COPD in 2023 (*CDC Web site 2025*).
  - Treatment goals in COPD aim to reduce symptoms and the risk of future exacerbations. Choice of therapy depends on a patient's severity of dyspnea and risk of exacerbations and often includes the use of inhaled bronchodilators (ie, long-acting muscarinic antagonists [LAMAs] or LABAs) and ICSs (*GOLD 2026*). Biologic agents in this review FDA-approved for patients with COPD include dupilumab and mepolizumab.
  - Type 2 inflammation is associated with an increased risk of exacerbations.
    - An estimated 885,000 (0.6% of the U.S. adult population) patients ≥ 40 years of age with COPD in the U.S. are treated with triple therapy; 36% (319,000) of these patients are in a subpopulation who have Type 2 inflammation with blood eosinophils ≥ 300/µL and moderate-to-severe uncontrolled COPD (*Dupixent formulary dossier 2024*).
    - GOLD guidelines provide recommendations for the use of dupilumab and mepolizumab in patients with inadequately controlled COPD with an eosinophilic phenotype (*GOLD 2026*).
- Descriptions of the respiratory and allergy biologics are as follows:
  - Reslizumab, benralizumab, mepolizumab, and depemokimab-ulaa are humanized monoclonal antibody IL-5 antagonists. The mechanism of action of benralizumab is slightly different in that it binds to the IL-5 receptor on immune effector cells, whereas reslizumab, mepolizumab, and depemokimab-ulaa bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through the release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
  - Omalizumab is a recombinant DNA-derived monoclonal antibody that selectively binds to human anti-IgE. Omalizumab, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, omalizumab is approved for CSU in patients ≥ 12 years of age who remain symptomatic despite antihistamine treatment, as add-on maintenance treatment of CRSwNP in adult patients with inadequate response to nasal corticosteroids, and for IgE mediated food allergy in patients ≥ 1 year of age for the reduction of allergic reactions with accidental exposure. Omalizumab-igec is an FDA-approved biosimilar and is designated as interchangeable with omalizumab.
  - Dupilumab is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for eosinophilic asthma, EoE, CSU inadequately controlled with H1-antihistamine treatment, add-on therapy for inadequately controlled COPD (with eosinophilic phenotype), add-on therapy for inadequately controlled CRSwNP, allergic fungal rhinosinusitis. Dupilumab is also approved to treat moderate-to-severe atopic dermatitis, bullous pemphigoid and prurigo nodularis; these indications for dermatologic conditions are not discussed in this review.
  - Tezepelumab-ekko, a human monoclonal antibody, is a TSLP blocker. Tezepelumab-ekko binds to human TSLP, an epithelial cell-derived cytokine, and blocks its interaction with the TSLP receptor to reduce biomarkers and cytokines associated with inflammation (eg, blood and airway submucosal eosinophils, IgE, fractional exhaled nitric oxide [FeNO], IL-5, and IL-13); however, the mechanism of tezepelumab-ekko action in asthma has not been definitively established.
    - TSLP has also been shown to affect non-Type 2 inflammatory processes between airway structural and immune cells, and there are many cell types activated by, or that respond to, TSLP (including mast cells, basophils, natural killer T cells, innate lymphoid cells, and neutrophils) that may play a role in inflammation in asthma beyond Type 2 inflammation (*Corren et al 2017a, Menzies-Gow et al 2021*).
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)[a]
Innovator agents	
Cinqair (reslizumab)	-
Dupixent (dupilumab)	-
Exdensur (depemokimab-ulaa)	-
Fasenra (benralizumab)	-
Nucala (mepolizumab)	-
Xolair (omalizumab)	✔ [b]
Tezspire (tezepelumab-ekko)	-
Biosimilar agent	
Omlyclo (omalizumab-igec)	✔ [b]

[a] For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
[b] Omlyclo (omalizumab-igec) is an FDA-approved biosimilar agent to Xolair (omalizumab). Omlyclo (omalizumab-igec) has also been designated as interchangeable to its reference product, Xolair (omalizumab).

(*Drugs@FDA 2026, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2026*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Cinqair[b] (reslizumab)	Dupixent (dupilumab)	Fasenra[b] (benralizumab)	Exdensur (depemokimab-ulaa)	Nucala (mepolizumab)	Xolair[c] (omalizumab) and Omlyclo (omalizumab-igec)	Tezspire (tezepelumab-ekko)
Moderate-to-severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS						✔ (≥ 6 years of age)	
Add-on maintenance treatment for patients with severe asthma with an			✔ (≥ 6 years of age)				

Indication	Cinqair[b] (reslizumab)	Dupixent (dupilumab)	Fasenra[b] (benralizumab)	Exdensur (depemokimab-ulaa)	Nucala (mepolizumab)	Xolair[c] (omalizumab) and Omlyclo (omalizumab-igec)	Tezspire (tezepelumab-ekko)
eosinophilic phenotype							
Add-on maintenance treatment for patients with severe asthma							✔ (≥ 12 years of age)
Add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype					✔ (≥ 6 years of age)		
Add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype				✔ (≥ 12 years of age)			
Add-on maintenance treatment for patients with moderate-to-severe asthma with an eosinophilic phenotype or with OCS dependent asthma		✔ (≥ 6 years of age)					
Add-on maintenance treatment for patients with severe asthma with an	✔ (≥ 18 years of age)						

Indication	Cinqair[b] (reslizumab)	Dupixent (dupilumab)	Fasenra[b] (benralizumab)	Exdensur (depemokimab-ulaa)	Nucala (mepolizumab)	Xolair[c] (omalizumab) and Omlyclo (omalizumab-igec)	Tezspire (tezepelumab-ekko)
eosinophilic phenotype							
Treatment of patients with EGPA			✔ (adults)		✔ (adults)		
Treatment patients with CSU who remain symptomatic despite H1-antihistamine treatment.		✔ (≥ 2 years of age)				✔ (≥ 6 years of age)	
Add-on maintenance treatment in patients with inadequately controlled CRSwNP					✔ (adults)	✔ (adults)	
Add-on maintenance treatment in patients with inadequately controlled CRSwNP		✔ (≥ 12 years of age)					✔ (≥ 12 years of age)
Allergic fungal rhinosinusitis in patients who have a history of sino-nasal surgery		✔ (≥ 6 years of age)					
Treatment of adult and pediatric patients with HES[d] without an identifiable non-hematologic secondary cause			✔ (≥ 12 years of age)		✔ [d] (≥ 12 years of age)		

Indication	Cinqair[b] (reslizumab)	Dupixent (dupilumab)	Fasenra[b] (benralizumab)	Exdensur (depemokimab-ulaa)	Nucala (mepolizumab)	Xolair[c] (omalizumab) and Omlyclo (omalizumab-igec)	Tezspire (tezepelumab-ekko)
Treatment of patients with EoE		✔ (≥ 1 year of age and weighing ≥ 15 kg)					
IgE-mediated food allergy for the reduction of allergic reactions with accidental exposure						✔ (≥ 1 year of age)	
Add-on maintenance treatment of patients with inadequately controlled COPD with an eosinophilic phenotype		✔ (adults)			✔ (adults)		

[a] None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
[b] Not indicated for the treatment of other eosinophilic conditions.
[c] Not indicated for other allergic conditions or other forms of urticaria. Not indicated for the emergency treatment of allergic reactions, including anaphylaxis.
[d] For mepolizumab, HES present for ≥ 6 months

(*Prescribing information: Cinqair 2025, Dupixent 2026, Fasenra 2026, Nucala 2025, Omlyclo 2025, Xolair 2025, Tezspire 2025*)

- 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

Cinqair (reslizumab)

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter randomized controlled trials (RCTs). In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al 2016*).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/µL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg intravenously (IV) administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: relative risk [RR], 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001)

compared with those receiving placebo. In both trials, an improvement in forced expiratory volume in 1 second (FEV_1) was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in Asthma Quality of Life Questionnaire (AQLQ) total score, Asthma Control Questionnaire (ACQ)-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/μL). Patients were not allowed to be on maintenance OCS. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/μL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/μL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
  - An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer, and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
  - A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with OCS-dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2020)*.
- A 2017 meta-analysis of 5 RCTs comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab-treated patients vs placebo (odds ratio [OR], 0.46; 95% CI, 0.35 to 0.59; p < 0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; p < 0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; p < 0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 RCTs (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83; 95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) (*Virchow et al 2020*).

Dupixent (dupilumab)

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or LTRA). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300 cells/μL was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo (p < 0.0001). Patients with higher blood eosinophil levels had a greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of

dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both $p < 0.01$) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both $p < 0.001$) *(Corren et al 2020)*.

- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).
- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; $p < 0.01$). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; $p < 0.01$). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; $p < 0.01$) (*Zayed et al 2018*).
- A randomized, double-blind, placebo-controlled trial (Liberty Asthma VOYAGE) evaluated the safety and efficacy of dupilumab in pediatric patients 6 to 11 years of age with moderate-to-severe asthma on a medium- or high-dose ICS and a second controller medication or high-dose ICS alone. In the 52-week trial, patients were randomized to receive dupilumab (n = 273) or placebo (n = 135) every other week. Dosing was dependent on body weight: patients ≤ 30 kg received 100 mg every 2 weeks and those > 30 kg received 200 mg every 2 weeks. The annualized rate of severe asthma exacerbation events (the primary endpoint) during the study period was 0.31 for dupilumab and 0.75 for placebo (RR reduction, 59.5%; $p < 0.001$). Among patients with a baseline eosinophil count of ≥ 300 cells/μL, the annualized rate of asthma exacerbations was 0.24 with dupilumab and 0.67 with placebo (RR reduction, 64.7%; $p < 0.001$). Mean change from baseline in percent predicted FEV_1 was also significantly improved in the dupilumab group compared to placebo (least squares [LS] mean difference vs placebo, 5.32; 95% CI, 1.76 to 8.88). The efficacy of dupilumab 300 mg every 4 weeks in patients 6 to 11 years of age with body weight 15 to < 30 kg was extrapolated from efficacy of a clinical trial of 100 mg every 2 weeks with support from population pharmacokinetic analyses. The risks of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo with the addition of helminth infections (*Bacharier et al 2021*).
  - The EXCURSION study was a 52-week, multinational, multicenter, open-label extension of the Phase 3 VOYAGE trial. A total of 365 out of 408 eligible children who completed the VOYAGE trial were enrolled. Patients received weight-based subcutaneous (SC) dupilumab either as continued therapy (dupilumab/dupilumab group; n = 240) or as newly initiated therapy following prior placebo in VOYAGE (placebo/dupilumab group; n = 125). Standard dosing was 100 mg every 2 weeks for children ≤ 30 kg and 200 mg every 2 weeks for those > 30 kg. The primary outcome was the incidence of treatment-emergent adverse events over the 52-week period, analyzed descriptively. Results demonstrated that 63.6% of children experienced ≥ 1 adverse event: 61.3% in the dupilumab/dupilumab group and 68.0% in the placebo/dupilumab group. The most common treatment-emergent adverse events were nasopharyngitis, pharyngitis, and upper respiratory tract infections (*Bacharier et al 2024*).
- The Phase 4 VESTIGE trial was a multinational, randomized, double-blind, placebo-controlled study conducted across 72 sites to evaluate the effects of dupilumab on airway structure and function in adults with uncontrolled, moderate-to-severe Type 2 asthma, a blood eosinophil count ≥ 300 cells/μL, and FeNO ≥ 25 parts per billion (ppb), all on medium- or high-dose ICS plus other controller therapies. Patients were randomly assigned 2:1 to receive SC dupilumab 300 mg or placebo every 2 weeks for 24 weeks. Primary outcomes included the proportion of patients achieving FeNO < 25 ppb at week 24 and the percentage change in specific regional airway volume corrected for lung volume ([s]iVaw) at total lung capacity. Of the 109 patients enrolled, 72 received dupilumab and 37 received placebo. At week 24, 57% of patients in the dupilumab group vs 11% in the placebo group achieved FeNO < 25 ppb (OR, 9.8; 95% CI, 3.1 to 30.8). Dupilumab also produced a nonsignificant improvement in (s)iVaw at total lung capacity (LS mean change, 19.7% [standard error, 8.1] vs -2.0% [standard error, 11.5]; LS mean difference, 21.8%; 95% CI, -7.7 to 51.3). Treatment-emergent adverse

events related to the intervention occurred in 15% of patients in the dupilumab group and 11% in the placebo group, with no deaths reported (*Castro et al 2025*).

COPD

- Two identically designed, 52-week Phase 3, double-blind, placebo-controlled, RCTs (BOREAS and NOTUS) evaluated the efficacy of dupilumab in adult patients 40 to 80 years of age with inadequately controlled moderate-to-severe COPD. Inclusion criteria were FEV_1/forced vital capacity [FVC] ratio < 0.70 and post-bronchodilator FEV_1 % predicted > 30% and ≤ 70%, an elevated exacerbation risk (defined as ≥ 2 moderate exacerbations or ≥ 1 severe exacerbations within the year before screening) despite the use of standard triple therapy (LAMA/LABA/ICS), and a blood eosinophil count ≥ 300 cells/μL. A total of 98.2% of enrolled patients were receiving background triple therapy; double therapy (LAMA/LABA alone) was allowed if ICS was contraindicated. Patients were randomized 1:1 to receive dupilumab 300 mg via SC injection as add-on maintenance therapy or placebo every 2 weeks (*Bhatt et al 2023, Bhatt et al 2024*).
  - The primary endpoint, the annualized rate of moderate or severe exacerbations of COPD over the 52-week treatment period, demonstrated significant improvement with dupilumab vs placebo in both studies:
    - BOREAS: 0.78 events/year vs 1.10 events/year (rate ratio, 0.70; 95% CI, 0.58 to 0.86; p < 0.001).
    - NOTUS: 0.86 events/year vs 1.30 events/year (rate ratio, 0.66; 95% CI, 0.54 to 0.82; p < 0.001).
- In a pooled analysis of BOREAS and NOTUS (N = 1874), the annualized rate of moderate or severe asthma exacerbations was 0.794 with dupilumab and 1.156 with placebo (rate ratio, 0.687; 95% CI, 0.595 to 0.793) (*Bhatt et al 2025*).
- A meta-analysis of 8 RCTs (N = 4512) evaluated the efficacy and safety of monoclonal antibodies in managing eosinophilic COPD over a median follow-up of 52 weeks. Eligible patients had ≥ 1 exacerbation in the prior year and evidence of eosinophilic/Type 2 inflammation based on serum eosinophil counts. Patients received standard-of-care therapy plus one of the following monoclonal antibodies: dupilumab, mepolizumab, benralizumab, or the investigational agents astegolimab or itepekimab. The primary outcome, annualized rate of moderate-to-severe exacerbations, was significantly reduced with monoclonal antibody therapy vs placebo (rate ratio, 0.79; 95% CI, 0.73 to 0.86). Results for key secondary outcomes included a mean FEV_1 increase of 48.9 mL (95% CI, 20.1 to 77.6) and a reduction in St. George's Respiratory Questionnaire score of -2.24 points (95% CI, -3.45 to -1.03) with the addition of monoclonal antibody therapy. All-cause mortality did not differ significantly between groups (OR, 0.91; 95% CI, 0.63 to 1.30). In subgroup analyses, dupilumab demonstrated the greatest reduction in exacerbation risk (risk ratio, 0.68; 95% CI, 0.59 to 0.78), followed by mepolizumab and benralizumab (*Mohamed et al 2025*).

CSU

- Two randomized, double-blind, placebo-controlled trials (LIBERTY-CSU CUPID) evaluated dupilumab in patients with CSU inadequately controlled with H1 antihistamines. Study A included omalizumab-naive patients ≥ 6 years of age (n = 138), and Study B included omalizumab-incomplete responders or intolerant patients ≥ 12 years of age (n = 108). The primary endpoint was change from baseline at week 24 in either Urticaria Activity Score over 7 days (UAS7) or ISS7. In Study A, dupilumab significantly improved UAS7 (difference, -8.5; 95% CI, -13.2 to -3.9; p = 0.0003) and ISS7 (difference, -4.2; 95% CI, -6.6 to -1.8; p = 0.0005) vs placebo. In Study B, dupilumab showed a significant UAS7 improvement (difference, -5.8; 95% CI, -11.4 to -0.3; p = 0.0390) but only a non-significant numerical trend for ISS7 (difference, -2.9; 95% CI, -5.7 to -0.07; p = 0.0449) (*Maurer et al 2024*).
- Study C used the same design as Study A and further evaluated dupilumab in patients ≥ 6 years of age with CSU inadequately controlled with H1-antihistamines (N = 151). Dupilumab significantly improved UAS7 (difference, -4.65; 95% CI, -8.65 to -0.65; p = 0.02) and ISS7 (difference, -2.54; 95% CI, -4.65 to -0.43; p = 0.02) vs placebo at week 24. Pooled data from Studies A and C also demonstrated greater improvements with dupilumab for UAS7 and ISS7 (p < 0.001 for both) (*Casale et al 2026*).
- The expanded indication of dupilumab in patients ≥ 2 years of age with CSU was based on efficacy data extrapolated from CUPID studies A and C, as well as pharmacokinetic data from the single arm CUPIDKids trial (*clinicaltrials.gov [NCT05526521], Regeneron press release 2026).*

CRSwNP

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral CRSwNP. Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by LS mean differences in NPS (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13;

95% CI, -5.80 to -4.46, respectively). The risks of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo (*Bachert et al 2019*).

Allergic Fungal Rhinosinusitis

- The 52-week, randomized, double-blind, placebo-controlled AIMS trial evaluated the safety and efficacy of dupilumab in 62 adult and pediatric patients ≥ 6 years of age with allergic fungal rhinosinusitis and a history of sino-nasal surgery. Enrolled patients had to have evidence of sinus opacification on the Lund Mackay (LMK) sinus computed tomography (CT) scan with a LMK score of > 9 for those with unilateral polyps and > 12 for those with bilateral polyps. The LMK sinus CT scan score evaluates the opacification of each sinus, with higher scores indicating more opacification. In the dupilumab group, adults and children who weighed > 60 kg received dupilumab 300 mg every 2 weeks; children who weighed > 30 kg to < 60 kg received dupilumab 200 mg every 2 weeks. Results demonstrated significant improvements in LMK sinus CT scan score from baseline to Week 52 (primary outcome) with dupilumab (LS mean change, -9.17) vs placebo (LS mean change, -1.81) with a LS mean difference vs placebo of -7.36 (95% CI, -9.38 to -5.25) (*Dupixent prescribing information 2026).*

EoE

- A 2-part placebo-controlled clinical trial with two 24-week treatment periods evaluated the efficacy of weekly and twice monthly SC injections of dupilumab 300 mg in patients ≥ 12 years of age and weighing ≥ 40 kg with EoE. The coprimary endpoints in parts A and B of the study were 1) the proportion of patients achieving histological remission (defined as peak esophageal intraepithelial eosinophil count of ≤ 6 eosinophils/high-power field [hpf]) and 2) the absolute change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score (range, 0 to 84). Results for weekly dupilumab administration (FDA-approved dose for EoE in patients ≥ 12 years of age) are as follows (*Dellon et al 2022*):
  - In part A (dupilumab, n = 42; placebo, n = 39), histologic remission was achieved in 60% of patients who received weekly dupilumab vs 5% who received placebo (difference, 55 percentage points; 95% CI, 40 to 71). The absolute reduction from baseline in DSQ score was also significantly higher with dupilumab vs placebo (21.9 vs 9.6; difference, -12.32; 95% CI, -19.11 to -5.54).
  - In part B (dupilumab, n = 80; placebo, n = 79), histologic remission was achieved in 59% of patients who received weekly dupilumab vs 6% who received placebo (difference, 54 percentage points; 95% CI, 41 to 66). The absolute reduction from baseline in DSQ score was also significantly higher with dupilumab vs placebo (23.78 vs 13.86; difference, -9.92; 95% CI, -14.81 to -5.02).
  - The histological, symptomatic, endoscopic, and molecular features of EoE showed sustained or continued improvement up to week 52 with weekly dupilumab treatment (*Rothenberg et al 2023*).
- A 12-week Phase 2 study compared weekly injections of dupilumab 300 mg (n = 23) or placebo (n = 24) in adults with EoE (*Hirano et al 2020b*). The primary endpoint was change from baseline to week 10 in Straumann Dysphagia Instrument (SDI) patient-reported outcome score. At the beginning of the study, the mean SDI score was 6.4. After 10 weeks, SDI scores were reduced by a mean value of 3.0 in the dupilumab group compared with a mean reduction of 1.3 in the placebo group (p = 0.0304).
- A 2-part placebo-controlled clinical trial evaluated the efficacy of dupilumab in children 1 to 11 years of age and weighing ≥ 15 kg with EoE (*Chehade et al 2024*).
  - Part A evaluated lower-exposure (LE) dupilumab (200 mg every 2 weeks), higher-exposure (HE) dupilumab (300 mg every 2 weeks), or placebo, in 61 children during a 16-week treatment period. The primary outcome of histological remission, defined as a decrease in esophageal eosinophil count to ≤ 6 eosinophils/hpf, was achieved by 68% of children who received HE dupilumab vs 3% of children who received placebo (difference, 65%; 95% CI, 48 to 81). In the LE dupilumab group, the primary outcome was achieved in 58% of children (difference vs placebo, 55%; 95% CI, 37 to 73). At the end of Part A, eligible patients in each dupilumab group continued the same regimen, and those in the placebo groups were assigned to HE or LE dupilumab for 36 weeks (Part B).
  - In Part B, histological remission was achieved at 52 weeks in 22/37 children treated with HE dupilumab in Parts A and B and 19/29 children treated with LE dupilumab in Parts A and B. Of the children who transitioned from placebo to HE dupilumab, 9 of 18 achieved histologic remission at Week 52 (ie, after 36 weeks of treatment). Of the children who transitioned from placebo to LE dupilumab, 13 of 14 achieved histologic remission at Week 52.
- A meta-analysis evaluated the efficacy of dupilumab for EoE, pooling data from 3 trials summarized above (*Dellon et al 2022, Hirano et al 2020b, and Chehade et al 2024).* Both HE and LE dupilumab regimens demonstrated significant improvements in histologic remission vs placebo. Specifically, LE dupilumab had an OR of 26.88 (95% CI, 11.98 to 60.29), while HE dupilumab had an OR of 29.15 (95% CI, 13.68 to 62.12). No statistically significant difference was found between the HE and LE dosing regimens (OR, 1.07; 95% CI, 0.63 to 1.82). Adverse events were similar across

groups, but HE dupilumab was associated with a statistically significant increase in serious adverse events (OR, 5.00; 95% CI, 1.08 to 23.20), while the increase in serious adverse events for LE dupilumab was not significant (OR, 1.91; 95% CI, 0.28 to 13.29) (*Chu et al 2025a*).

Exdensur (depemokimab-ulaa)

Asthma

- The safety and efficacy of depemokimab-ulaa were evaluated in the 52-week SWIFT-1 and SWIFT-2 randomized, double-blind, placebo-controlled trials in patients ≥ 12 years of age with severe asthma of an eosinophilic phenotype (defined by blood eosinophils ≥ 300 cells/μL in the prior year or ≥ 150 cells/μL at screening). Enrolled patients had persistent symptoms despite treatment with medium- or high-dose ICS plus ≥ 1 controller, with ≥ 2 exacerbations in the preceding year. Patients were randomized 2:1 to depemokimab-ulaa 100 mg (n = 502) or placebo (n = 260), administered via SC injection at weeks 0 and 26. The primary endpoint was the annualized exacerbation rate at week 52. In SWIFT-1, annualized rates were 0.46 (95% CI, 0.36 to 0.58) with depemokimab-ulaa vs 1.11 (95% CI, 0.86 to 1.43) with placebo, yielding a rate ratio of 0.42 (95% CI, 0.30 to 0.59). In SWIFT-2, corresponding rates were 0.56 (95% CI, 0.44 to 0.70) vs 1.08 (95% CI, 0.83 to 1.41), yielding a rate ratio of 0.52 (95% CI, 0.36 to 0.73). Adverse event rates were similar across groups, with no treatment-related serious adverse events identified (*Jackson et al 2024*).
- A meta-analysis of both trials found that depemokimab significantly reduced the annualized rate of exacerbations ((MD, -0.59, 95% CI, -0.76 to -0.42, p < 0.00001) (*Gill et al 2025*).

Fasenra (benralizumab)

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 4 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017, Harrison et al 2021*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; p = 0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/μL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; p = 0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; p = 0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; p < 0.0001) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; p < 0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; p = 0.0018) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; p = 0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORA Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to receive benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age)

were treated for 108 weeks. A total of 1576 patients were included in the full analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to those observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2019a*).

  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (p < 0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; p = 0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; p < 0.001).
  - ANDHI was a randomized, multicenter, double-blind, placebo-controlled, Phase 3b study that assessed the effect of benralizumab in adults with severe eosinophilic asthma and at least 2 exacerbations in the previous year despite use of medium- to high-dose ICS plus another asthma controller (*Harrison et al 2021*). Patients were randomized to receive benralizumab 30 mg every 8 weeks (with the first 3 doses given 4 weeks apart; n = 427) or placebo (n = 229). Benralizumab significantly reduced annualized asthma exacerbation rate over the 24-week treatment period compared to placebo (RR, 0.51; 95% CI, 0.39 to 0.65; p < 0.0001).
- The safety of benralizumab in children 6 to 11 years of age with severe eosinophilic asthma was demonstrated in a 48-week, open-label, pharmacokinetic/pharmacodynamic study. A total of 28 children received benralizumab 10 mg (for those weighing < 35 kg) or 30 mg (for those weighing ≥ 35 kg) administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter. Authors concluded that the pharmacokinetics, decrease in blood eosinophil levels, and safety profile in children 6 to 11 years of age were similar to findings in adolescents and adults (*Wedner et al 2024*).
- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (N = 2295 patients) of the results from the SIROCCO and CALIMA Phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (95% CI, 0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 95% CI, 0.55 to 0.75; p < 0.0001). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (95% CI, 0.65 to 0.82); RR vs placebo was 0.63 (95% CI, 0.54 to 0.74; p < 0.0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- The Phase 4 SHAMAL trial evaluated the reduction in daily maintenance ICS use with benralizumab in patients with severe eosinophilic asthma. Patients were randomized 3:1 to taper their high-dose ICS to a medium-dose, low-dose, and as-needed dose (collectively referred to as the reduction group; n = 168) or continue their ICS/formoterol therapy (reference group; n = 43) for 32 weeks, with maintenance follow up at 48 weeks. The primary endpoint was the proportion of patients an ICS/formoterol dose reduction by week 32. Results demonstrated that by the end of week 32, 92% of patients were able to reduce their ICS/formoterol dose: 61% to as-needed only, 17% to low-dose, and 15% to medium-dose. Of these patients, 96% of patients were able to maintain the dose that was used from week 32 to week

48. Throughout the entire study period, there were 16 asthma exacerbations in the reduction group and 5 in the reference group (rate ratio, 1.05; 95% CI, 0.41 to 2.68) (*Jackson et al 2024*).

- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; p < 0.00001) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as AQLQ and ACQ score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration did not result in an increased incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; p = 0.96) *(Tien et al 2017)*.

EPGA

- MANDARA was a Phase 3, multicenter, double-blind, active-controlled noninferiority trial comparing the efficacy of benralizumab vs mepolizumab in 140 adult patients with relapsing or refractory EGPA. For the primary endpoint, the adjusted proportion of patients with remission at weeks 36 and 48 was 59% in patients treated with benralizumab vs 56% with mepolizumab (difference, 3%; 95% CI, -13 to 18; p = 0.73), demonstrating the noninferiority of benralizumab to mepolizumab. For secondary endpoints, the accrued duration of remission and time to first relapse were similar between agents, and complete withdrawal of corticosteroids during weeks 48 to 52 was achieved in 41% of patients taking benralizumab and 26% of patients taking mepolizumab (*Wechsler et al 2024b*).
  - Following MANDARA, 128 patients entered an open-label extension in which they continued treatment with benralizumab (benralizumab/benralizumab [n = 66]) or switched from mepolizumab to benralizumab (mepolizumab/benralizumab [n = 62]). At week 104, 41 (62.1%) benralizumab/benralizumab patients and 42 (67.7%) mepolizumab/benralizumab patients were in remission (*Merkel et al 2025*).

HES

- NATRON was a 24-week, Phase 3, randomized, double-blind, placebo-controlled trial evaluating the efficacy of benralizumab vs placebo in 133 patients with HES (75% idiopathic; 12% lymphocytic). For the primary endpoint, benralizumab reduced the time to first flare and reduced the risk of a first flare occurring by 65% compared to placebo (hazard ratio [HR],0.35; 95% CI, 0.18 to 0.69; p = 0.0024) (*Ogbogu et al 2026*).

Nucala (mepolizumab)

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter RCTs in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg IV mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (p < 0.0001), 1.46 in the 250 mg mepolizumab group (p = 0.0005), and 1.15 in the 750 mg mepolizumab group (p < 0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in ACQ scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (p < 0.001), and 0.83 per patient per year in the SC mepolizumab group (p < 0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (p < 0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared OCS requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; p = 0.008). The median reduction in daily OCS dose was 50% (95%

CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (p = 0.007) *(Bel et al 2014)*.

- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; p < 0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/µL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/µL. At a baseline count < 150 cells/µL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and OCS dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for the treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

EGPA

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (RR, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).

- Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

HES

- A 32-week, double-blind, placebo-controlled, multicenter, RCT evaluated the efficacy and safety of mepolizumab in patients ≥ 12 years of age with HES (without an identifiable nonhematologic secondary cause) for at least 6 months (*Nucala prescribing information 2025, Roufosse et al 2020)*. A total of 108 patients were assigned to mepolizumab 300 mg every 4 weeks (n = 54) or placebo (n = 54). Results demonstrated the following for mepolizumab and placebo groups, respectively:
  - Proportion of patients with ≥ 1 HES flare or withdrew from the trial: 28% vs 56% (OR, 0.28; 95% CI, 0.12 to 0.64; p = 0.002)
  - Adjusted mean rate of HES flares per year: 0.50 vs 1.46 (rate ratio, 0.34; 95% CI, 0.19 to 0.63; p < 0.001)
  - Probability of first HES flare by week 32: 26.3% vs 52.7% (HR, 0.34; 95% CI, 0.18 to 0.67; p = 0.002)

CRSwNP

- SYNAPSE, a 52-week, double-blind, randomized, placebo-controlled, multicenter trial, evaluated the efficacy and safety of mepolizumab in adult patients with CRSwNP. A total of 407 patients with recurrent, refractory, severe, bilateral nasal polyp symptoms despite standard care treatment were enrolled. Patients were randomly assigned to receive 100 mg mepolizumab (n = 206) or placebo (n = 201) every 4 weeks. The total endoscopic nasal polyp score significantly improved from baseline with mepolizumab vs placebo (adjusted difference in medians, -0.73; 95% CI, -1.11 to -0.34; p < 0.0001). The nasal obstruction visual analogue score (VAS) during weeks 49 to 52 also significantly improved (adjusted difference in medians, -3.14; 95% CI, -4.09 to -2.18; p < 0.0001). Adverse events related to study treatment occurred in 15% of the mepolizumab group and 9% of the placebo group (*Han et al 2021*).

COPD

- The approval of mepolizumab in patients with COPD was based on the MATINEE and METREX trials, both of which were Phase 3, randomized, placebo-controlled, double-blind, parallel-group trials evaluating the efficacy and safety of mepolizumab in patients with eosinophilic COPD. In both trials, patients were ≥ 40 years of age with a ≥ 1-year COPD diagnosis, had a history of ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the prior year despite ≥ 3 months of triple inhaled therapy (high-dose ICS plus LABA plus LAMA), and a post-bronchodilator FEV_1 between 20% and 80% predicted (*Pavord et al 2017, Sciurba et al 2025*).
  - In MATINEE (N = 804), patients had a blood eosinophil count ≥ 300 cells/μL at screening and ≥ 150 cells/μL in the previous year, and were randomized 1:1 to receive 100 mg of mepolizumab or placebo via SC injection every 4 weeks for 52 to 104 weeks. Results demonstrated that mepolizumab significantly reduced the annualized rate of moderate or severe exacerbations (primary outcome) vs placebo (0.80 vs 1.01 events/year; rate ratio, 0.79; 95% CI, 0.66 to 0.94), as well as the annualized rate of exacerbations leading to emergency visits or hospitalization (0.13 vs 0.20 events/year; rate ratio, 0.65; 95% CI, 0.43 to 0.96). Time to first exacerbation was also longer with mepolizumab (median, 419 vs 321 days; HR, 0.77; 95% CI, 0.64 to 0.93) (*Sciurba et al 2025*).
  - In METREX (N = 837), patients were randomized 1:1 to receive 100 mg of mepolizumab or placebo via SC injection every 4 weeks for 52 weeks, and stratified by eosinophilic (blood eosinophils ≥ 150 cells/mm³ at screening or ≥ 300 cells/mm³ in prior year) or non-eosinophilic type (blood eosinophils < 150 cells/mm³ at screening and no evidence of levels ≥ 300 cells/mm³ in prior year). Results demonstrated that among 462 patients with an eosinophilic phenotype, the mean annual exacerbation rate (primary outcome) was significantly lower with mepolizumab (1.40 events/year) vs placebo (1.71 events/year; rate ratio, 0.82; 95% CI, 0.68 to 0.98). No significant reduction was seen in the overall METREX population (rate ratio, 0.98; 95% CI, 0.85 to 1.12) (*Pavord et al 2017)*.
- A meta-analysis of 4 RCTs (N = 1953) evaluated mepolizumab for eosinophilic COPD and determined that mepolizumab reduced the annualized rate of moderate or severe exacerbations (rate ratio, 0.80; 95% CI, 0.73 to 0.89) and prolonged time to first exacerbation (HR, 0.78; 95% CI, 0.69 to 0.88) when compared to placebo (*Sinclair De Frías et al 2025*).

Tezspire (tezepelumab-ekko)

Severe asthma

- A 52-week, Phase 3, randomized, double-blind, placebo-controlled study (NAVIGATOR) evaluated the efficacy of tezepelumab-ekko in 1061 patients ≥ 12 years of age with severe asthma uncontrolled with a medium-to-high dose ICS and ≥ 1 controller medication. Patients were randomized 1:1 to receive tezepelumab-ekko (210 mg SC injection every 4 weeks) or matching placebo. The annual rate of severe exacerbations during the 52-week study period was the primary

outcome, with a subgroup analysis of patients with a baseline blood eosinophil count of < 300 cells/µL. Secondary endpoints included change in FEV_1 from baseline and changes in quality of life and asthma severity questionnaires (ACQ, AQLQ, and Asthma Symptom Diary [ASD]). Tezepelumab-ekko was associated with an annualized asthma exacerbation rate of 0.93 vs 2.10 with placebo (rate ratio, 0.44; p < 0.001). For a subgroup of patients with baseline eosinophil counts < 300 cells/µL, the annual rate of asthma exacerbations was 1.02 with tezepelumab-ekko vs 1.73 with placebo (rate ratio, 0.59; p < 0.001). Change from baseline in FEV_1 was 0.23 L with tezepelumab-ekko and 0.09 L with placebo (p < 0.001). Changes in AQLQ and asthma severity scores were also significant in favor of tezepelumab-ekko *(Menzies-Gow et al 2021*).
    - In a long-term extension study (DESTINATION), for patients initially enrolled in NAVIGATOR, the annualized asthma exacerbation rate ratio over 104 weeks was 0.42 (95% CI, 0.35 to 0.51) in favor of tezepelumab-ekko vs placebo (*Menzies-Gow et al 2023).*
- In an additional analysis of data from the NAVIGATOR and DESTINATION trials, on-treatment clinical remission (ACQ-6 total score ≤ 1.5, stable lung function, and no exacerbations or use of OCS during the time periods assessed) was observed in 33.5% of patients who received tezepelumab-ekko vs 26.7% who received placebo during weeks > 52 to 104 (OR, 1.44; 95% CI, 0.97 to 2.14) (*Wechsler et al 2024a*).
- The PATHWAY trial was a 52-week, Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging trial which evaluated the efficacy of tezepelumab-ekko in patients 18 to 75 years of age with asthma uncontrolled with medium-to-high dose ICS and a controller medication. A total of 550 patients were randomized to treatment with tezepelumab-ekko 70 mg every 4 weeks, tezepelumab-ekko 210 mg every 4 weeks, tezepelumab-ekko 280 mg every 2 weeks, or placebo every 2 weeks, administered via SC injection, for 52 weeks. The primary endpoint was the annualized rate of asthma exacerbations at week 52. Secondary endpoints included change in FEV_1 from baseline and quality of life/asthma severity scores. Outcomes were also assessed by baseline blood eosinophil counts (≥ 250 or ≤ 250 cells/µL) and Th2 lymphocyte status (high: IgE > 100 international units [IU]/mL and blood eosinophil ≥ 140 cells/µL; low: IgE ≤ 100 IU/mL and blood eosinophil < 140 cells/µL). At week 52, asthma exacerbation rates were lower with tezepelumab-ekko compared with placebo by 62%, 71%, and 66% for 70 mg, 210 mg, and 280 mg doses of tezepelumab-ekko, respectively (p < 0.001 for all comparisons). Asthma exacerbation rates were also lower with tezepelumab-ekko vs placebo, regardless of baseline eosinophil count or Th2 status. Change in FEV_1 was greater with tezepelumab-ekko than with placebo (differences from placebo ranging from 8.30 to 10.44 L). Quality of life and asthma severity scores (ACQ-6, AQLQ, and Asthma Symptom Scores) were also improved significantly with tezepelumab-ekko over placebo *(Corren et al 2017a).*
- In patients with severe uncontrolled asthma, a pooled analysis of 6 placebo-controlled RCTs demonstrated that treatment with tezepelumab-ekko improved FEV_1 by 0.15 L (95% CI, 0.12 to 0.17) and reduced the asthma exacerbation rate per year by 0.60 (95% CI, 0.51 to 0.70) when compared with placebo (*Zoumot et al 2022*).

CRSwNP

- The efficacy and safety of -ekko for the treatment of patients with CRSwNP were evaluated in WAYPOINT, a Phase 3, randomized, double-blind, placebo-controlled trial in 408 patients ≥ 18 years of age with severe, uncontrolled CRSwNP for ≥ 12 months. Patients were randomized 1:1 to receive tezepelumab-ekko 210 mg or placebo every 4 weeks for 52 weeks, in addition to standard care, including intranasal glucocorticoids. The coprimary endpoints were the change from baseline to week 52 in nasal polyp score and mean nasal congestion score. Treatment with tezepelumab-ekko significantly improved endoscopic nasal polyp scores and mean daily nasal congestion scores vs placebo. Time-to-event analyses demonstrated fewer surgical interventions in the tezepelumab-ekko group vs placebo (0.5% vs 22.0%, respectively; HR, 0.02; 95% CI, 0.00 to 0.09) and reduced use of systemic glucocorticoids (5.2% vs 19.3%; HR, 0.11; 95% CI, 0.04 to 0.25) (*Lipworth et al 2025*).

Xolair (omalizumab)

Asthma

- The original FDA approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate-to-severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
    - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose

unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60% vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (p-value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate-to-severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate-to-severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and FEV_1 were not significantly different in omalizumab-treated patients compared to placebo.
- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (OR, 0.55; 95% CI, 0.42 to 0.6; 10 studies; n = 3261). This represents an absolute reduction from 26% for patients suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate-to-severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; n = 1889). A significant benefit was noted for SC omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16; 95% CI, 0.06 to 0.42; 4 studies; n = 1824), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the number of patients who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption must be considered in light of the high cost of omalizumab (*Normansell et al 2014*).

- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate-to-severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (RR, 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse events was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9% vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The RCTs did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years of age *(Corren et al 2017b)*.
- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the Asthma Control Test (ACT) score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3-point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 RCTs was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit (*Ledford et al 2017*).

CSU

- The safety and efficacy of omalizumab for the treatment of CSU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CSU who remained symptomatic despite H1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo (p ≤ 0.001) (*Saini et al 2015*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CSU. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to

continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; p < 0.0001). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CSU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CSU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose-dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group (p < 0.00001) and dose-dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials and a 2020 meta-analysis of 9 trials, both comparing omalizumab with placebo (*Jia and He 2020, Rubini et al 2019*).

CRSwNP

- The efficacy and safety of omalizumab for the treatment of CRSwNP in adult patients with an inadequate response to intranasal corticosteroids were based on results from 2 randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies, POLYP 1 (n = 138) and POLYP 2 (n = 127) (*Gevaert et al 2020*). Patients were randomly assigned to omalizumab 75 to 600 mg SC every 2 or 4 weeks (based upon pretreatment serum total IgE level and body weight) or placebo for 24 weeks. All patients received background intranasal mometasone therapy. Results from both studies revealed that omalizumab was associated with a significantly greater improvement from baseline at week 24 in Nasal Polyp Score (NPS) and weekly average Nasal Congestion Score (NCS) as compared to placebo. In POLYP 1 and POLYP 2, the mean changes in NPS from baseline to week 24 for omalizumab compared to placebo were -1.08 vs 0.06 (p < 0.0001) and -0.9 vs -0.31 (p = 0.014), respectively, and mean changes in NCS from baseline were -0.89 vs -0.35 (p = 0.0004) and -0.7 vs -0.2 (p = 0.0017), respectively. Adverse events were similar between treatment groups.

IgE-mediated food allergy

- Omalizumab was FDA-approved for IgE-mediated food allergy in adults and children ≥ 1 year of age based on the results of a randomized, multicenter, double-blind, placebo-controlled trial in 180 patients with allergies to peanut and at least 2 other foods, including milk, egg, wheat, cashew, hazelnut, or walnut. Patients with a history of severe anaphylaxis (defined as neurological compromise or requiring intubation) were excluded from the study. Results demonstrated a significantly higher response with omalizumab vs placebo (67% vs 7%, respectively; p < 0.001) for the primary outcome (ie, the percentage of patients able to tolerate a single dose of ≥ 600 mg of peanut protein without experiencing dose-limiting symptoms [ie, moderate-to-severe skin, respiratory, or gastrointestinal symptoms]) (*Wood et al 2024*).
- A systematic review and meta-analysis of 8 studies (N =734; 7 RCT, 1 controlled clinical trial) evaluated the efficacy of omalizumab (monotherapy or combined with oral immunotherapy) in achieving target maintenance dose for IgE-mediated food allergy in children and young adults vs controls (placebo, placebo + oral immunotherapy, or strict allergen avoidance). Four studies included patients with ≥ 2 food allergies, 2 focused on peanut allergy, and 2 on cow's milk allergy. One study evaluated omalizumab monotherapy, 7 evaluated omalizumab combined with oral immunotherapy. Pooled analysis of the 8 studies demonstrated that omalizumab based therapy (monotherapy or combination) increased the likelihood of achieving a clinically meaningful target maintenance dose compared to controls (RR, 3.07; 09% CI, 1.42 to 6.62; p < 0.001) (*Zhang et al 2025*).

Omlyclo (omalizumab-igec)

- Omalizumab-igec is an FDA-approved biosimilar to omalizumab and also designated as interchangeable with omalizumab.
- In a double-blind, randomized, active-controlled Phase 3 trial, 619 patients with CSU inadequately controlled on H1-antihistamines were randomized to receive either omalizumab-igec or reference omalizumab (ref-OMA) at doses of 300 mg or 150 mg over two 12-week treatment periods. The primary outcome was the change from baseline in the weekly itch severity score (ISS7) at week 12. In the modified intention-to-treat global analysis, omalizumab-igec 300 mg achieved a mean ISS7 change of -9.21, compared to -9.98 with ref-OMA 300 mg, yielding a treatment difference of 0.77 (95% CI, -0.37 to 1.90), which was within the predefined equivalence margin of -2.0 to 2.0, demonstrating therapeutic equivalence. Similar results were observed in the U.S.-specific analysis (treatment difference, 0.70; 90% CI, -0.22 to 1.63) (*Saini et al 2025*).

Comparative reviews

Asthma

- In 2017, *Cockle et al* conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, RCTs, ≥ 12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥ 1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CI, 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both RCTs and cohort studies with duration of ≥ 12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria (*Nachef et al 2018*).
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 16 studies (N = 7600) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.15 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (42/2026) than placebo (11/1227) due to adverse events (*Farne et al 2022*).
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019).*
- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/µL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/µL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/µL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/µL (difference, -0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/µL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/µL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/µL *(Busse et al 2019b)*.

- A 2019 systematic review and network meta-analysis of 30 RCTs compared biologic therapies for treatment of Type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the U.S. (lebrikizumab, tralokinumab) *(Edris et al 2019)*.
- In a 2020 meta-analysis including data from 3 trials (n = 2640), dupilumab and benralizumab were compared in patients with inadequately controlled asthma. While there were no significant differences in the annual exacerbation rates between both drugs in the overall population (RR, 0.83; 95% CI, 0.62 to 1.09) and in the subgroup with the blood eosinophil count < 150 cells/µL (RR, 1.57; 95% CI, 0.73 to 2.82), dupilumab was superior to benralizumab for the subgroup with a blood eosinophil count of ≥ 300 cells/µL (RR, 0.58; 95% CI, 0.39 to 0.84) and ≥ 150 to < 300 cells/µL (RR, 0.51; 95% CI, 0.29 to 0.92). The incidence of adverse events was similar between groups (OR, 1.023; 95% CI, 0.688 to 1.526) (*Ando et al 2020*).
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018, Yan et al 2019).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score, and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2 tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. An increase in FEV_1, reduction in ACQ score, and increase in AQLQ score were observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).
- In a 2020 network meta-analysis including 9 studies, treatment rankings estimated that dupilumab was most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab. Similar to other indirect treatment comparisons, there were no within-group differences as related to the risk for asthma exacerbations (*Ramonell et al 2020*).
- A 2022 network meta-analysis of 8 RCTs (N = 6461) compared the safety and efficacy of mepolizumab, benralizumab, and dupilumab in patients with severe eosinophilic asthma. Dupilumab had the highest probability (> 95%) of having the highest or second-best overall surface under the cumulative ranking curve (SUCRA) score in reducing exacerbation rates and improving lung function. Mepolizumab and benralizumab had a 30% and ~10% chance of being ranked best, respectively (*Akenroye et al 2022*).
- A 2023 network meta-analysis of 10 RCTs (N = 9201) compared the efficacy of tezepelumab-ekko compared to mepolizumab, benralizumab, and dupilumab in patients with eosinophilic asthma. Tezepelumab-ekko was associated with lower exacerbation rates compared to benralizumab (RR, 0.63; 95% CI, 0.46 to 0.86), but no difference was seen compared to dupilumab or mepolizumab. Improvements in FEV_1 were non-significantly larger with tezepelumab-ekko compared to mepolizumab and benralizumab. Tezepelumab-ekko had the highest SUCRA score for reducing exacerbation rate (89% probability of having the highest- or second-best rank), followed by dupilumab (38%), mepolizumab (6%), and benralizumab (< 1%) (*Nopsopon et al 2023*).
- A systematic review and network meta-analysis of 64 trials (N = 26,630) compared the efficacy of biologic therapies for asthma in adults with moderate, moderate-to-severe, or severe asthma. Key findings included (*Pitre et al 2023*):
  - Treatment with tezepelumab-ekko, dupilumab, benralizumab, mepolizumab, reslizumab, and omalizumab probably reduced exacerbations vs placebo in patients with blood eosinophil levels ≥ 300 cells/µL (moderate to high certainty).
  - Dupilumab, tezepelumab-ekko and reslizumab probably improved lung function vs to placebo (moderate to high certainty).

- Dupilumab and tezepelumab-ekko were the most effective for reducing exacerbations in patients with blood eosinophil levels ≥ 300 cells/µL (RR, 0.32 [95% CI, 0.24 to 0.42] and 0.30 [95% CI, 0.22 to 0.43], respectively) and improving lung function compared to other agents (mean difference [MD], 0.25 L [95% CI, 0.21 to 0.29] and MD, 0.24 L [95% CI, 0.16 to 0.32], respectively) (high certainty for both outcomes); neither demonstrated superiority over the other for both endpoints.
- Moderate-certainty evidence showed that dupilumab, omalizumab, and tezepelumab-ekko probably reduced hospitalizations compared to placebo (moderate certainty). The authors also concluded that in patients with low eosinophils, biologics likely do not improve asthma outcomes.

CRSwNP

- In a 2022 network meta-analysis including 9 RCTs, 4 different biologics (dupilumab [n = 3], omalizumab [n = 4], mepolizumab [n = 2]) and placebo were compared in patients with CRSwNP. Dupilumab was found to be the most efficacious in terms of NPS, Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and NCS with SUCRA values of 0.900, 0.916, 1.000, and 0.807, respectively. Omalizumab ranked second in efficacy in SNOT-22, UPSIT, and NCS scores with SUCRA values of 0.606, 0.500, and 0.693, respectively. Mepolizumab had the highest risk of adverse events for SUCRA values of 0.746 (*Wu et al 2022*).
- An indirect treatment comparison of dupilumab and mepolizumab for CRSwNP was published using data from the SINUS-24/52 and SYNAPSE trials. Authors created a "SYNAPSE-like" subgroup from the SINUS trials by applying SYNAPSE inclusion criteria (≥ 1 prior nasal polyp surgery, nonsmoker/former smoker [≥ 6 months], and visual analog scale score > 7). These patients received dupilumab 300 mg every 2 weeks and were compared with SYNAPSE patients who received mepolizumab 100 mg every 4 weeks. Outcomes were assessed at 24 and 52 weeks. The primary efficacy endpoint was the change in NPS. At 24 weeks, dupilumab showed a significantly greater NPS reduction (MD, -1.38; 95% CI, -1.86 to -0.90) and higher odds of achieving ≥ 1 point improvement in NPS (OR, 6.03; 95% CI, 2.97 to 12.21). At 52 weeks, dupilumab also demonstrated superior improvement in NPS (MD, -1.35; 95% CI, -2.14 to -0.56) and a higher odds of achieving ≥ 1 point improvement in NPS (OR, 4.36; 95% CI, 1.71 to 11.13) (*Hopkins et al 2024*).
- A 24-week, multicenter, double-blind, randomized, Phase 4 trial (EVEREST) enrolled 360 adults with any severity asthma and severe, uncontrolled CRSwNP of ≥ 12 months' duration. Enrolled patients were randomly assigned to receive SC dupilumab 300 mg every 2 weeks (n = 181) or omalizumab every 2 or 4 weeks (n = 179), dosed according to body weight and baseline IgE concentrations. All patients continued background mometasone furoate nasal spray throughout the study. Primary outcomes were changes from baseline to week 24 in endoscopic nasal-polyp score and University of Pennsylvania Smell Identification Test (UPSIT). The LS mean change in nasal-polyp score was -2.65 with dupilumab vs -1.05 with omalizumab (difference, -1.60; 95% CI, -1.96 to -1.25; $p < 0.0001$), and the change in UPSIT score was 12.70 vs 4.70 (difference, 8.0; 95% CI, 6.3 to 9.7; $p < 0.0001$) (*De Corso et al 2025*).

CSU

- A network meta-analysis of 93 studies (N = 11,398) compared the efficacy of 42 systemic treatments for CSU. Standard-dose omalizumab 300 mg every 4 weeks was rated among the most effective biologics, demonstrating high-certainty reductions in urticaria activity (MD, -8.37, 95% credible interval [CrI], -10.28 to -6.46). Dupilumab improved urticaria activity with moderate-certainty evidence (MD, -6.01; 95% CrI, -10.57 to -1.46), ranking slightly below standard-dose omalizumab in overall UAS7 performance. For urticaria-related quality of life, omalizumab provided high-certainty improvement (MD, -12.68; 95% CrI, -15.85 to -9.52), whereas dupilumab showed low-certainty improvement (MD, -9.73; 95% CrI, -21.51 to 2.05) (*Chu et al 2025b*).
- Another network meta-analysis of 15 studies (N = 4,913) evaluating the comparative efficacy of omalizumab, dupilumab, and remibrutinib (Rhapsido) in CSU found omalizumab 300 mg every 4 weeks to have the greatest efficacy across UAS7, ISS7, symptom remission, and disease control at weeks 12 and 24. Remibrutinib demonstrated the greatest improvement in quality of life score and the second-highest reduction in UAS7 and odds of symptom remission, while dupilumab provided sustained itch relief but appeared to have a slower onset of effect. The authors concluded that omalizumab 300 mg had the highest overall effect sizes across major outcomes, followed by remibrutinib (*Xiong et al 2025*).

Clinical Guidelines

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene

modifiers, cromolyn, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - A 2020 focused update of the 2007 NAEPP guideline has provided additional updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*).
- The 2026 GINA report also provides a stepwise approach to asthma management (*GINA 2026*).
  - Treatment recommendations are based on patient age, and stepping down should be considered when asthma symptoms have been well-controlled and lung function has been stable for ≥ 2 to 3 months. Asthma should be assessed 1 to 3 months after starting a treatment, then every 3 to 12 months.
    - Low dose ICS/formoterol combination products are preferred for both controller (ie, maintenance treatment) and reliever use in adults and adolescents ≥ 12 years of age; the preferred controller option in children 6 to 11 years of age is daily low dose ICS and ICS/formoterol or ICS/SABA for reliever use; In patients ≤ 5 years the preferred controller option consists of low-dose ICS for Step 2 and double low-dose ICS for Step 3, with a specialist assessment recommended for Step 4 if a patient's asthma is not well-controlled on double low-dose ICS.
  - In patients ≥ 6 years of age diagnosed with severe asthma and uncontrolled on Step 4 treatment (eg, with maintenance ICS/LABA therapy), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Add-on treatment with a biologic agent should be considered as follows:
    - Severe allergic asthma: Anti-IgE treatment with omalizumab and its biosimilar omalizumab-igec are recommended for patients ≥ 6 years of age.
    - Severe eosinophilic asthma: Add-on anti-IL-5 therapy is recommended for patients ≥ 6 years of age (mepolizumab), ≥ 12 years of age (benralizumab, depemokinab) or ≥ 18 years of age (reslizumab).
    - Severe eosinophilic/Type 2 asthma: Anti-IL4 therapy (dupilumab) is recommended for patients ≥ 6 years of age.
    - Adults or adolescents requiring OCS for maintenance therapy: Anti-IL4 therapy (dupilumab) is recommended.
    - Severe asthma: Anti-TSLP therapy (tezepelumab-ekko) is recommended for patients ≥ 12 years of age.
    - Prior to initiation of a biologic agent, several factors should be considered including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency, and patient preference.
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled and lung function has been maintained for 2 to 3 months. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse events), improving adherence by simplifying a treatment regimen, and reducing cost (*Chipps et al 2019, GINA 2026*). In general, stepping down ICS doses by 25 to 50% at 3 month intervals is feasible and safe for most patients. Various options for stepping down are presented in the guideline depending on the current step of treatment; examples include reducing OCS and decreasing dose or frequency of ICS with concurrent use of LABA, or switching to as needed dosing, among others. During step-down therapy, patients should be evaluated for asthma symptoms, use of rescue medications, and lung function. Patients in step 2 should not stop ICS completely due to the increased risk of exacerbations with SABA only treatment.
- The European Respiratory Society/American Thoracic Society guideline on the management of severe asthma suggests the use of anti-IL-5 therapy as an add-on in adults with severe uncontrolled eosinophilic asthma or severe corticosteroid-dependent asthma. A blood eosinophil count of ≥ 150 cells/μL is suggested as a cut-point to guide initiation of anti-IL-5 therapy in adults with severe asthma and prior exacerbations. A blood eosinophil count of ≥ 260 cells/μL or an exhaled nitric oxide level of ≥ 19.5 ppb may be used to identify adolescents and adults with severe allergic asthma who are likely to benefit from anti-IgE treatment. Dupilumab is suggested for adults with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (*Holguin et al 2020*).
- The American College of Chest Physicians (ACCP) also developed a guideline addressing biologic management in adults with severe asthma. For adults with moderate to severe allergic asthma and ≥ 1 exacerbation per year requiring OCS, the panel recommends treatment with either omalizumab or dupilumab, using individual clinical characteristics to guide selection. For severe, steroid-dependent asthma, the panel recommends either anti-IL-5/IL-5 receptor alpha (IL-Rα) therapy or dupilumab and recommends dupilumab over tezepelumab-ekko. For moderate to severe asthma that does not demonstrate a clinical response to omalizumab after 4 to 6 months, the panel recommends switching to either

anti-IL-5/IL-5Rα therapy or dupilumab. For severe asthma that does not respond to anti-IL-5/IL-5Rα therapy after 4 to 6 months, the panel recommends either dupilumab or tezepelumab-ekko, with dupilumab preferred in those who are steroid dependent. For those who do not respond to dupilumab after 4 to 6 months, the panel recommends either anti-IL-5/IL-5Rα therapy or tezepelumab-ekko, with anti-IL-5/IL-5Rα therapy preferred in steroid-dependent patients. Finally, for those with severe asthma receiving anti-IL-5/IL-5Rα therapy who have not demonstrated a clinical response by 4 to 6 months, the panel recommends using a post-treatment FeNO ≥25 ppb to guide switching to dupilumab. All recommendations carry a conditional strength of recommendation and are based primarily on very low-certainty evidence (*Oberle et al 2026*).

COPD

- The 2026 GOLD guidelines state that the initial management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history and severity. Key recommendations from the GOLD guidelines are as follows (*GOLD 2026*):
  - Inhaled bronchodilators are central to symptom management in COPD and are commonly administered on a regular basis to prevent or reduce symptoms.
    - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  - For initial pharmacologic treatment, recommendations are based on the patient's GOLD group status (ie, Group A, B, or E; see Table 3).
    - Group A: Patients should be offered bronchodilator treatment (either short- or long-acting), based on its effect on breathlessness. If available and affordable, long-acting bronchodilator treatment is preferred except in patients with very occasional dyspnea. The treatment should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a LAMA + LABA combination, given there are no issues regarding availability, affordability, and adverse events. In patients for whom this combination is not appropriate, treatment with either a LAMA or LABA is recommended.
    - Group E: The preferred initial choice is a LAMA + LABA combination, given there are no issues regarding availability, affordability, and adverse events. The use of ICS + LABA is not encouraged; if use of an ICS is indicated, ICS + LABA + LAMA is preferred since this combination has been shown to be superior to ICS + LABA. The use of ICS + LABA + LAMA may be considered in patients with a blood eosinophil count ≥ 300 cells/μL. Patients with concomitant asthma should be treated like patients with asthma, requiring use of an ICS.
  - Follow-up pharmacological treatment: Subsequent adjustments to maintenance therapy may be to manage dyspnea or exacerbations irrespective of the patient GOLD group, as follows:
    - Dyspnea pathway: For persistent dyspnea, use of 2 long-acting bronchodilators (LAMA + LABA) is recommended in patients receiving bronchodilator monotherapy and experiencing persistent breathlessness or exercise limitation. If the addition of a second long-acting bronchodilator does not improve patient symptoms, the following options may be considered:
      - Switching inhaler devices or molecules
      - Implementing or escalating non-pharmacologic treatment(s)
      - Adding ensifentrine if available
      - Investigating and treating other causes of dyspnea
    - Exacerbation pathway: In patients with persistent exacerbations on bronchodilator monotherapy, escalation to LAMA + LABA (or LAMA + LABA + ICS if blood eosinophil count ≥ 300 cells/μL) is recommended. For patients who develop further exacerbations, additional therapy options include escalation to:
      - A LAMA + LABA + ICS if eosinophil counts are ≥ 100 cells/μL
      - Addition of roflumilast and/or azithromycin to LAMA + LABA if eosinophil counts are < 100 cells/μL
      - Addition of dupilumab (if chronic bronchitis) or mepolizumab (with and without chronic bronchitis) to LAMA + LABA + ICS if eosinophil counts are ≥ 300 cells/μL

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
≥ 1 moderate or severe exacerbations in the previous year	E	

0 moderate or severe exacerbations in the previous year	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council dyspnea questionnaire

CRSwNP

- Treatment of CRSwNP is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; AAAAI, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; the International Forum of Allergy & Rhinology; the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)/European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA); and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) (*Fokkens et al 2023*, *Orlandi et al 2021, Peters et al 2014, Payne et al 2025, Rank et al 2023*).
- Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms (*Orlandi et al 2021, Peters et al 2014, Payne et al 2025, Rank et al 2023*). Biologics rather than no biologics are recommended for patients with CRSwNP, and dupilumab is specifically recommended by ICAR-RS (*Orlandi et al 2021, Rank et al 2023*). The American Academy of Otolaryngology-Head and Neck Surgery guideline states that biologics (including, but not limited to, monoclonal antibodies such as dupilumab, mepolizumab, or omalizumab) should not be used for the treatment of adults with CRS *without* polyps (*Payne et al 2025*).
- In 2023, EPOS/EUFOREA published an updated expert consensus focused on the use of biologics for CRSwNP. Biologics are indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of Type 2 inflammation (biological biomarkers); the need for systemic corticosteroids (≥ 2 courses per year or > 3 months of low dose steroids) or contraindications to systemic corticosteroids, significant quality-of-life impairment, significant loss of smell, and diagnosis of comorbid asthma. Once eligibility according to the EUFOREA 2023 criteria has been determined, a patient's preference for a surgical or non-surgical approach should be considered if funding within the healthcare system allows. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of Type 2 inflammation, cystic fibrosis, unilateral nasal polyps, mucoceles, general contraindications for biological treatments (eg, immunodeficiencies), and patient-related factors such as noncompliance to therapy (*Fokkens et al 2023*).

Allergic fungal rhinosinusitis

- A guideline from the AAAAI recommends a combination of surgery and systemic and/or topical corticosteroids for the treatment of allergic fungal rhinosinusitis; systemic or topical antifungals are also recommended as adjunctive treatments (*Peters et al 2014*). This guideline does not provide recommendations for the use of biologics for this condition.
- The 2020 EPOS recommends 3 principles for the treatment of fungal rhinosinusitis including systemic antifungal therapy, surgical debridement and reduced immune suppression when possible (*Fokkens et al 2020).*

CSU

- Guidelines developed by the Joint Council of Allergy, Asthma & Immunology, comprised of members from the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology, recommend a stepwise treatment approach for CSU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a LTRA (*Bernstein et al 2014*).
- The 2026 International guideline for the definition, classification, diagnosis and management of urticaria recommends a stepwise approach to CSU management, with second-generation H1-antihistamines as first-line therapy and escalation to up to a 4-fold dose if needed. For patients who remain uncontrolled, the guideline recommends omalizumab (strong recommendation), dupilimab (conditional recommendation) or remibrutinib (Rhapsido; conditional recommendation) as the next add on treatment; biologic agents may be switched in cases of inadequate control. Due to the risk of adverse events and the lack of an approved indication, cyclosporine should only be considered if approved agents (omalizumab, dupilumab, remibrutinib) do not provide an adequate response (*Zuberbier et al 2026*).

EGPA

- In 2023, a European guideline developed by a panel of multidisciplinary experts provided recommendations for the diagnosis and management of EGPA. For remission maintenance in patients with severe EGPA, the panel recommended the use of rituximab, mepolizumab, or traditional disease-modifying therapies in combination with glucocorticoids. In patients with non-severe EGPA, the panel suggested treatment with glucocorticoids, either alone or in combination with mepolizumab. Glucocorticoids should be tapered to the minimum effective dosage to reduce toxicity. Key efficacy trials with benralizumab in patients with EGPA were published after these guidelines; benralizumab is recommended only for consideration in patients with disease refractory to mepolizumab (*Emmi et al 2023*).
- In 2021, a joint guideline from the American College of Rheumatology and Vasculitis Foundation published recommendations for the management of EGPA along with other related conditions (*Chung et al 2021*). The following relevant conditional recommendations were provided:
  - Patients with active, severe EGPA should be treated with cyclophosphamide or rituximab over mepolizumab for remission induction.
  - Patients with active, nonsevere EGPA should be treated with mepolizumab and glucocorticoids over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids.
  - Patients with severe EGPA whose disease has entered remission should be treated with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.
  - Patients with EGPA who have experienced relapse with nonsevere disease manifestations (ie, asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil: mepolizumab should be added over switching to another agent.
  - Patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose glucocorticoids and no other therapy: mepolizumab should be added over adding methotrexate, azathioprine, or mycophenolate mofetil.
  - Patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil: mepolizumab should be added over adding omalizumab.
- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Connelly-Smith et al 2023, Groh et al 2015*).

EoE

- In 2025, the American College of Gastroenterology (ACG) updated their guidelines on the diagnosis and management of EoE. Recommended treatments include proton pump inhibitors, topical steroids, empiric diet elimination, a biologic, and esophageal dilation; feeding therapy is used adjunctively in children with food aversion or feeding dysfunction. With regard to biologics, the guideline conditionally recommends dupilumab in patients ≥ 1 year of age who are nonresponsive to proton pump inhibitor therapy (*Dellon et al 2025*).
- In 2020, the American Gastroenterological Association and the Joint Task Force on Allergy Immunology Practice Parameters (AGA/JTF) published a guideline on the management of EoE (*Hirano et al 2020a)*. In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment. Furthermore, for patients with EoE, topical glucocorticoids are recommended over no treatment and topical glucocorticoids are suggested rather than oral glucocorticoids. Authors did not recommend the use of the following therapies outside of a clinical trial setting based on the available data in patients with EoE at the time of guideline publication: anti-IL13, anti-IL4, anti-IL5, and anti-tumor necrosis factor therapies, montelukast, cromolyn sodium, and immunomodulators.

HES

- The World Health Organization (WHO) guidance on eosinophilic disorders has stated that identification of rearranged *PDGFRA* or *PDGFRB* is important in the management of eosinophilic disorders as those variants respond to imatinib

(*Shomali and Gotlib 2024*). For patients with idiopathic HES (without imatinib-sensitive variants), corticosteroids are first-line therapy; second-line options include hydroxyurea, interferon-alfa, other cytotoxic chemotherapy agents, and hematopoietic stem cell transplantation. The WHO states that mepolizumab is FDA-approved for idiopathic HES, but other biologic agents are considered investigational.

IgE-mediated food allergy

- A 2025 guideline from the AAAAI provides several statements regarding the use of omalizumab in patients with food allergy. Notably, candidates for omalizumab therapy for food allergy should have (1) a qualifying total IgE level to assist with dosing along the nomogram (> 30 to < 1850 IU/mL), as well as (2) evidence of sensitization determined via either (or both) a positive result of food-specific skin prick test or measurement of serum-specific IgE level to a food that would indicate a high likelihood of having an IgE-mediated reaction within the context of the patient's history. It is suggested that testing be obtained within 12 to 18 months of starting therapy. While an oral food challenge is not required prior to omalizumab therapy, candidates for omalizumab should have a clear reaction history in the setting of evidence of IgE sensitization to the food (*Anagnostou et al 2025*).
- Older national guidelines for food allergies focus on nutritional interventions (*Fleischer et al 2021, Sampson et al 2014*).
- A 2025 guideline from the European Academy of Allergy and Clinical Immunology provides recommendations for the management of IgE-mediated food allergy. In children ≥ 1 year of age and adults with IgE-mediated food allergy, omalizumab is suggested to achieve desensitization (*Santos et al 2025*).

Safety Summary

- All the antiasthmatic monoclonal antibodies are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients of the formulation.
- Abrupt discontinuation of systemic, topical, or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

Cinqair (reslizumab)

- Boxed warning: Anaphylaxis has been observed with reslizumab infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of reslizumab. Patients should be observed for an appropriate period of time after reslizumab administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg reslizumab had ≥ 1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in reslizumab-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with reslizumab. If patients become infected while receiving reslizumab and do not respond to anti-helminth treatment, reslizumab should be discontinued until the parasitic infection resolves.
- The most common adverse event (≥ 2%) included oropharyngeal pain.

Dupixent (dupilumab)

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, erythema multiforme, serum sickness, angioedema, urticaria, and rash) have occurred after administration of dupilumab. Dupilumab should be discontinued in the event of a hypersensitivity reaction.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of OCS should be monitored.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of dupilumab therapy; if appropriate, corticosteroid treatment should be reduced gradually.
  - New or worsening eye symptoms (conjunctivitis, keratitis and blepharitis) should be evaluated. Visual disturbances associated with conjunctivitis, keratitis or blepharitis have been reported (except in patients taking dupilumab for EoE) and may require discontinuation and/or surgical intervention.

- New onset symptoms associated with psoriasis or psoriatic arthritis (eg, arthralgias) should be reported to healthcare provider. If symptoms persist or worsen, consider evaluation or discontinuation.
- Dupilumab should not be used to treat acute symptoms or acute exacerbations of asthma or COPD.
- Pre-existing helminth infections should be treated before therapy with dupilumab. If a patient becomes infected while receiving dupilumab and does not respond to anti-helminth treatment, dupilumab should be discontinued until the parasitic infection resolves.
- Use of live vaccines should be avoided.

• Adverse reactions:
- Asthma: the most common adverse events included injection site reactions, oropharyngeal pain, and eosinophilia.
  - The safety profile in patients 6 to 11 years of age was similar to the safety profile from studies in adults and adolescents with the addition of helminth infections. Adverse reactions of helminth infections were reported in pediatric patients (5 cases of *enterobiasis* and 1 case of *ascariasis*) who participated in clinical studies.
- COPD: the most common adverse events included viral infection, headache, nasopharyngitis, back pain, diarrhea, arthralgia, urinary tract infection, local administration reactions, rhinitis, eosinophilia, toothache, and gastritis.
- CRSwNP: the most common adverse events included injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.
- EoE: the most common adverse events included injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections.

Exdensur (depemokimab-ulaa)

• Key warnings and precautions:
- Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of depemokimab-ulaa. Depemokimab-ulaa should be discontinued in the event of a hypersensitivity reaction.
- Depemokimab-ulaa should not be used to treat acute asthma symptoms or asthma exacerbations.
- Pre-existing helminth infections should be treated before therapy with depemokimab-ulaa. If patients become infected while receiving depemokimab-ulaa and do not respond to anti-helminth treatment, depemokimab-ulaa should be discontinued until the parasitic infection resolves.
- Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of depemokimab-ulaa therapy for asthma; if appropriate, corticosteroid treatment should be reduced gradually.
- The most common adverse events (≥ 4%) included upper respiratory tract infection, allergic rhinitis, influenza, arthralgia, and pharyngitis.

Fasenra (benralizumab)

• Key warnings and precautions:
- Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of benralizumab. Benralizumab should be discontinued in the event of a hypersensitivity reaction.
- Pre-existing helminth infections should be treated before therapy with benralizumab. If patients become infected while receiving benralizumab and do not respond to anti-helminth treatment, benralizumab should be discontinued until the parasitic infection resolves.
- Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of benralizumab for asthma; if appropriate, corticosteroid treatment should be reduced gradually.

• The most common adverse events (≥ 5%) included:
- Asthma: headache and pharyngitis.
- EGPA: headache.
- HES: headache, hypersensitivity reactions and influenza like illness.

Nucala (mepolizumab)

• Key warnings and precautions:
- Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of mepolizumab.
- Herpes zoster infections have occurred in patients receiving mepolizumab. Vaccination should be considered if clinically appropriate.

- Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of mepolizumab therapy; if appropriate, corticosteroid treatment should be reduced gradually.
- Pre-existing helminth infections should be treated before therapy with mepolizumab. If patients become infected while receiving mepolizumab and do not respond to anti-helminth treatment, mepolizumab should be discontinued until the parasitic infection resolves.
- Mepolizumab should not be used to treat acute symptoms or acute exacerbations of asthma or COPD.

- The most common adverse events (≥ 5%) included headache, injection site reaction, back pain, and fatigue. Mouth/throat pain and joint pain have been reported in patients with CRSwNP. Diarrhea and cough have been reported in patients with COPD.

Xolair (omalizumab)

- Boxed warning: Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Initiate omalizumab in a healthcare setting and closely observe patients for an appropriate period of time after administration. Health care providers administering omalizumab should be prepared to manage anaphylaxis that can be life-threatening. Selection of patients for self-administration of omalizumab should be based on criteria to mitigate risk from anaphylaxis.
  - Patients with a prior history of anaphylactic reactions to foods, medications, or other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment. Approximately 60 to 70% of anaphylaxis cases have been reported to occur within the first 3 doses.
- Key warnings and precautions:
  - Malignant neoplasms were observed at a higher rate in omalizumab-treated patients (0.5%) compared to control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in omalizumab- and non- omalizumab-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - Rarely, patients on therapy with omalizumab may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of OCS therapy.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of omalizumab therapy for asthma or nasal polyps.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy; omalizumab should be stopped for signs and symptoms of serum sickness.
  - Serum IgE levels increase following omalizumab therapy and may persist for up to 1 year following discontinuation of therapy.
  - Omalizumab should not be used for emergency treatment of allergic reactions, including anaphylaxis.
- Adverse events:
  - Asthma: In patients ≥ 12 years of age, commonly observed adverse events in clinical studies (≥ 1% in omalizumab-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse events were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
    - Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non- omalizumab-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - CSU: Adverse reactions from 3 placebo-controlled, multiple-dose CSU studies that occurred in ≥ 2% of patients receiving omalizumab and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
  - CRSwNP: The most common adverse events (≥ 3% of patients) in clinical studies included headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness.

Tezspire (tezepelumab-ekko)

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, rash, allergic conjunctivitis) have occurred after administration of tezepelumab-ekko, either within hours after administration or after days.
  - Tezepelumab-ekko should not be used to treat acute asthma symptoms or asthma exacerbations.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of tezepelumab-ekko therapy for asthma; if appropriate, corticosteroid treatment should be reduced gradually.
  - Pre-existing helminth infections should be treated prior to therapy with tezepelumab-ekko. If patients become infected while receiving tezepelumab-ekko and do not respond to anti-helminth treatment, tezepelumab-ekko should be discontinued until the parasitic infection resolves.
  - Use of live attenuated vaccines should be avoided in patients receiving tezepelumab-ekko.
- Adverse reactions:
  - In patients ≥ 12 years of age, commonly observed adverse events in clinical studies (≥ 3%) were pharyngitis, arthralgia, and back pain.

Dosing and Administration

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	Single-use vials	IV	Every 4 weeks	• Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Reslizumab should be administered by a healthcare professional by IV infusion over 20 to 50 minutes.
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Asthma: In adults and pediatric patients (6 to 11 years of age) weighing ≥ 30 kg, every other week; in pediatric patients (6 to 11 years of age) weighing 15 to < 30 kg, every 4 weeks Allergic fungal rhinosinusitis: Every other week; dosage is weight based in children 6 to 17 years old. COPD: Every other week CSU: Every other week; dosage is weight based in children 2 to 5 years old. CRSwNP: Every other week EoE: Weight-based dosing in adults and	• Safety and efficacy in patients < 1 year of age (EoE), < 6 years of age (asthma, allergic fungal rhinosinusitis), < 2 years of age (CSU), and < 18 years of age (bullous pemphigoid, CRSwNP) have not been established. • Dupilumab may be administered by a healthcare professional or self-administered via pre-filled syringe or pen.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			children ≥ 1 year of age: 15 to < 30 kg, 200 mg every other week; 30 to < 40 kg, 300 mg every other week; ≥ 40 kg, 300 mg every week	
Exdensur (depemokimab-ulaa)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Asthma: Every 6 months	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Should be administered by a healthcare professional
Fasenra (benralizumab)	Single-dose pre-filled syringe, single-dose pre-filled pen (autoinjector)	SC	Asthma: Every 4 weeks for first 3 doses, followed by every 8 weeks EGPA: Every 4 weeks HES: Every 4 weeks	• Safety and efficacy in pediatric patients < 6 years for asthma, < 12 for HES, and < 18 for EGPA have not been established • Benralizumab may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	Single-dose vial for reconstitution, single-dose pre-filled pen (autoinjector), single-dose prefilled syringe	SC	Asthma: Every 4 weeks EGPA: Every 4 weeks HES: Every 4 weeks CRSwNP: Every 4 weeks COPD: Every 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age (asthma), < 18 years of age (COPD and EGPA), < 12 years of age (HES) of age, and < 18 years of age (CRSwNP) have not been established. • Mepolizumab may be administered by a healthcare professional or self-administered via an autoinjector or pre-filled syringe. • The 40 mg/0.4 mL prefilled syringe for patients 6 to 11 years of age should be administered by a healthcare professional or a patient caregiver.
Xolair (omalizumab) and Omlyclo (omalizumab-igec)	Single-dose vial for reconstitution; single-dose prefilled syringe or autoinjector	SC	Allergic asthma: Every 2 or 4 weeks CSU: Every 4 weeks CRSwNP: Every 2 or 4 weeks IgE-mediated food allergy: Every 2 or 4 weeks	• Safety and efficacy in patients < 1 year of age (IgE-mediated food allergy); < 6 years of age (asthma), < 12 years of age (CSU), < 18 years of age (CRSwNP) have not been established. • Omalizumab should be initiated in a healthcare setting: once therapy has been safely established, omalizumab may be administered by a healthcare professional or self-administered via a pre-filled syringe. • For allergic asthma, CRSwNP, and IgE-mediated food allergy, the dose and frequency are determined by serum total IgE level (measured before the start of treatment) and body weight; dosage determination should be based

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				on the primary diagnosis for which omalizumab is being prescribed. • Doses should be adjusted for significant changes in bodyweight. • Dosing in CSU is not dependent on serum IgE level or body weight.
Tezspire (tezepelumab-ekko)	Single-dose glass vial, single-dose prefilled syringe, single-dose prefilled pen	SC	Asthma: Every 4 weeks CRSwNP: Every 4 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • The tezepelumab-ekko vial and prefilled syringe are intended for administration by a healthcare professional. The prefilled pen may be self-administered after proper training.

See the current prescribing information for full details.

Conclusion

- The respiratory and allergy biologics include the IgE inhibitor Xolair (omalizumab) and its biosimilar Omlyclo (omalizumab-igec); the IL-4 inhibitor Dupixent (dupilumab); the IL-5 antagonists Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Exdensur (depemokimab-ulaa); and the TSLP blocker Tezspire (tezepelumab-ekko).
  - These agents are a mainstay of treatment for severe asthma; in addition, various agents in the class are indicated for use in EGPA, CSU, COPD, CRSwNP, allergic fungal rhinosinusitis, HES, EoE, and IgE-mediated food allergy.
- Omalizumab and its biosimilar omalizumab-igec are humanized monoclonal antibodies FDA-approved for patients ≥ 6 years of age with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients.
  - Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that omalizumab may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
  - Omalizumab carries a boxed warning due to the risk of anaphylaxis, and thus must be initiated in a healthcare setting. Once therapy has been safely established, select patients may be able to self-administer omalizumab using a pre-filled syringe.
  - Although omalizumab therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving omalizumab compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
  - Asthma guidelines recommend omalizumab and omalizumab-igec as add-on therapy in patients ≥ 6 years of age with severe allergic asthma (*GINA 2026*).
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- Omalizumab, its biosimilar omalizumab-igec and dupilumab are approved for the treatment of CSU in patients who remain symptomatic despite H1-antihistamine treatment; omalizumab is approved in patients ≥ 6 years of age; dupilumab is approve in patients ≥ 2 years of age.
  - Two randomized, placebo-controlled trials demonstrated omalizumab's efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12.
  - In the LIBERTY-CSU CUPID trials, dupilumab significantly improved UAS7 and ISS7 vs placebo at week 24 in omalizumab-naive patients with CSU inadequately controlled with H1-antihistamines in Studies A and C, with pooled

data supporting greater improvements for both endpoints; in Study B, dupilumab significantly improved UAS7 but showed only a numerical ISS7 trend in omalizumab-incomplete responders or intolerant patients.
  - A 2026 international guideline for the treatment of urticaria recommends omalizumab (preferred), dupilimab or remibrutinib as the next add on treatment in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines; biologic agents may be switched in cases of inadequate control (*Zuberbier et al 2026*).
  - In patients with CSU, omalizumab is administered at 150 or 300 mg SC every 4 weeks. Dupilumab is administered SC every 2 weeks.
- Omalizumab and its biosimilar omalizumab-igec are approved as add-on maintenance treatment for CRSwNP in adult patients with an inadequate response to nasal corticosteroids, based on results from 2 identical, randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies of omalizumab (POLYP 1 and POLYP 2) (*Gevaert et al 2020*). Results from both studies revealed that omalizumab was associated with a significantly greater improvement from baseline at week 24 in NPS and weekly average NCS as compared to placebo. Adverse events were similar between groups.
- Omalizumab and its biosimilar omalizumab-igec were approved for IgE-mediated food allergy in patients ≥ 1 year of age based on the results of a randomized, multicenter, double-blind, placebo-controlled trial of omalizumab in patients with allergies to peanut and ≥ 2 other foods (*Wood et al 2024)*. Results demonstrated a significantly higher response with omalizumab vs placebo for the primary outcome (percentage of patients able to tolerate a single dose of ≥ 600 mg of peanut protein without experiencing dose-limiting symptoms). A 2025 AAAAI guideline provides several statements regarding the use of omalizumab in patients with food allergy, and a 2025 European guideline suggests omalizumab to achieve desensitization in children ≥ 1 year of age and adults with IgE-mediated food allergy (*Anagnostou et al 2025, Santos et al 2025)*. A biosimilar for omalizumab, omalizumab-igec, carries the same FDA approvals as omalizumab and is designated as interchangeable with omalizumab.
- Dupilumab is an IL-4/IL-13 antagonist approved for the treatment of patients ≥ 6 years of age with moderate-to-severe asthma of the eosinophilic type or dependent on OCS, patients ≥ 2 years of age with CSU inadequately controlled with H1-antihistamine treatment, patients ≥ 1 year of age and weighing ≥ 15 kg with EoE, and as an add-on treatment in patients ≥ 12 years of age with inadequately controlled CRSwNP and as add-on maintenance treatment in adults with inadequately controlled COPD.
  - According to GINA guidelines, the use of dupilumab for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking OCS (*GINA 2026*).
- Dupilumab was approved for CRSwNP after the publication of several guidelines, although some acknowledged the potential role for biologic therapies (*Orlandi et al 2021, Peters et al 2014, Rank et al 2023).*
  - The updated 2023 EPOS/EUFOREA expert consensus publication focused on the use of biologics for CRSwNP, biologics were indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of Type 2 inflammation (biological biomarkers), need for systemic corticosteroids (≥ 2 courses per year or > 3 months of low dose steroids) or contraindications to systemic corticosteroids, significant quality-of-life impairment; significant loss of smell, and diagnosis of comorbid asthma (*Fokkens et al 2023*).
    - Dupilumab is approved for allergic fungal rhinosinusitis (a subtype of CRSwNP) in adults and pediatric patients ≥ 6 years of age who have a history of sino-nasal surgery; The 2020 EPOS recommends 3 principles for the treatment of fungal rhinosinusitis including systemic antifungal therapy, surgical debridement and reduced immune suppression when possible (*Fokkens et al 2020).*
- Dupilumab is guideline-recommended for EoE for patients ≥ 1 year of age who are nonresponsive to proton pump inhibitor therapy (*Dellon et al 2025*).
- Dupilumab and mepolizumab are approved for the add-on treatment of COPD and an eosinophil phenotype; the 2026 GOLD guidelines recommend dupilumab (if chronic bronchitis) or mepolizumab (with and without chronic bronchitis) in patients with eosinophil counts of ≥ 300 cells/µL who continue to experience exacerbations while on triple therapy (LAMA + LABA + ICS) (*GOLD 2026*).
- Reslizumab, benralizumab, mepolizumab, and depemokimab-ulaa are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Jackson et al 2024, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*).
  - The mechanism of action of benralizumab is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas reslizumab, mepolizumab, and depemokimab-ulaa bind to the IL-5 cytokine. All these agents provide

a more targeted treatment option for patients with severe asthma and should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS (*GINA 2026*).

- Mepolizumab and benralizumab are approved for the treatment of adult patients with EGPA. In a head-to-head trial, benralizumab was shown to be noninferior to mepolizumab in adult patients with relapsing or refractory disease (*Wechsler et al 2024b)*. A joint guideline from the American College of Rheumatology and Vasculitis Foundation provides recommendations for the place in therapy for mepolizumab in the management of EGPA based on the severity of disease and prior treatments (*Chung et al 2021*). A 2023 European guideline recommends mepolizumab in combination with glucocorticoids for patients with severe or non-severe EGPA, while benralizumab is considered only for those with disease refractory to mepolizumab, as supporting evidence for benralizumab in EGPA emerged after the guideline publication (*Emmi et al 2023).*
- Mepolizumab is also approved as an add-on treatment in adults with inadequately controlled COPD with eosinophilic phenotype and CRSwNP, and in patients ≥ 12 years of age with HES. The WHO states that mepolizumab is FDA-approved for idiopathic HES, but other biologic agents are considered investigational (*Shomali and Gotlib 2024).* The aforementioned 2023 EUFOREA expert consensus provides recommendations on the use of biologics for CRSwNP (*Fokkens et al 2023)*.
- Tezepelumab-ekko, a human monoclonal antibody, is a TSLP blocker approved for severe, uncontrolled asthma in patients ≥ 12 years of age. Efficacy of tezepelumab-ekko was shown in the NAVIGATOR trial, with significant reductions in asthma exacerbations compared to placebo. While approximately one-half of enrolled patients had eosinophil counts of ≥ 300 cells/µL, efficacy was seen in patients with low and high eosinophil counts *(Menzies-Gow et al 2021).* The GINA guideline recommends add-on therapy with tezepelumab-ekko in patients ≥ 12 years of age with severe asthma (*GINA 2026*). Tezepelumab-ekko is also approved for CRSwNP in patients ≥ 12 years of age; the 2023 EUFOREA expert consensus provides recommendations on the use of biologics for CRSwNP (*Fokkens et al 2023)*.
- There are no head-to-head trials comparing reslizumab, benralizumab, dupilumab, mepolizumab, or tezepelumab-ekko for the treatment of asthma.
  - A systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.15 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (42/2026) than placebo (11/1227) due to adverse events (*Farne et al 2022*).
  - One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab; other analyses found that dupilumab, mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Ando et al 2020, Edris et al 2019, Iftikhar et al 2018, Ramonell et al 2020*).
  - Treatment rankings in a 2020 network meta-analysis estimate that dupilumab is most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab (*Ramonell et al 2020*).
  - A systematic review and network meta-analysis of 64 trials in 26,630 patients with moderate, moderate-to-severe, or severe asthma determined that treatment with benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, and tezepelumab-ekko probably reduces exacerbations vs placebo in patients with eosinophilic asthma (blood eosinophil levels ≥ 300 cells/µL; moderate to high certainty). Overall, dupilumab and tezepelumab-ekko were the most effective for reducing exacerbations in patients with eosinophilic asthma and improving lung function compared to other agents (both high certainty). Of note, the authors concluded that in patients with low eosinophils, biologics likely do not improve asthma outcomes (*Pitre et al 2023*).
- Compared to dupilumab, mepolizumab, benralizumab, and depemokimab-ulaa, reslizumab has various limitations for use in eosinophilic asthma, including an indication for patients ≥ 18 years of age (vs ≥ 6 years of age with mepolizumab, dupilumab, and benralizumab and ≥ 12 years of age for tezepelumab-ekko and depemokimab-ulaa), IV administration (vs SC administration with dupilumab, mepolizumab, benralizumab, tezepelumab-ekko, and depemokimab-ulaa), and a boxed warning for anaphylaxis.
- SC autoinjector formulations are available for benralizumab, mepolizumab, and omalizumab; single-dose prefilled syringes and/or pens are available for dupilumab, benralizumab, mepolizumab, omalizumab, omalizumab-igec, tezepelumab-ekko, and depemokimab-ulaa.

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Therapeutic Class Overview

Antiemetics

Introduction

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (*Longstreth 2025[b]*).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (*Hesketh 2024[a], Hesketh 2024[b]*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth 2025[b]*).
- Three distinct types of CINV have been defined, including (*Hesketh 2024[a], Hesketh 2024[b]*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours.
  - Delayed emesis, occurring beyond 24 hours after chemotherapy.
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy.
- Approximately one-third of surgical patients have n/v or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (*Longstreth 2025[b]*).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (*Jordan et al 2024)*.
- Nausea with or without vomiting is common in early pregnancy. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (*American College of Obstetrics and Gynecologists [ACOG] 2018, Smith et al 2025*).
- Nausea is common in motion sickness and symptoms may also include sweating, malaise, vomiting, and headache. Motion sickness is thought to result from incongruent vestibular, visual, and somatosensory sensory cues *(Priesol 2026)*.
- The mechanism of action differs for various antiemetic agents:
  - The 5-hydroxytryptamine (5-HT3, or serotonin) antagonists cause the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the CNS. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (*Mannix 2006*).
  - The substance P/neurokinin 1 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
  - Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Dronabinol may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
  - The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown (*Diclegis prescribing information 2025, Bonjesta prescribing information 2025*).
  - The dopamine receptor antagonist prochlorperazine (a phenothiazine) primarily works by blocking D_2-dopamine receptors in the postrema area of the midbrain; trimethobenzamide (a benzamide) works by blocking central and peripheral D_2-dopamine receptors, and exerts weak blockade of 5-HT3 at higher doses used for vomiting. The dopamine receptor antagonists also have M1-muscarinic and H1-histamine antagonizing effects. Scopolamine, an anticholinergic drug, is an M1-muscarinic receptor antagonist. Antihistamines are primarily used for motion sickness *(Longstreth et al 2025[a])*.

- The 5-HT3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The D_2 antagonist Barhemsys (amisulpride) is FDA-approved for treatment and prevention of PONV.
- The substance P/NK1 receptor antagonists (aprepitant, fosaprepitant, and rolapitant) are FDA-approved for the prevention of CINV; aprepitant is also approved for the prevention of PONV. Tradipitant is also a substance P/NK1 receptor antagonist, but it is only approved for the treatment of motion sickness.
- The combination product, Akynzeo, contains palonosetron (a 5-HT3 receptor antagonist) and a substance P/NK1 receptor antagonist (netupitant in the oral formulation and fosnetupitant in the injectable formulation). This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- Diclegis and Bonjesta are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. Diclegis and Bonjesta are indicated for the initial treatment of NVP in women who do not respond to conservative management.
  - The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin. However, this product was removed from the market in 1983 due to lawsuits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication.
- Prescription meclizine is FDA-approved for vertigo; however, over-the-counter (OTC) meclizine products are used for n/v and dizziness associated with motion sickness. Transdermal scopolamine is FDA-approved for n/v associated with motion sickness and for PONV. Prochlorperazine is FDA-approved for treatment of severe n/v, promethazine is approved for motion sickness and n/v associated with certain anesthesia and surgery, and trimethobenzamide is approved for PONV and nausea related to gastroenteritis.
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV, PONV, or n/v associated with other conditions such as pregnancy and motion sickness, with a focus on CINV. Other agents including glucocorticoids may also be effective antiemetics; however, they have been excluded from this review. Although certain agents are FDA-approved for other indications, only those related to n/v are included in this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Dopamine Antagonist; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)[a]
Akynzeo (palonosetron/netupitant) capsule	-
Akynzeo (palonosetron/fosnetupitant) IV solution	-
Aponvie (aprepitant) IV emulsion	-
Barhemsys (amisulpride) IV solution	-
Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	-
Cinvanti (aprepitant) IV emulsion	-
Compro (prochlorperazine) rectal suppository	✔
Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	✔
Emend (aprepitant) oral suspension	-
Emend (aprepitant) capsule, combination pack	✔
Emend (fosaprepitant) IV solution [b]	✔
Focinvez (fosaprepitant) IV solution [b]	-
granisetron injection, tablets	✔
Marinol (dronabinol) capsule	✔
meclizine tablet, chewable tablet, ODT	✔ [c]
Nereus (tradipitant) capsule[d]	-

Data as of January 22, 2026 HJI-U/HJ-U/DKB

Drug	Alternative Available (same molecular entity)[a]
ondansetron injection	✔
ondansetron ODT, tablet	✔
ondansetron oral solution	✔
Phenergan (promethazine) injection	✔
Posfrea (palonosetron) IV solution	✔
prochlorperazine injection, tablet	✔
promethazine tablet, syrup, oral solution	✔
Promethegan (promethazine) rectal suppository	✔
Sancuso (granisetron) transdermal patch	-
Sustol (granisetron) extended-release subcutaneous injection	-
Syndros (dronabinol) oral solution	-
trimethobenzamide capsule	✔
Tigan (trimethobenzamide) injection	-
Transderm Scop (scopolamine) transdermal film	✔
Varubi (rolapitant) tablet	-

Abbreviations: IV = intravenous, ODT = orally disintegrating tablet, OTC = over-the-counter.
[a] For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
[b] Focinvez (fosaprepitant) is a ready to use IV formulation; Emend (fosaprepitant) requires reconstitution.
[c] The 50 mg tablet is Rx only; 12.5 mg and 25 mg strengths are available OTC.
[d] Approved; launch expected in coming months.

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

Indications

Table 2. Food and Drug Administration Approved Indications – 5HT3 Receptor Antagonist

Indication	Granisetron	Ondansetron	Palonosetron
CINV			
Prevention of acute n/v associated with initial and repeat courses of HEC in adults			✔
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years			✔
Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m^2		✔ (tablet, ODT, oral solution)	
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin	✔ (injection, tablets)		
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age		✔ (injection)	
prevention of acute and delayed n/v associated with initial and repeat courses in adults taking MEC			✔
Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days	✔ (TD)		

Indication	Granisetron	Ondansetron	Palonosetron
CINV			
Prevention of n/v associated with initial and repeat courses of MEC		✔ (tablet, ODT, oral solution)	
Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens in adults	✔ [a] (ER injection)		
PONV			
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated[c]			✔
Prevention of PONV in adults		✔ (tablet, ODT, oral solution)	
Prevention of PONV[c]		✔ (injection[b])	
RT			
Prevention of n/v associated with RT, including TBI and fractionated abdominal RT	✔ (tablets)		
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose fraction to the abdomen, or daily fractions to the abdomen		✔ (tablet, ODT, oral solution)	

Abbreviations: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, ER = extended-release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch.
[a] When used in combination with other antiemetic agents.
[b] For patients who do not receive prophylactic ondansetron injection and experience n/v postoperatively, ondansetron injection may be given to prevent further episodes.
[c] As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur postoperatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.

Table 3. Food and Drug Administration Approved Indications – D_2 Antagonist

Indication	amisulpride
Prevention and treatment of PONV in adults; for prevention may use either alone or in combination with another antiemetic	✔

Abbreviations: PONV = postoperative nausea and vomiting.

Table 4. Food and Drug Administration Approved Indications – Substance P/NK1 Receptor Antagonists

Indication	aprepitant	fosaprepitant	rolapitant	tradipitant
CINV				
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC including high-dose cisplatin in patients ≥ 6 months of age	✔ [a] (oral suspension)	✔ [a]		
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin as a single dose regimen, in adults	✔ [a] (Cinvanti IV emulsion)	✔		

Indication	aprepitant	fosaprepitant	rolapitant	tradipitant
CINV				
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in patients ≥ 12 years of age	✔ [a] (capsule)			
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC			✔ [a]	
Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age	✔ (oral suspension)			
Prevention of delayed n/v associated with initial and repeat courses of MEC in patients ≥ 6 months of age		✔ [a]		
Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age	✔ [a] (capsule)			
Prevention of n/v associated with initial and repeat courses of MEC as a 3-day regimen, in adults	✔ [a] (Cinvanti IV emulsion)			
Prevention of delayed n/v associated with initial and repeat courses of MEC as a single dose regimen, in adults	✔ [a] (Cinvanti IV emulsion)			
PONV				
Prevention of PONV in adults	✔ (generic aprepitant and Aponvie IV emulsion)			
Other				
Prevention of vomiting induced by motion in adults				✔

Abbreviations: CINV = chemotherapy induced nausea and vomiting, HEC = highly emetogenic cancer chemotherapy, IV = intravenous , MEC = moderately emetogenic cancer chemotherapy, NK1 = neurokinin 1, n/v = nausea/vomiting, PONV = postoperative nausea and vomiting.
[a] When used in combination with other antiemetic agents.

Table 5. Food and Drug Administration Approved Indications – THC Derivatives

Indication	Dronabinol
Anorexia associated with weight loss in adults with AIDS	✔
n/v associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments	✔

Abbreviations: AIDS = acquired immunodeficiency syndrome, n/v = nausea and vomiting, THC = tetrahydrocannabinol.

Table 6. Food and Drug Administration Approved Indications – Combination Products

Indication	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC	✔ (oral)	
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC in combination with dexamethasone	✔ [a] (IV)	
Treatment of n/v of pregnancy in women who do not respond to conservative management		✔

Abbreviations: HEC = highly emetogenic cancer chemotherapy, IV = intravenous, n/v = nausea/vomiting.
[a]Not studied for prevention of n/v associated with anthracycline plus cyclophosphamide chemotherapy.

Table 7. Food and Drug Administration Approved Indications – Other Agents

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
PONV					
Treatment of PONV					✔ [a] (capsules, injection)
Prevention and control of n/v associated with certain types of anesthesia and surgery		✔ [b] (injection, suppository, solution, syrup, tablet)			
Antiemetic therapy in postoperative patients		✔ [b] (suppository, solution, syrup, tablet)			
Prevention of PONV associated with recovery from anesthesia and/or opiate analgesia and surgery				✔	
Motion Sickness					
Prevents and treats n/v or dizziness associated with motion sickness	✔ [c]				
Prevention of n/v associated with motion sickness				✔	
Active treatment of motion sickness		✔ [b] (injection)			
Active and prophylactic treatment of motion sickness		✔ [b] (suppository, solution, syrup, tablet)			
Nausea associated with gastroenteritis					

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
Nausea associated with gastroenteritis					✔ [a] (capsules, injection)
Severe nausea and vomiting					
Control of severe n/v			✔ [d] (tablets, injection, suppository		

Abbreviations: CNS = central nervous system, FDA = Food and Drug Administration, n/v = nausea and vomiting, OTC = over the counter, PONV = postoperative nausea and vomiting.
[a]Tigan is not recommended to use in pediatric patients due to risk of extrapyramidal signs and symptoms, other CNS effects, and risk of exacerbating underlying disease in patients with Reye's syndrome or other hepatic impairment.
[b] Promethazine is also FDA-approved for multiple indications including those related to allergic conditions, surgical analgesia, and sedation.
[c] Meclizine is FDA-approved for treatment of vertigo; however, OTC meclizine prevents and treats nausea, vomiting or dizziness associated with motion sickness.
[d]Prochlorperazine tablets are also FDA-approved for treatment of schizophrenia and anxiety; prochlorperazine injection is also approved for treatment of schizophrenia.

(Prescribing information: Akynzeo 2023, Aponvie 2025, Barhemsys 2025, Bonjesta 2025, Cinvanti 2025, Compro 2024, Diclegis 2025, Emend capsules and oral suspension 2024, Focinvez 2025, fosaprepitant dimeglumine for injection 2024, granisetron injection 2022, granisetron tablets 2024, Marinol 2023, meclizine chewable tablets 2024, meclizine tablets 2025, meclizine tablets ODT 2025, Micromedex 2026, Nereus 2025, ondansetron injection 2025, ondansetron ODT tablets 2025, ondansetron solution 2025, ondansetron tablets 2025, Posfrea 2025, prochlorperazine injection 2023, prochlorperazine tablets 2024, promethazine injection 2025, promethazine oral solution 2023, promethazine syrup 2025, promethazine tablets 2024, Promethegan suppository 2023, Sancuso 2024, Sustol 2025, Syndros 2024, Tigan injection 2025, Transderm Scop 2025, trimethobenzamide capsules 2024, Varubi 2020)

- 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

Anorexia in patients with acquired immunodeficiency syndrome (AIDS)

- A 2015 meta-analysis (MA) (N = 6462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in human immunodeficiency virus (HIV)/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), and a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials). A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

CINV

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone (no longer available), are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Granisetron and ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of one over another, but this has not been a consistently proven outcome (*Dabbous et al 2010, del Giglio et al 2000, Dempsey et al 2004, Gan et al 2005, Jaing et al 2004, Kalaycio et al 1998, Lacerda et al 2000, Orchard et al 1999, White et al 2006*).
- Sancuso (granisetron) transdermal patch was noninferior to orally administered granisetron for CINV in a randomized trial (*Boccia et al 2011*). However, an MA of 3 studies found that oral granisetron significantly reduced the odds of CINV compared with transdermal granisetron *(Chua et al 2020)*.
- Palonosetron was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (*Aapro et al 2005, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gralla et al 2003, Kaushal et al 2010, Likun et al 2011, Massa et al 2009, Suzuki et al 2016, Chow et al 2018, Matsumoto et al 2020, Hsu et al 2021*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving highly emetogenic cancer chemotherapy (HEC) or moderately emetogenic cancer chemotherapy (MEC) (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*). In the modified intention-to-treat population, both granisetron extended-release (ER) 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was noninferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs and are superior to placebo (*del Giglio et al 2000, George et al 2009, Singhal et al 2012, Tang et al 2012*). A 2016 MA comparing ondansetron to other 5-HT3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron (no longer available) for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (*Simino et al 2016*).
- A 2021 Cochrane review found, through a network MA including 12 treatment combinations with substance P/NK1 and 5-HT3 receptor antagonists (N = 21,642; 39 RCTs) in patients receiving HEC, in the overall phase (0 to 120 hours), more participants treated with fosaprepitant plus palonosetron experienced no nausea than participants treated with fosaprepitant plus granisetron (relative risk [RR], 1.43; 95% CI, 1.10 to 1.85), aprepitant plus granisetron (RR, 1.46; 95% CI, 1.12 to 1.90), netupitant plus palonosetron (RR, 1.52; 95% CI, 1.13 to 2.05), fosaprepitant plus ondansetron (RR, 1.62; 95% CI, 1.20 to 2.19), and aprepitant plus ondansetron (RR, 1.68; 95% CI, 1.23 to 2.30). In patients receiving MEC, aprepitant plus palonosetron showed higher complete control of nausea in the overall phase than palonosetron (RR, 1.68; 95% CI, 1.09 to 2.58) and ondansetron (RR, 1.91; 95% CI, 1.24 to 2.95). All treatment combinations included in the trial showed benefit in improving nausea compared to placebo. No other differences between treatment combinations were observed (*Piechotta et al 2021)*.
- A 2016 Cochrane review found that 5-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).
- A randomized, DB, noninferiority study comparing single-dose palonosetron 20 mcg/kg to multi-dose ondansetron 150 mcg/kg x 3 doses for the prevention of CINV in pediatric patients, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was noninferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*). A randomized, DB study in pediatric patients, aged 0 to 18 years, receiving HEC found that complete response rates were not significantly different during the acute phase between palonosetron 5 mcg/kg, 10 mcg/kg, and ondansetron 150 mcg/kg x 3 doses *(Tan et al 2018).* Palonosetron 10 mcg/kg was superior to ondansetron and palonosetron 5 mcg/kg in the delayed phase. In a randomized, open-label study, palonosetron was found to be noninferior and cost-effective in comparison to ondansetron for the prevention of acute CINV in children (2 to 18 years of age) with cancer (*Jain et al 2018*).

- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron intravenous (IV) was not more efficacious than granisetron IV at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (*Suzuki et al 2016*).
- A phase 3, randomized, DB trial compared oral with IV palonosetron in cancer patients receiving MEC *(Cui et al 2020)*. The primary endpoint, complete response rate in the acute phase, was not significantly different between treatment arms, and the authors concluded that oral palonosetron was noninferior to IV palonosetron.
- A MC, DB, RCT evaluated dexamethasone compared to aprepitant in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 receptor antagonists and/or dexamethasone (*Herrington et al 2008, Rapoport et al 2010, Yeo et al 2009, Herrstedt et al 2005, Warr et al 2005, Gralla et al 2005, De Wit et al 2004, Poli-Bigelli et al 2003, Hesketh et al 2003, Hesketh et al 2012, Martin et al 2003, Gore et al 2009, Jordan et al 2009, Grunberg et al 2009*).
- Oral aprepitant- and IV fosaprepitant-based regimens were compared in a phase 3, randomized, DB trial for the prevention of CINV in patients treated with cisplatin-based chemotherapy *(Zhang et al 2020)*. The primary endpoint, complete response during the overall phase, was not significantly different between treatment arms, and the authors concluded that the IV fosaprepitant-based regimen was noninferior to the oral aprepitant-based regimen.
- A DB, placebo-controlled noninferiority trial demonstrated that omission of fosaprepitant from a standard 4-drug antiemetic regimen is not noninferior to including it for prevention of CINV in patients receiving HEC. The authors evaluated an antiemetic regimen containing a 5-HT3 receptor antagonist, dexamethasone, and olanzapine, with or without fosaprepitant. The proportion of patients who did not experience nausea for 5 days following chemotherapy was 7.4% lower in the 3-drug arm than the 4-drug arm, with an upper 95% CI bound exceeding the noninferiority margin of 10% (*Navari et al 2023*).
- In combination regimens with granisetron and dexamethasone, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 receptor antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be statistically superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). In a small pilot study, palonosetron/netupitant was no better than placebo in treating chronic nausea in patients with cancer (*Hui et al 2021*). A noninferiority, pragmatic trial (N = 211) compared a single-dose netupitant and palonosetron regimen to an aprepitant regimen and found higher complete response in patients receiving MEC (77.1% vs 57.8%; difference, 19.2%; 95% CI, 6.8% to 31.6%; p = 0.003) in an extended follow-up (0 to 144 hours), but no significant difference between treatments in an analysis of 0 to 120 hours follow-up (76.1% vs 63.1%; difference, 12.0%; 95% CI, -1.3% to 25.3%) (*Zelek et al 2023*).
- A MA of 7 studies compared fixed-dose combination palonosetron and netupitant + dexamethasone to aprepitant + dexamethasone-based regimens along with 5-HT3 receptor antagonists. The palonosetron and netupitant-based regimens were more effective in promoting complete response in the overall (RR, 1.15; 95% CI, 1.02 to 1.30) and delayed phases (RR, 1.20; 95% CI, 1.03 to 1.41) of chemotherapy *(Luo et al 2025)*.
- The efficacy of interventions to prevent acute CINV in adults and pediatrics was evaluated in a systematic review of 295 studies (25 of which were pediatric studies). In patients receiving HEC, the addition of olanzapine or addition of a substance P/NK1 receptor antagonist to a corticosteroid plus 5-HT3 receptor antagonist demonstrated complete control of n/v. Complete control of vomiting was achieved with palonosetron alone or with dexamethasone compared to granisetron or ondansetron alone or with dexamethasone. Complete control of vomiting was observed with the addition of dexamethasone to a 5-HT3 receptor antagonist in patients receiving MEC (*Patel et al 2022*).

- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- Trimethobenzamide has limited data supporting its use in CINV *(Hurley and Eshelman 1980).*
- In a large MA (13 dronabinol studies and 16 nabilone [no longer available] studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (RR, 1.38; 95% CI, 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).
- In another MA, authors concluded that regarding antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI, 0.47 to 0.96; NNT = 3.4). Nabilone (no longer available) was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; p = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).
- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone [no longer available] studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).
- A Bayesian network MA of 16 RCTs ranked the efficacy of antiemetic regimens in pediatric patients aged 0 to 18 years receiving MEC or HEC. The regimens included aprepitant or fosaprepitant + ondansetron ± dexamethasone, ondansetron or palonosetron ± dexamethasone, granisetron without dexamethasone, and metoclopramide + dexamethasone (*Walker et al 2024*).
  - Overall, out of the dexamethasone-containing regimens, aprepitant + ondansetron + dexamethasone had the highest probability of being ranked most effective for complete response in the acute and overall phases, partial response (1 or 2 vomiting episodes) in the acute, delayed, or overall phases, and for decreased food intake during any phase; fosaprepitant + ondansetron ± dexamethasone ranked second.
  - Ondansetron + dexamethasone had a high probability of being ranked the least effective compared to palonosetron ± dexamethasone or substance P/NK1 receptor antagonist regimens.
  - The remaining antiemetic regimens given with dexamethasone either lacked consistency across outcomes in their ranking position or did not have a high probability of being ranked in any position.

NVP

- In an MA on interventions for hyperemesis gravidarum, drowsiness, dizziness, and dystonia were experienced by more women treated with promethazine compared to metoclopramide in a single study. In another study, duration of hospital admission was not different between promethazine and ondansetron groups, but sedation was more common with promethazine *(Boelig et al 2016).*
- The FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on a DB, randomized, MC, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine HCl treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8-point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to a 3.9-point decrease in the placebo group (p = 0.006). For quality of life, there was also a 2.8-point mean increase from baseline in the score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to a 1.8-point decrease in the placebo group (p = 0.005) (*Koren et al 2010*).
  - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine succinate/pyridoxine HCl as compared to placebo. Based on the results of this analysis, doxylamine

succinate/pyridoxine HCl was not associated with an overall increase in rate of adverse effects as compared to placebo (*Koren et al 2015*).

PONV

- A Cochrane network MA of drugs for PONV concluded with high certainty that aprepitant (RR, 0.26; 95% CI, 0.18 to 0.38), granisetron (RR, 0.45; 95% CI, 0.38 to 0.54), and ondansetron (RR, 0.55; 95% CI, 0.51 to 0.60) effectively reduce vomiting, and with moderate certainty that fosaprepitant (RR, 0.06; 95% CI, 0.51 to 0.60) and droperidol (RR, 0.61, 95% CI, 0.54 to 0.69) also effectively reduce vomiting. Monotherapy with substance P/NK1 receptor antagonists was found to be as effective as other drugs used in combination, but in general, combination therapy was more effective than monotherapy in preventing vomiting. There was a lack of certainty in safety analyses with the individual drugs that were found to be effective, although the authors concluded that droperidol probably reduces headache compared to placebo (RR, 0.76; 95% CI, 0.67 to 0.86) (*Weibel et al 2020*).
- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).
- In prevention of PONV, amisulpride was studied in 2 randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2025, Gan et al 2017, Kranke et al 2018)*. In one study, patients received amisulpride monotherapy; in another, patients received amisulpride in combination with IV ondansetron, dexamethasone, or betamethasone. The primary endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.
- In treatment of PONV, amisulpride was studied in 2 randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2025, Candiotti et al 2019, Habib et al 2019)*. In one study, patients received no PONV prophylaxis; in another, patients received and failed PONV prophylaxis with an antiemetic of another class. The primary endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.

RINV

- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in this class that have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving total body irradiation (TBI), which is associated with high emetogenic risk. The study was only powered to demonstrate a difference between each active treatment group and historical controls. In the intention-to-treat population, significantly more patients given granisetron (33.3%) or ondansetron (26.7%) had no emetic episodes over 4 days, the primary efficacy endpoint, than those within the historical control group (0%) ($p < 0.01$) (*Spitzer et al 2000).*
- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR, 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

Motion sickness

- In a MA of 14 studies, scopolamine prevented symptoms of motion sickness more effectively than placebo (RR, 0.48; 95% CI, 0.32 to 0.73), but conclusions could not be made regarding its efficacy compared to antihistamines and calcium channel blockers *(Spinks and Wasiak 2011).*
- In a Cochrane review of antihistamines for motion sickness, 9 studies were evaluated in which motion sickness was induced naturally in 6 studies which evaluated first-generation agents only (dimenhydrinate and cinnarizine). Antihistamines were found to be 'probably' more effective at prevention of motion sickness compared to placebo (symptoms prevented: 25% placebo vs 40% antihistamines; RR, 1.81; 95% CI, 1.23 to 2.66) and more likely to cause sedation compared to placebo (RR, 1.51; 95% CI, 1.12 to 2.02). No difference was found in prevention of motion sickness between scopolamine and antihistamines (symptoms prevented: 81% scopolamine vs 71% antihistamines; RR, 0.89; 95% CI, 0.68 to 1.16). No studies reported results on treatment of existing symptoms (*Karrim et al 2022*).

- The efficacy of tradipitant for motion sickness was established in 3 clinical trials: Motion Syros, Motion Serifos (unpublished), and Motion Sifnos. Motion Syros investigated the efficacy of tradipitant (given 60 minutes before travel) in preventing motion sickness induced by boat travel in 365 individuals with a history of motion sickness on boat trips. The primary outcome (incidence of vomiting) was lower in patients who received tradipitant (85 mg or 170 mg) than placebo (19.5%, 18.3%, and 44.3%, respectively; $p < 0.0001$ for 85 mg and 170 mg vs placebo) *(Polymeropoulos et al 2025)*. Motion Sifnos was a placebo-controlled RCT in 126 individuals with a history of motion sickness (*Polymeropoulos et al 2020*). A single dose of tradipitant 170 mg or placebo was given about 60 minutes before the travel began, and the boat ride lasted 148 to 250 minutes. The incidence of vomiting was significantly less with tradipitant than placebo (17.5% vs 39.7%; $p = 0.0039$). All other symptom assessments were similar between groups.

Clinical Guidelines

- The 5-HT3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV. Treatment of CINV, RINV, or PONV generally involves the use of multiple agents that affect different receptor types (*Herrstedt et al 2023, Hesketh et al 2020, Gan et al 2020, Gupta et al 2016, National Comprehensive Cancer Network [NCCN] 2025, Patel et al 2022).*
- The 2020 Fourth Consensus guidelines from the American Society for Enhanced Recovery (ASER) and Society for Ambulatory Anesthesia for the prophylaxis and management of PONV provide the following recommendations (*Gan et al 2020*):
  - Identify and stratify the risk of PONV based on patient characteristics, history, surgery type, and analgesia used.
  - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
- The 2020 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2020*):
  - For the prevention of n/v induced by HEC, a 4-drug combination of a substance P/NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC, other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a substance P/NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended.
  - For children receiving HEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant or fosaprepitant cannot be given; palonosetron and aprepitant or fosaprepitant can be used if dexamethasone cannot be given.
  - For children receiving MEC, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended. If dexamethasone cannot be used, a 2-drug combination of a 5-HT3 receptor antagonist and aprepitant or fosaprepitant is recommended.
  - Cannabinoids (eg, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).
  - Dopamine receptor antagonists (eg, prochlorperazine, metoclopramide) are included as agents that may be added on to regimens for patients who experience n/v despite optimal prophylaxis.
- The 2025 NCCN antiemesis guideline recommends the following regimens for prevention of CINV depending on emetic risk *(NCCN 2025):*
  - For high emetic risk IV chemotherapy on day 1: 1) olanzapine, substance P/NK1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone (preferred); 2) olanzapine, palonosetron, plus dexamethasone; 3) substance P/NK1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Additional agents depending on the regimen are used on days 2, 3, and 4.
  - For moderate emetic risk IV chemotherapy on day 1: 1) 5-HT3 receptor antagonist (palonosetron or subcutaneous granisetron ER injection preferred) plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) substance P/NK1 receptor antagonist (aprepitant oral or injectable emulsion, fosaprepitant, netupitant, fosnetupitant, or oral rolapitant), 5-HT3 receptor antagonist, plus dexamethasone. Additional agents depending on the regimen are used on days 2 and 3.

- For low emetic risk IV chemotherapy: dexamethasone, metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist (granisetron, ondansetron, or dolasetron [no longer available]) started before chemotherapy and continued daily.
- For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist (granisetron, ondansetron, or dolasetron [no longer available]) or olanzapine started before chemotherapy and continued daily.
- For low to minimal emetic risk oral chemotherapy (as needed): metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist (granisetron, ondansetron, or dolasetron [no longer available]) given as needed.
- For breakthrough treatment for CINV (add an agent from a different drug class to the current regimen): olanzapine (preferred), lorazepam, dronabinol, haloperidol, metoclopramide, scopolamine, prochlorperazine or promethazine, 5-HT3 receptor antagonist, or dexamethasone. Switching to a different 5-HT3 receptor antagonist or substance P/NK1 receptor antagonist with a different pharmacokinetic/pharmacodynamic profile may be helpful.

- The NCCN antiemesis guideline recommends granisetron or ondansetron ± dexamethasone for pretreatment for RINV in patients receiving RT (upper abdomen/localized site) or TBI. If RT is combined with chemotherapy, antiemetic prophylaxis should be based on the modality with the highest emetic risk *(NCCN 2025).*
- The NCCN has acknowledged the recent clinical controversy surrounding dexamethasone and its potential blunting of the effects of immune checkpoint inhibitors (ICIs), and states that clinicians may want to consider a dexamethasone-sparing regimen, or alternative agents (such as olanzapine), for delayed CINV prophylaxis until more definitive data are available (*NCCN 2025*).
- The 2018 ACOG Practice Bulletin for NVP (reaffirmed in 2024) recommends the following algorithm (*ACOG 2018*):
  - First-line nonpharmacologic options: Change the prenatal vitamin to one that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
  - If symptoms persist, escalate to first-line pharmacologic interventions: pyridoxine (vitamin B6) monotherapy or pyridoxine in combination with doxylamine in various doses.
  - If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
  - If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
  - If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
    - If symptoms persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

Safety Summary

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists (except tradipitant) are contraindicated in the presence of hypersensitivity to these agents. Ondansetron is also contraindicated with apomorphine.
- The 5-HT3 receptor antagonists are generally very well-tolerated. Warnings and precautions include:
  - Serotonin syndrome
  - Ondansetron and granisetron: risk of QTc prolongation, masked progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
  - Ondansetron: Myocardial ischemia has been reported in patients with underlying coronary artery spasm; therefore, do not exceed the recommended infusion rate of ondansetron and monitor for signs and symptoms of myocardial ischemia during and after administration.
  - Granisetron patch may be affected by direct natural or artificial sunlight, which can lead to photogenotoxicity. External heat sources applied to the patch can increase granisetron concentrations.
  - Palonosetron can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock. If hypersensitivity reactions occur, discontinue palonosetron and administer appropriate medical therapy. Do not reinitiate therapy with palonosetron.
- The D_2 antagonist amisulpride carries a warning for QT prolongation, and it should be avoided in patients with congenital long QT syndrome and patients taking droperidol. Electrocardiogram (ECG) monitoring is recommended in patients with pre-existing arrhythmia, electrolyte abnormalities, congestive heart failure, and patients taking other drugs or with other conditions that prolong the QT interval.
- Aprepitant and fosaprepitant are weak-to-moderate inhibitors of cytochrome P450 (CYP) 3A4 and aprepitant is an inducer of CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore,

dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated in patients taking agents that are CYP substrates of their respective enzymes, with a narrow therapeutic index. Increased plasma concentrations may result in QT prolongation and torsades de pointes. Tradipitant is a CYP3A4 substrate; levels may be increased when used with strong CYP3A4 inhibitors. Aprepitant has a warning regarding concurrent therapy with warfarin, a CYP2C9 substrate, and with hormonal contraceptives (during and for 28 days after stopping therapy) due to decreased exposure of the interacting medication.

- Fosaprepitant, aprepitant, and rolapitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant or fosaprepitant, or rolapitant IV (which is currently discontinued) in patients who experience hypersensitivity symptoms with first-time use. Infusion site reactions have been reported with fosaprepitant IV; avoid infusion into small veins or through a butterfly catheter.
- Dronabinol has the potential to be abused and produce psychological dependence. Dronabinol may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).
- Dronabinol is contraindicated in individuals who are allergic to cannabinoids. Marinol (dronabinol capsules) is contraindicated in patients with a hypersensitivity to sesame oil. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- Common adverse events with cannabinoids are dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance.
- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. Additional warnings and precautions include:
  - Avoid dronabinol in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of dronabinol cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking dronabinol.
- Meclizine may cause drowsiness and should be used with caution in patients with asthma, glaucoma, or an enlarged prostate due to its anticholinergic effects. Headache, fatigue, and vomiting are other common adverse events.
- Promethazine has a boxed warning that it should not be used in patients < 2 years old because of the risk of fatal respiratory depression. It should be used with caution in pediatric patients 2 years and older. The injection has a boxed warning for severe tissue injury. Promethazine is also contraindicated in comatose states, hypersensitivity, or for treatment of lower respiratory tract symptoms including asthma. Promethazine injection should not be administered by intra-arterial injection, IV injection at concentrations greater than 1 mg/mL, or subcutaneously. Warnings related to promethazine include CNS depression, respiratory depression, lower seizure threshold, bone-marrow depression, and neuroleptic malignant syndrome (NMS).
- Prochlorperazine has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. Contraindications include hypersensitivity, comatose states or in the presence of large amounts of CNS depressants, pediatric surgery, in pediatric patients < 2 years or weighing < 20 pounds, or for use in pediatric conditions where the dose has not been determined. Other warnings include tardive dyskinesia, NMS, and falls. Adverse events include drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, and hypotension.
- Transdermal scopolamine is contraindicated in acute closure glaucoma and hypersensitivity. Warnings and precautions include acute angle closure glaucoma, neuropsychiatric adverse reactions, and eclamptic seizures in pregnant women. Scopolamine may cause reduced gastrointestinal motility, urinary retention, and blurred vision if it comes into contact with eyes. Additionally, patients may experience withdrawal symptoms, and transdermal scopolamine should be removed prior to magnetic resonance imaging. The most common reactions in treatment of motion sickness include dry mouth, drowsiness, blurred vision, and pupil dilation, and in treatment of PONV include dry mouth, dizziness, somnolence, agitation, visual impairment, confusion, mydriasis, and pharyngitis.

- Trimethobenzamide is contraindicated in cases of hypersensitivity. Warnings and precautions include acute dystonic reactions and other extrapyramidal symptoms, other CNS reactions (eg, coma, depression of mood, disorientation, and seizures), hepatotoxicity, and impairment of mental and/or physical activities. Other adverse events include blurred vision, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, and muscle cramps.
- Doxylamine succinate/pyridoxine HCl is contraindicated when used with monoamine oxidase inhibitors (MAOIs), as they intensify and prolong the adverse effects of the agent. The most common adverse effect observed with doxylamine succinate/pyridoxine HCl is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, are not recommended (unless cleared to do so by a health care provider). Doxylamine succinate/pyridoxine HCl is also not recommended when using CNS depressants, such as alcohol. Doxylamine succinate/pyridoxine HCl has anticholinergic properties. It should be used with caution in women with increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. Additionally, false positive urine screening tests for methadone, opiates, and phencyclidine have been reported with doxylamine succinate/pyridoxine HCl use.

Dosing and Administration

Table 8. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
5-HT3 Receptor Antagonists				
Granisetron	Tablet, injection, injection ER, TD patch	Oral, IV, SC, TD	Take orally within 1 hour before chemotherapy or radiation, or twice daily (with the second dose given 12 hours after the first). Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion. Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week.	Injection approved for CINV in children 2 to 16 years of age. Recommended dosing is weight-based. Tablet, injection ER, and TD patch have not been studied in pediatric patients. Injection ER not recommended in pediatric patients < 12 years of age due to need for large gauge needle and extended administration time. Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment. Apply patch to upper outer arm and cover application site with clothing to avoid exposure to light. The patch may be worn for up to 7 days depending on the duration of the chemotherapy regimen. Prolonged exposure of patch to heat increases exposure to drug. Do not apply an external heat source over patch. Pregnancy category (tablet, injection): B.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy category (TD patch): Unclassified. [a] Published data and postmarketing reports have not identified drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnancy category (injection ER): Unclassified. [a]
Ondansetron	Tablet, oral solution, ODT, injection	Oral, IV, IM	Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) give twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy. IV administrations vary: (1) administer IV over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic	Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥ 10). There is no experience beyond first-day administration in these patients. Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month. Pregnancy: Unclassified. [a]

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery. Administer IM as a single dose.	
Palonosetron	IV solution	IV	IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy.	IV solution approved for prevention of CINV in pediatric patients aged ≥ 1 month. Pregnancy: Unclassified. [a]
D_2 antagonist				
Amisulpride	IV solution	IV	Prevention of PONV: 5 mg as a single IV injection over 1 to 2 minutes at induction of anesthesia. Treatment of PONV: 10 mg as a single IV injection over 1 to 2 minutes.	Use for prevention of PONV may be as monotherapy or in combination with an antiemetic of a different class. Use for treatment of PONV may be in patients who received prophylaxis with an agent of a different class or who have not received prophylaxis. Avoid use in patients with severe renal impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified. [a]
Substance P/NK1 Receptor Antagonists				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aprepitant	Capsule, combination pack, oral suspension, IV emulsion	Oral, IV	Take orally within 1 hour before chemotherapy and once daily for 2 additional days. Administer IV over 2 minutes or 30 minutes, completing the administration approximately 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3). For PONV prevention, IV emulsion should be administered as a 30 second injection prior to induction of anesthesia; capsule should be administered within 3 hours prior to induction of anesthesia.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 receptor antagonist. Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years. Give with or without food. Use with caution in severe hepatic impairment. Pregnancy: Unclassified. [a] Avoid use of IV emulsion in pregnant women due to alcohol content.
Fosaprepitant	IV solution	IV	Adults: Administer IV over 20 to 30 minutes before chemotherapy. Children: Administer IV over 30 minutes (12 to 17 years of age) or 60 minutes (6 months to < 12 years of age) (for the 3-day regimen, continue capsules or oral suspension on days 2 and 3). Complete infusion approximately 30 minutes prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 receptor antagonist. Use with caution in severe hepatic impairment. Pregnancy: Unclassified. [a]
Rolapitant	Tablet	Oral	Administer orally within 2 hours prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 receptor antagonist. Avoid use in severe hepatic impairment; if use cannot be avoided, monitor for adverse events. Contraindicated in children < 2 years of age due to irreversible impaired reproductive development observed in animal studies Pregnancy: Unclassified. [a]
Tradipitant	Capsule	Oral	Administer orally approximately 60 minutes before the event that	Avoid use in patients with severe renal impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			is anticipated to cause vomiting induced by motion. Administer on an empty stomach (1 hour before or 2 hours after a meal).	Avoid in patients with any degree of hepatic impairment. Pregnancy: Unclassified. [a]
THC derivatives				
Dronabinol	Capsule, oral solution	Oral	CINV: Take orally 1 to 3 hours before chemotherapy and subsequent doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day. Anorexia associated with AIDS: Take orally twice daily, 1 hour prior to lunch and dinner.	If adverse effects occur and do not resolve in 1 to 3 days with continued use, consider dose reductions. In elderly patients, consider decreasing the initial dose to reduce risk of CNS adverse reactions. Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water (oral solution). Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified. [a] Avoid use in pregnant women due to risk of fetal harm.
Other single-agent products				
Meclizine	Chewable tablet, immediate-release tablet, ODT	Oral	Take orally 1 hour before travel (may repeat every 24 hours as needed).	Start at the lowest dose for elderly patients due to anticholinergic effects. OTC labeling for motion sickness includes recommendations for children > 12 years of age. Safety and effectiveness of non-OTC products have not been established in pediatric patients. Pregnancy: Unclassified. [a] Epidemiologic studies have not indicated drug-associated risk of major birth defects.
Promethazine	Tablet, oral syrup, rectal	Oral,	Oral and rectal administration (motion sickness): Take orally	Deep IM injection is the preferred parenteral route of administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	suppository, injectable solution	rectal, IV, IM	30 to 60 minutes before departure, then repeat in 8 to 12 hours as needed. Oral and rectal administration (PONV): Take orally or rectally every 4 to 6 hours as needed. IV and IM (PONV): Administer no more frequently than every 4 hours.	Can be given IV after dilution through an IV catheter inserted in a large vein (CVC recommend). Contraindicated for use in pediatric patients < 2 years of age. Pregnancy category C.
Prochlorperazine	Tablet, rectal suppository, injectable solution	Oral, rectal, IV, IM	Oral administration: 3 to 4 times per day Rectal administration: Twice daily IV or IM administration: Administer 3 to 4 hours as needed; or administer 1 to 2 hours (IM) or 15 to 30 minutes (IV) before induction of anesthesia and repeat once if necessary.	Lower doses are usually sufficient for elderly patients; increase doses gradually. Contraindicated for use in pediatric surgery, in pediatric patients < 2 years of age or weighing < 20 lbs, or in children for conditions for which dosage has not been established. Pregnancy: Unclassified. [a]
Scopolamine	Transdermal	TD	Motion sickness: Apply patch at ≥ 4 hours before antiemetic effects are needed – for use up to 3 days. If therapy for more than 3 days is required, remove the first transdermal system and apply a new one behind the other ear. PONV: Apply patch the evening before scheduled surgery; remove 24 hours after surgery.	Apply to hairless area of the skin behind the ear. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified. [a] Published data and postmarketing reports have not identified drug-associated risk of major birth defects, miscarriage, or adverse fetal outcomes. Avoid use in pregnant patients with severe eclampsia due to risk of eclamptic seizures.
Trimethobenzamide	Capsule, IM solution	Oral, IM	Oral: Take orally 3 to 4 times daily. IM: Administer 3 to 4 times per day; adjust dose according to indication, severity of symptoms, and patient response.	Reduce daily oral dose in elderly and patients with renal impairment. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified. [a]
Combination products				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Palonosetron/ netupitant Palonosteron/ fosnetupitent	Capsule Powder or solution for injection	Oral IV	Oral administration: Take orally approximately 1 hour before the start of chemotherapy. IV administration: Infuse over 30 minutes starting approximately 30 minutes prior to the initiation of chemotherapy.	Given as part of a regimen that includes a corticosteroid. Do not use in severe renal or hepatic impairment. The oral capsule may be taken with or without food. Safety and effectiveness have not been established in pediatric patients. Pregnancy: Unclassified. [a]
Doxylamine succinate/ pyridoxine HCl	Tablet ER, tablet DR	Oral	Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR).	Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water. Safety and effectiveness have not been established in pediatric patients.

Abbreviations: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, CINV = chemotherapy-induced nausea and vomiting, CNS = central nervous system, CVC = central venous catheter, DR = delayed-release, ECG = electrocardiogram, ER = extended-release, FDA = Food and Drug Administration, HEC = highly emetogenic cancer chemotherapy, IM = intramuscular, IV = intravenous, NK1 = neurokinin 1, ODT = orally disintegrating tablet, OTC = over the counter, PONV = postoperative nausea and vomiting, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal; THC = tetrahydrocannabinol.
See the current prescribing information for full details.
[a] In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

(Micromedex 2026)

Conclusion

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v.
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or RT. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms.
- Guideline recommendations vary according to indication:
  - The 2020 ASCO antiemetic guidelines recommend a 4-drug combination of a substance P/NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for patients treated with regimens not involving carboplatin AUC ≥ 4 mg/mL/min; a 3-drug combination of a substance P/NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min.
  - A 2020 consensus guideline from ASER and the Society for Ambulatory Anesthesia states that the number of risk factors guides the number of agents required for PONV prophylaxis.

- The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first-line pharmacologic therapy.
- The NCCN antiemetic guidelines state that in patients receiving ICIs, a dexamethasone-sparing regimen, or alternative agent (such as olanzapine) may be considered for delayed CINV prophylaxis until more definitive data on dexamethasone with ICIs become available.

- The 5-HT3 receptor antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials have not demonstrated a clear treatment leader between granisetron and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV; the 5-HT3 receptor antagonists are the only agents in this class review with demonstrated efficacy and, of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV.
- The 5-HT3 receptor antagonists are generally well tolerated, with mild headache being the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with granisetron and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists.
  - All 5-HT3 receptor antagonist formulations are available generically with the exception of Sancuso (granisetron) transdermal patch and Sustol (granisetron) ER injection.
- The substance P/NK1 receptor antagonists (except tradipitant) are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists that are generally effective for acute emesis only. These include aprepitant, fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically a 5-HT3 receptor antagonist, a glucocorticoid, ± olanzapine, for patients receiving HEC. One MA concluded that aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and substance P/NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization.
  - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and the combination pack.
  - Tradipitant is only approved for motion sickness.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have limited clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol is recommended for later line therapy.
- Amisulpride is approved for the prevention and treatment of PONV. Supporting evidence includes randomized trials in each indication demonstrating superiority over placebo *(Barhemsys prescribing information 2025)*.
  - Amisulpride is not available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) and Akynzeo (palonosetron/netupitant and palonosetron/fosnetupitant). Doxylamine succinate/pyridoxine HCl is the only agent in this class FDA-approved for NVP and is guideline-recommended as a first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available OTC.
- The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be superior to each agent administered individually for CINV prevention following MEC; however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone. Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.

- Other agents used for n/v include meclizine, promethazine, prochlorperazine, scopolamine, and trimethobenzamide. Meclizine and scopolamine are generally used for motion sickness. Prochlorperazine may be used in low emetic risk chemotherapy while prochlorperazine, scopolamine, or promethazine may be used for breakthrough treatment.

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