South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

December 12, 2025

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

December 12, 2025
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_NDAzMDNkYmUtYjkzMi00ODk2LWIxNzUtYWM5ZWIwMTIyZGI5%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
teams@optum.onpexip.com
Video Conference ID: 115 890 196 12

Join by phone
+1 952-222-7450
Phone Conference ID: 948 304 893#

Call to order

Approval of previous meeting minutes

PA update
Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Vykat XR**
- **Opioid update**

New business
- **Bimzelx**
- **Dupixent**
- **Neffy**
- **Zilbrysq**
- **Vyalev**
- **Anzupgo**

Public input accepted after individual topic discussion
Next meeting date March 27, 2026 (tentative) & adjournment

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

Friday, September 26, 2025
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Van Gilder called the meeting to order at 1:01 pm. Jockheck announced Stanley will be stepping down. The minutes of the June meeting were presented. Baack made a motion to approve. Oehlke seconded the motion. The motion to approve the minutes was approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from April 1, 2025, to June 30, 2025. A total of 4,230 PAs were reviewed of which 121 requests (2.6%) were received via telephone, 109 requests (2.9%) were received via fax, 1,559 requests (36.8%) were reviewed electronically, and 2,441requests (57.7%) were received via ePA. There was a 7% decrease in PAs received compared to the previous quarter. There was a 5.6% increase in number of appeals. Baack inquired about Dexcom

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from April 1, 2025, to June 30, 2025. The top five therapeutic classes based on paid amount were atypical antipsychotics, immunomodulator agents, incretin mimetics, interleukin-mediated agents, and tumor necrosis factor inhibitors. These top 15 therapeutic classes comprise 18.3% 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 7.48% of total claims. Vykat XR made its debut on the Top 50 drug list by paid amount.

Old Business

CGRP oral and SubQ review

Committee reviewed utilization of members taking both oral and SubQ CGRP medication. Most members were taking as preventative and as acute treatment. Jockheck will coordinate with DUR vendor to educate prescribers on the members taking duplicate therapy. Jasmine Inman, Field Value Evidence and Outcomes pharmacist at Teva, provided public comment.

Antipsychotics review

Committee reviewed the new biometric screening criteria on the Atypical Antipsychotic PA. Providing the biometric screening information will start on 1/1/2026 but will be mandatory effective 1/1/2027. Baack provided perspective on the hurdles of obtaining blood pressure and blood work on severely autistic

children. Jockheck discussed options for these patients. Baack asked for an exemption or physician attestation for these members. Barnes added that providers had shared in the difficulty of obtaining labs for autism patients, however they agreed on the importance of obtaining biometric screening information on all patients. Metrics such as finger sticks for A1C and glucose to ease the screening for these patients were discussed. Aaron Feyos, Director of Health Economics and Outcomes at Bristol Myers, Squibb provided public comment.

Opioid Update
The committee reviewed opioid outcomes compared to the previous quarter from the opioid initiatives. There was an increase in opioid utilization and utilizers during 2Q2025. The average MME/day/utilizer stayed steady.

New Business

Stelara and biosimilars review
Committee reviewed utilization of ustekinumab and discussed preferred products. McGill asked about keeping patients who have been historically hard to treat on the reference product. Jockheck replied each patient would need to be assessed and would be similar to DAW 1 policy. Jasmine Inman provided public comment. Baack made a motion of trial and failure of biosimilar preferred product before Stelara. Ladwig seconded the motion. The motional approved unanimously.

Oxervate
Committee reviewed Oxervate utilization and member diagnosis. Van Gilder inquired if there was any public comment. There was none. Ladwig made a motion to adopt State A criteria. McGill seconded the motion. Motion approved unanimously.

Cholbam
Committee reviewed Cholbam utilization and member diagnoses. Van Gilder and Ladwig commented utilization looked appropriate for the population. Van Gilder inquired if there was any public comment. There was none.

Promacta
Committee reviewed Promacta utilization and member diagnoses. Baack commented utilization is appropriately prescribed for members reviewed and PA not necessary. Ladwig agreed. Van Gilder inquired if there was any public comment. There was none.

Symbravo
Symbravo clinical information was presented for review. Ladwig also commented on utilization of meloxicam capsules. Van Gilder inquired if there was any public comment. There were none. Baack made a motion to adopt State B and commercial PA criteria. Ladwig seconded the motion. The motion was approved unanimously. Ladwig also made a motion to add PA criteria of dysphagia to meloxicam capsules. Baack seconded the motion. The motion was approved unanimously.

Adjournment
The next meeting is scheduled for December 12, 2025. The March and June meetings are tentatively scheduled for March 27, 2026, and June 12, 2026. All motioned and were in favor of adjourning the meeting. The meeting adjourned at 2:17 pm CT.

PA Report
7/1/2025 – 9/30/2025

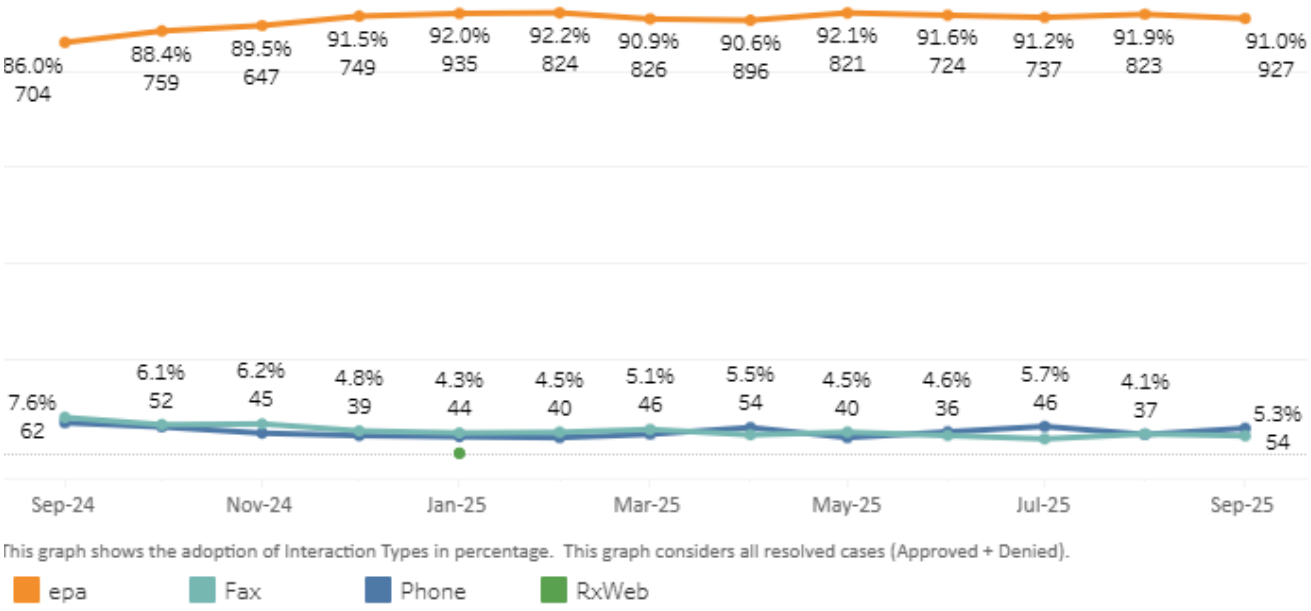
Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	4,939	4,939	0	100.00%	0.00%
Urgent	557	557	0	100.00%	0.00%
Grand Total	**5,496**	**5,496**	**0**		

Priority	Standard	Urgent
ePA	1,968	519
Fax	91	9
Phone	110	29
Real-Time	2,770	0

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**5,496**	**139**	**2.5%**	**100**	**1.8%**	**2,770**	**50.4%**	**2,487**	**45.3%**

Adoption By Interaction



PA Initial Requests Summary

Month	Approved	Denied	Total
July-25	1,119	213	1,332
August-25	1,159	223	1,382
September-25	2,531	251	2,782
3Q25	**4,809**	**687**	**5,496**
Percent of Total	**87.5%**	**12.5%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIPSYCHOTICS/ANTIMANIC	1,815	61	1,876	96.75%	34.13%	, ARIPIPRAZOLE
ANTIDIABETICS	684	79	763	89.65%	13.88%	, OZEMPIC
MEDICAL DEVICES & SUPPLIES	345	119	464	74.35%	8.44%	, FREESTYLE LIBRE
ANALGESICS - OPIOID	341	21	362	94.20%	6.59%	HYDROCODONE/APAP, TRAMADOL
DERMATOLOGICALS	227	52	279	81.36%	5.08%	DUPIXENT,
OTHERS -	1,397	355	1,752	79.74%	31.88%	
3Q25	**4,809**	**687**	**5,496**	**87.5%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
July-25	9	60.00%	6	40.00%	15
August-25	23	85.19%	4	14.81%	27
September-25	19	61.29%	12	38.71%	31
3Q25	**51**	**69.86%**	**22**	**30.14%**	**73**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	1815	61	1876	96.75%
27 - ANTIDIABETICS*	684	79	763	89.65%
97 - MEDICAL DEVICES AND SUPPLIES*	345	119	464	74.35%
65 - ANALGESICS - OPIOID*	341	21	362	94.20%
90 - DERMATOLOGICALS*	227	52	279	81.36%
58 - ANTIDEPRESSANTS*	232	27	259	89.58%
67 - MIGRAINE PRODUCTS*	200	35	235	85.11%
52 - GASTROINTESTINAL AGENTS - MISC.*	195	31	226	86.28%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	96	96	192	50.00%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	98	12	110	89.09%
66 - ANALGESICS - ANTI-INFLAMMATORY*	91	9	100	91.00%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	76	6	82	92.68%
12 - ANTIVIRALS*	50	3	53	94.34%
16 - ANTI-INFECTIVE AGENTS - MISC.*	51	2	53	96.23%
41 - ANTIHISTAMINES*	33	13	46	71.74%
72 - ANTICONVULSANTS*	29	9	38	76.32%
54 - URINARY ANTISPASMODICS*	22	15	37	59.46%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	29	3	32	90.63%
39 - ANTIHYPERLIPIDEMICS*	22	6	28	78.57%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	14	14	28	50.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	19	4	23	82.61%
75 - MUSCULOSKELETAL THERAPY AGENTS*	16	7	23	69.57%
28 - THYROID AGENTS*	20	2	22	90.91%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	19	2	21	90.48%
94 - DIAGNOSTIC PRODUCTS*	7	12	19	36.84%
40 - CARDIOVASCULAR AGENTS - MISC.*	14	2	16	87.50%
83 - ANTICOAGULANTS*	9	3	12	75.00%
34 - CALCIUM CHANNEL BLOCKERS*	3	8	11	27.27%
50 - ANTIEMETICS*	11	0	11	100.00%
36 - ANTIHYPERTENSIVES*	7	1	8	87.50%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	7	8	12.50%
03 - MACROLIDES*	2	5	7	28.57%
33 - BETA BLOCKERS*	6	1	7	85.71%
64 - ANALGESICS - NONNARCOTIC*	0	7	7	0.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	5	0	5	100.00%
02 - CEPHALOSPORINS*	3	1	4	75.00%
45 - RESPIRATORY AGENTS - MISC.*	4	0	4	100.00%
74 - NEUROMUSCULAR AGENTS*	3	1	4	75.00%
86 - OPHTHALMIC AGENTS*	2	2	4	50.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	3	0	3	100.00%
56 - GENITOURINARY AGENTS - MISCELLANEOUS*	1	1	2	50.00%
82 - HEMATOPOIETIC AGENTS*	2	0	2	100.00%
00 - COMPOUND & MISCELLANEOUS	1	0	1	100.00%
01 - PENICILLINS*	1	0	1	100.00%
04 - TETRACYCLINES*	0	1	1	0.00%
05 - FLUOROQUINOLONES*	0	1	1	0.00%
11 - ANTIFUNGALS*	0	1	1	0.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	0	1	1	0.00%
32 - ANTIANGINAL AGENTS*	0	1	1	0.00%
38 - VASOPRESSORS*	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.*	0	1	1	0.00%
89 - ANORECTAL AND RELATED PRODUCTS*	0	1	1	0.00%
3Q25	**4,809**	**687**	**5,496**	
Percent of Total	**87.5%**	**12.5%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	4	1	5	80.00%
LISDEXAMFETAMINE DIMESYLATE	2	3	5	40.00%
WEGOVY	3	1	4	75.00%
DEXCOM G7 SENSOR	3	0	3	100.00%
FREESTYLE LIBRE	3	3	6	50.00%
QELBREE	0	3	3	0.00%
ADBRY	2	0	2	100.00%
AZELASTINE HYDROCHLORIDE/FLUTICASONE	0	2	2	0.00%
NORDITROPIN FLEXPRO	2	0	2	100.00%
NURTEC	2	0	2	100.00%
VENLAFAXINE HYDROCHLORIDE	1	1	2	50.00%
VRAYLAR	2	0	2	100.00%
ABILIFY MAINTENA	0	1	1	0.00%
AIMOVIG	1	0	1	100.00%
AJOVY	1	0	1	100.00%
AMITIZA	0	1	1	0.00%
ARIPIPRAZOLE	1	0	1	100.00%
BIMZELX	1	0	1	100.00%
CETIRIZINE HYDROCHLORIDE	1	0	1	100.00%
COMETRIQ	0	1	1	0.00%
CRESEMBA	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
ENBREL MINI	1	0	1	100.00%
ENTRESTO	1	0	1	100.00%
EPIDIOLEX	1	0	1	100.00%
EPIPEN 2-PAK	0	1	1	0.00%
FIDAXOMICIN	0	1	1	0.00%
FINTEPLA	1	0	1	100.00%
FOCALIN XR	1	0	1	100.00%
JOURNAVX	0	1	1	0.00%
LEVOFLOXACIN	1	0	1	100.00%
LUBIPROSTONE	0	1	1	0.00%
MAVYRET	1	0	1	100.00%
MOTEGRITY	1	0	1	100.00%
OLANZAPINE	1	0	1	100.00%
OXYCODONE HYDROCHLORIDE	1	0	1	100.00%
OZEMPIC	1	0	1	100.00%
PRUCALOPRIDE	1	0	1	100.00%
REPATHA SURECLICK	1	0	1	100.00%
SKYRIZI PEN	1	0	1	100.00%
SYNTHROID	1	0	1	100.00%
TALTZ	1	0	1	100.00%
TAVNEOS	0	1	1	0.00%
TRACLEER	1	0	1	100.00%
ZAVZPRET	1	0	1	100.00%
ZORYVE	1	0	1	100.00%
ZURZUVAE	1	0	1	100.00%
3Q25	**51**	**22**	**73**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 7/1/2025 – 9/30/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPT	18,394	$250,052.92	$13.59	5.86%
2	ATYPICAL ANTIPSYCHOTICS	12,915	$5,011,172.82	$388.01	4.11%
3	PROTON-PUMP INHIBITORS	9,897	$245,461.42	$24.80	3.15%
4	RESPIRATORY AND CNS STIMU	9,872	$1,108,072.81	$112.24	3.14%
5	SELECTIVE BETA-2-ADRENERG	9,486	$492,695.33	$51.94	3.02%
6	AMPHETAMINES	9,344	$773,939.42	$82.83	2.98%
7	SECOND GENERATION ANTIHIS	8,944	$97,263.00	$10.87	2.85%
8	GABA-MEDIATED ANTICONVULS	8,809	$232,353.95	$26.38	2.80%
9	OPIOID AGONISTS	8,321	$243,320.25	$29.24	2.65%
10	ADRENALS	8,257	$1,092,647.02	$132.33	2.63%
11	SEROTONIN MODULATORS	7,799	$229,509.52	$29.43	2.48%
12	ANTICONVULSANTS, MISCELLA	7,511	$1,072,912.42	$142.85	2.39%
13	HMG-COA REDUCTASE INHIBIT	7,059	$83,877.96	$11.88	2.25%
14	AMINOPENICILLIN ANTIBIOTI	6,374	$100,764.19	$15.81	2.03%
15	BETA-ADRENERGIC BLOCKING	6,270	$99,081.39	$15.80	2.00%
Total		**139,252**	**$11,133,124.42**	**$79.95**	**44.34%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 7/1/2025 – 9/30/2025					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	12,915	$5,011,172.82	$388.01	4.11%
2	IMMUNOMODULATORY AGENTS (	1,047	$4,714,724.12	$4,503.08	0.33%
3	INCRETIN MIMETICS	3,821	$3,784,413.76	$990.42	1.22%
4	TUMOR NECROSIS FACTOR INH	356	$2,886,637.19	$8,108.53	0.11%
5	INTERLEUKIN-MEDIATED AGEN	215	$2,450,984.05	$11,399.93	0.07%
6	ANTINEOPLASTIC AGENTS	401	$1,787,386.93	$4,457.32	0.13%
7	CYSTIC FIBROSIS (CFTR) CO	68	$1,708,795.24	$25,129.34	0.02%
8	HEMOSTATICS	76	$1,353,641.20	$17,811.07	0.02%
9	HIV INTEGRASE INHIBITOR A	334	$1,302,236.40	$3,898.91	0.11%
10	SODIUM-GLUC COTRANSPORT 2	2,062	$1,138,073.63	$551.93	0.66%
11	RESPIRATORY AND CNS STIMU	9,872	$1,108,072.81	$112.24	3.14%
12	ADRENALS	8,257	$1,092,647.02	$132.33	2.63%
13	ANTICONVULSANTS, MISCELLA	7,511	$1,072,912.42	$142.85	2.39%
14	CALCITONIN GENE-RELATED P	1,055	$991,410.91	$939.73	0.34%
15	AMPHETAMINES	9,344	$773,939.42	$82.83	2.98%
Total		**57,334**	**$31,177,047.92**	**$543.78**	**18.26%**

Total Rx Claims from 7/1/2025 – 9/30/2025	**314,050**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 7/1/2025 – 9/30/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Antidepressants	FLUOXETINE	6,363	$81,801.60	$12.86	2.03%
2	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	6,029	$187,510.69	$31.10	1.92%
3	Anticonvulsants - 2nd Generation	GABAPENTIN	5,909	$88,470.14	$14.97	1.88%
4	Proton Pump Inhibitors	**OMEPRAZOLE**	**5,804**	**$68,508.11**	**$11.80**	**1.85%**
5	Antidepressants	**SERTRALINE**	**5,683**	**$74,951.68**	**$13.19**	**1.81%**
6	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	**5,328**	**$265,282.06**	**$49.79**	**1.70%**
7	Antidepressants	TRAZODONE	5,298	$63,251.57	$11.94	1.69%
8	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAMP	4,871	$154,525.11	$31.72	1.55%
9	Thyroid Hormones	LEVOTHYROXINE	4,798	$54,404.65	$11.34	1.53%
10	Antidepressants	ESCITALOPRAM	4,568	$57,591.45	$12.61	1.45%
11	Antidepressants	**BUPROPION**	**4,531**	**$77,613.72**	**$17.13**	**1.44%**
12	Antihistamines	**CETIRIZINE**	**4,521**	**$46,737.62**	**$10.34**	**1.44%**
13	Penicillins	AMOXICILLIN	4,184	$55,393.35	$13.24	1.33%
14	Statins & Combos	ATORVASTATIN	4,090	$48,260.74	$11.80	1.30%
15	Biguanides & Combos	**METFORMIN**	**4,085**	**$53,042.66**	**$12.98**	**1.30%**
16	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	3,965	$475,288.11	$119.87	1.26%
17	ACE Inhibitors & Combos	LISINOPRIL	3,648	$37,420.85	$10.26	1.16%
18	Antidepressants	DULOXETINE	3,367	$51,618.24	$15.33	1.07%
19	Antianxiety Agents	**HYDROXYZINE**	**3,303**	**$43,636.89**	**$13.21**	**1.05%**
20	Opioid Agonists & Combos	HYDROCODONE BITARTRA/AC	3,212	$54,925.48	$17.10	1.02%
21	ADHD & Narcolepsy Medications	GUANFACINE	3,120	$49,333.12	$15.81	0.99%
22	Leukotriene Modulators	MONTELUKAST	3,090	$39,194.50	$12.68	0.98%
23	Antiadrenergic Antihypertensives	CLONIDINE	3,035	$30,489.97	$10.05	0.97%
24	Antianxiety Agents	**BUSPIRONE**	**2,876**	**$38,886.54**	**$13.52**	**0.92%**
25	Angiotensin II Receptor Antagonists & Combo	LOSARTAN	2,782	$31,718.02	$11.40	0.89%
26	Atypical Antipsychotics	ARIPIPRAZOLE	2,676	$38,581.51	$14.42	0.85%
27	Antiemetics	ONDANSETRON ODT	2,512	$35,783.18	$14.24	0.80%
28	Calcium Channel Blockers	AMLODIPINE BESYLATE	2,510	$26,603.12	$10.60	0.80%
29	Glucocorticosteroids	PREDNISONE	2,410	$24,160.75	$10.03	0.77%
30	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,408	$31,487.58	$13.08	0.77%
31↑	Cephalosporins	CEPHALEXIN	2,400	$37,528.02	$15.64	0.76%
32	Atypical Antipsychotics	QUETIAPINE	2,361	$32,454.01	$13.75	0.75%
33	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,352	$24,463.43	$10.40	0.75%
34	Statins & Combos	ROSUVASTATIN	2,299	$27,247.66	$11.85	0.73%
35	Proton Pump Inhibitors	PANTOPRAZOLE	2,297	$28,021.16	$12.20	0.73%
36	Beta Blockers & Combos	METOPROLOL SUCCINATE ER	2,179	$27,854.31	$12.78	0.69%
37	Penicillins	AMOXICILLIN/CLAVULANATE	2,169	$39,263.85	$18.10	0.69%
38	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,138	$28,045.65	$13.12	0.68%
39	Antihistamines	**ALLERGY RELIEF**	**2,047**	**$22,192.87**	**$10.84**	**0.65%**
40	Anticonvulsants - 2nd Generation	CLONAZEPAM	2,016	$23,290.13	$11.55	0.64%
41	Macrolides	AZITHROMYCIN	1,989	$28,839.06	$14.50	0.63%
42	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	1,985	$20,760.83	$10.46	0.63%
43	GLP-1 Receptor Agonists	MOUNJARO	1,949	$1,989,074.67	$1,020.56	0.62%
44	Atypical Antipsychotics	RISPERIDONE	1,923	$26,044.25	$13.54	0.61%
45	Nasal Steroids	FLUTICASONE PROPIONATE	1,895	$32,984.91	$17.41	0.60%
46	Antidepressants	**VENLAFAXINE**	**1,893**	**$28,836.11**	**$15.23**	**0.60%**
47	Opioid Agonists & Combos	**OXYCODONE**	**1,883**	**$30,075.12**	**$15.97**	**0.60%**
48	Antidepressants	MIRTAZAPINE	1,880	$25,713.40	$13.68	0.60%
49	Corticosteroids - Topical	TRIAMCINOLONE ACETONIDE	1,801	$24,560.91	$13.64	0.57%
50	Diuretics & Combos	SPIRONOLACTONE	1,765	$25,958.69	$14.71	0.56%
	Total Top 50 Drugs		**162,197**	**$4,909,682.05**	**$30.27**	**51.65%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 7/1/2025 – 9/30/2025						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Chronic Inflammatory Disease	DUPIXENT	686	$2,772,278.92	$4,041.22	0.22%
2	Chronic Inflammatory Disease	**HUMIRA/PEN/CD/UC/HS/UV**	**245**	**$2,135,089.73**	**$8,714.65**	**0.08%**
3	GLP-1 Receptor Agonists	MOUNJARO	1,949	$1,989,074.67	$1,020.56	0.62%
4	Atypical Antipsychotics	**INVEGA SUSTENNA/TRINZA/HAFYERA**	**469**	**$1,528,894.78**	**$3,259.90**	**0.15%**
5	Cystic Fibrosis	TRIKAFTA	60	$1,496,972.80	$24,949.55	0.02%
6	GLP-1 Receptor Agonists	OZEMPIC	1,528	$1,472,980.24	$963.99	0.49%
7	Chronic Inflammatory Disease	**SKYRIZI/PEN**	**63**	**$1,357,994.10**	**$21,555.46**	**0.02%**
8	Atypical Antipsychotics	VRAYLAR	838	$1,130,324.90	$1,348.84	0.27%
9	HIV-Multiclass Combo	BIKTARVY	234	$962,116.10	$4,111.61	0.07%
10	Chronic Inflammatory Disease	STELARA	37	$951,365.10	$25,712.57	0.01%
11	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY/UNOREADY**	**87**	**$885,542.40**	**$10,178.65**	**0.03%**
12	SGLT-2 Inhibitors & Combos	JARDIANCE	1,358	$798,770.89	$588.20	0.43%
13	Diabetes Monitoring and Testing	**DEXCOM**	**1,620**	**$576,746.80**	**$356.02**	**0.52%**
14	Chronic Inflammatory Disease	**ENBREL/SURECLICK/MINI**	**73**	**$564,818.59**	**$7,737.24**	**0.02%**
15	Anticonvulsants - 2nd Generation	EPIDIOLEX	174	$538,726.73	$3,096.13	0.06%
16	Oral Anticoagulants	**ELIQUIS/STARTER PACK**	**914**	**$512,713.48**	**$560.96**	**0.29%**
17	Atypical Antipsychotics	**ARISTADA/INITIO**	**174**	**$506,535.48**	**$2,911.12**	**0.06%**
18	Atypical Antipsychotics	**ABILIFY MAINTENA, ASIMTUFII**	**152**	**$492,567.41**	**$3,240.58**	**0.05%**
19	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	3,965	$475,288.11	$119.87	1.26%
20	Chronic Inflammatory Disease	TALTZ	53	$449,261.94	$8,476.64	0.02%
21	Atypical Antipsychotics	REXULTI	317	$431,219.55	$1,360.31	0.10%
22	Chronic Inflammatory Disease	RINVOQ	60	$394,122.55	$6,568.71	0.02%
23↑	Metabolic Modifiers	VYKAT XR	9	$390,814.95	$43,423.88	0.00%
24	Movement Disorder Drug Therapy	INGREZZA	52	$370,858.60	$7,131.90	0.02%
25	Chronic Inflammatory Disease	BIMZELX	17	$364,632.08	$21,448.95	0.01%
26	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	558	$362,782.06	$650.15	0.18%
27	Oncology	KISQALI	24	$357,202.35	$14,883.43	0.01%
28	Antihemophilic Products	HEMLIBRA	11	$355,574.93	$32,324.99	0.00%
29	Atypical Antipsychotics	CAPLYTA	209	$335,893.25	$1,607.14	0.07%
30	Anti-Infective Agents - Misc.	XIFAXAN	102	$313,671.80	$3,075.21	0.03%
31	Growth Hormones	NORDITROPIN FLEXPRO	70	$311,485.80	$4,449.80	0.02%
32	Migraine Products	NURTEC	271	$300,502.45	$1,108.87	0.09%
33	Irritable Bowel Syndrome (IBS) Agt	LINZESS	560	$291,579.40	$520.68	0.18%
34	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	**5,328**	**$265,282.06**	**$49.79**	**1.70%**
35	Antihemophilic Products	NOVOSEVEN RT	3	$252,931.65	$84,310.55	0.00%
36	Cystic Fibrosis	PULMOZYME	54	$247,927.50	$4,591.25	0.02%
37↑	Migraine Products	UBRELVY	226	$233,736.75	$1,034.23	0.07%
38↑	Ophthalmic Nerve Growth Factors	OXERVATE	4	$230,817.72	$57,704.43	0.00%
39↑	Antihemophilic Products	NUWIQ	3	$229,269.75	$76,423.25	0.00%
40↑	Chronic Inflammatory Disease	TREMFYA	16	$225,524.34	$14,095.27	0.01%
41	Movement Disorder Drug Therapy	AUSTEDO XR	26	$220,397.12	$8,476.81	0.01%
42	ADHD & Narcolepsy Medications	AZSTARYS	548	$218,201.28	$398.18	0.17%
43	ADHD & Narcolepsy Medications	JORNAY PM	483	$209,373.89	$433.49	0.15%
44↑	Psychotherapeutic & Neurological	LYBALVI	138	$205,143.31	$1,486.55	0.04%
45	Chronic Inflammatory Disease	OTEZLA	41	$201,840.70	$4,922.94	0.01%
46↑	Anticonvulsants - 2nd Generation	FINTEPLA	21	$196,720.33	$9,367.63	0.01%
47	Asthma	NUCALA	45	$189,164.85	$4,203.66	0.01%
48↑	HIV-Multiclass Combo	GENVOYA	46	$188,957.77	$4,107.78	0.01%
49	Inhaled Bronchodilator	ALBUTEROL SULFATE HFA	6,029	$187,510.69	$31.10	1.92%
50↓	Hepatitis C	SOFOSBUVIR/VELPATASVIR	23	$184,242.65	$8,010.55	0.01%
	Total Top 50 Drugs		**29,973**	**$29,865,445.30**	**$996.41**	**9.54%**

Old Business

Vykat XR (diazoxide) review

- For the treatment of hyperphagia in people with Prader-Willi syndrome, ICD-10 Q87.11

Utilization
Time frame: 4/1/2025 to 9/30/2025

	April – June 2025				July – August 2025			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
Vykat XR 75mg	2	$19,557.10	$9,778.55	1	6	$151,023.30	$25,170.55	2
Vykat XR 150mg	3	$191,839.65	$63,946.55		3	$237,791.65	$79,930.55	
TOTAL	**5**	**$211,396.75**	**$42,279.35**		**9**	**$390,814.95**	**$49,423.88**	

Utilizer	Demographics	Prescribed by	Treatment	Diagnosis
Member 1	female, 25 yrs	Nurse Practitioner *3 Family Practice *1 Pulmonology, Pediatrics	Vykat XR 75 #30/30 DS Vykat XR 150 #90/30 DS Ozempic 8mg/3ml metformin glipizide Humalog Lantus estradiol rosuvastatin aripiprazole sertraline venlafaxine ER	Q87.11 Prader Willi
Member 2	female, 17 yrs	Pediatrics	Vykat XR 75mg #90/30 DS sertraline levonorgestrel/ethinyl estradiol	Q87.11 Prader Willi

PA Criteria for Consideration

State A
Approval Criteria
1. Patient is greater than or equal to 4yrs of age;
2. Diagnosis of Prader-Willi Syndrome;
3. Submission of medical records (e.g. chart notes) documenting BOTH of the following:
   3.1. Methylation analysis genetic testing used to detect lack of active genetic material in particular region of Chromosome 15
   3.2. Patient has signs and symptoms of hyperphagia (e.g. intense persistent sensation of hunger, food preoccupations that cause distress or disrupt daily activities, lack of normal satiety, extreme drive to consume food);
4. Prescribed by, or in consultation with an endocrinologist, geneticists, neurologists, or specialist trained in the syndrome

Reauthorization Criteria
1. Submission of medical records (e.g. chart notes) documenting positive clinical response (i.e. decrease in sensation of hunger, less consumption of food, feeling satiated, decrease in food preoccupations, decrease in BMI, improvement in metabolic markers)

State B
Approval Criteria
1. Submission of medical records (e.g., chart notes) confirming a diagnosis of Prader-Willi syndrome (PWS)
2. Medication is being used for hyperphagia due to PWS
3. Submission of medical records (e.g., chart notes) documenting disease is confirmed by the presence of a mutation in chromosome 15 as detected by an FDA-approved test or a test performed at a facility approved by Clinical Laboratory Improvement Amendments (CLIA)
4. Patient is 4 years of age or older
5. Prescribed by or in consultation with one of the following:
   - Endocrinologist
   - Geneticist
   - Specialist knowledgeable in the treatment of Prader-Willi syndrome

Reauthorization criteria
1. Submission of medical records (e.g., chart notes) demonstrating positive clinical response to therapy (e.g., decreased hunger or thoughts about food, decreased weight or BMI)

Commercial C
Approval Criteria
1. Prader-Willi Syndrome. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A. Patient is ≥ 4 years of age; AND
   B. The diagnosis of Prader-Willi syndrome has been established by identification of abnormal DNA methylation of chromosome 15q11.2Q13; AND
   C. Patient has hyperphagia; AND
   D. The medication has been prescribed by or in consultation with an endocrinologist.
2. Conditions not covered: Hyperphagia in a patient without Prader-Willi syndrome

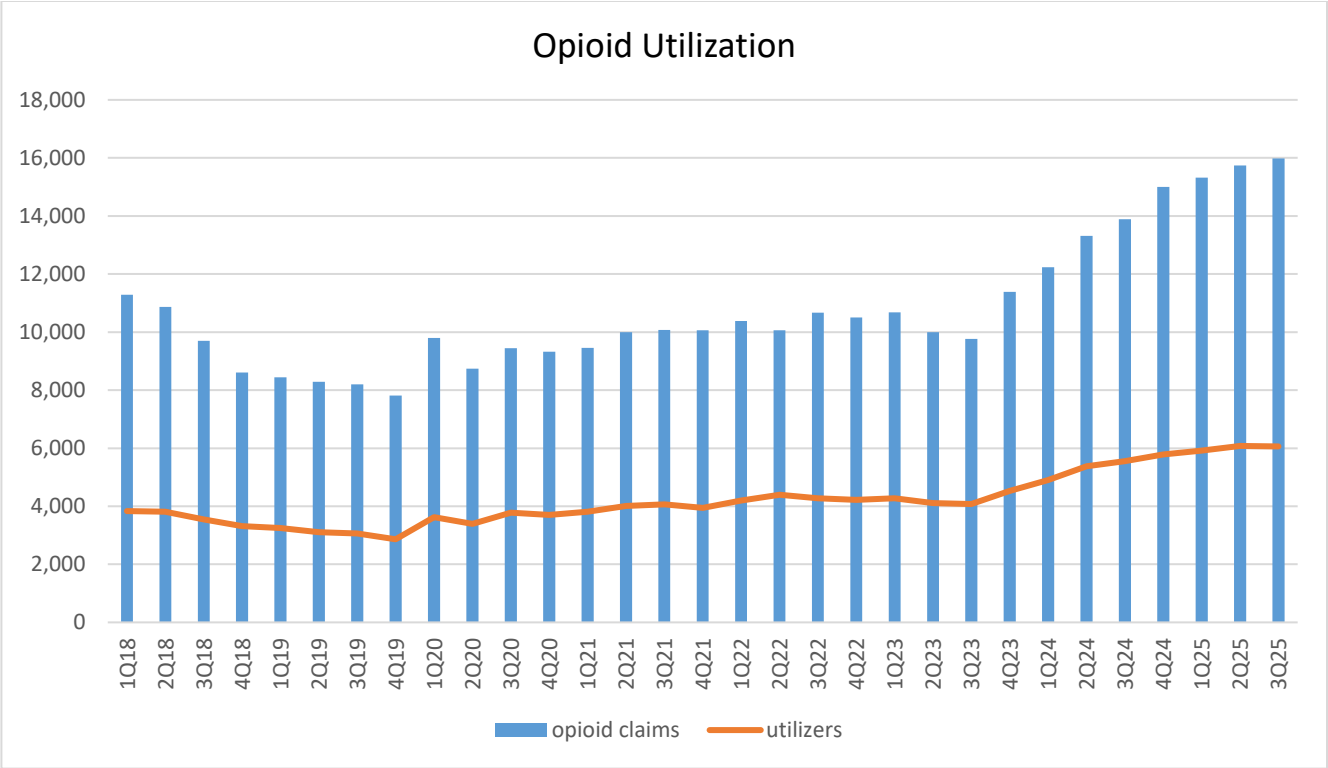
Commercial D
Approval Criteria
A. Patient is ≥ 4 years of age; AND
B. The diagnosis of Prader-Willi syndrome has been established by identification of abnormal DNA methylation of chromosome 15q11.2Q13; AND
C. Patient has hyperphagia; AND
D. The medication has been prescribed by or in consultation with an endocrinologist.

Continuation of Therapy
- Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for hyperphagia with Prader-Willi syndrome when the member has achieved or maintained a positive clinical response (e.g., reduction in hyperphagia, reduction in body fat mass, reduced levels of leptin).

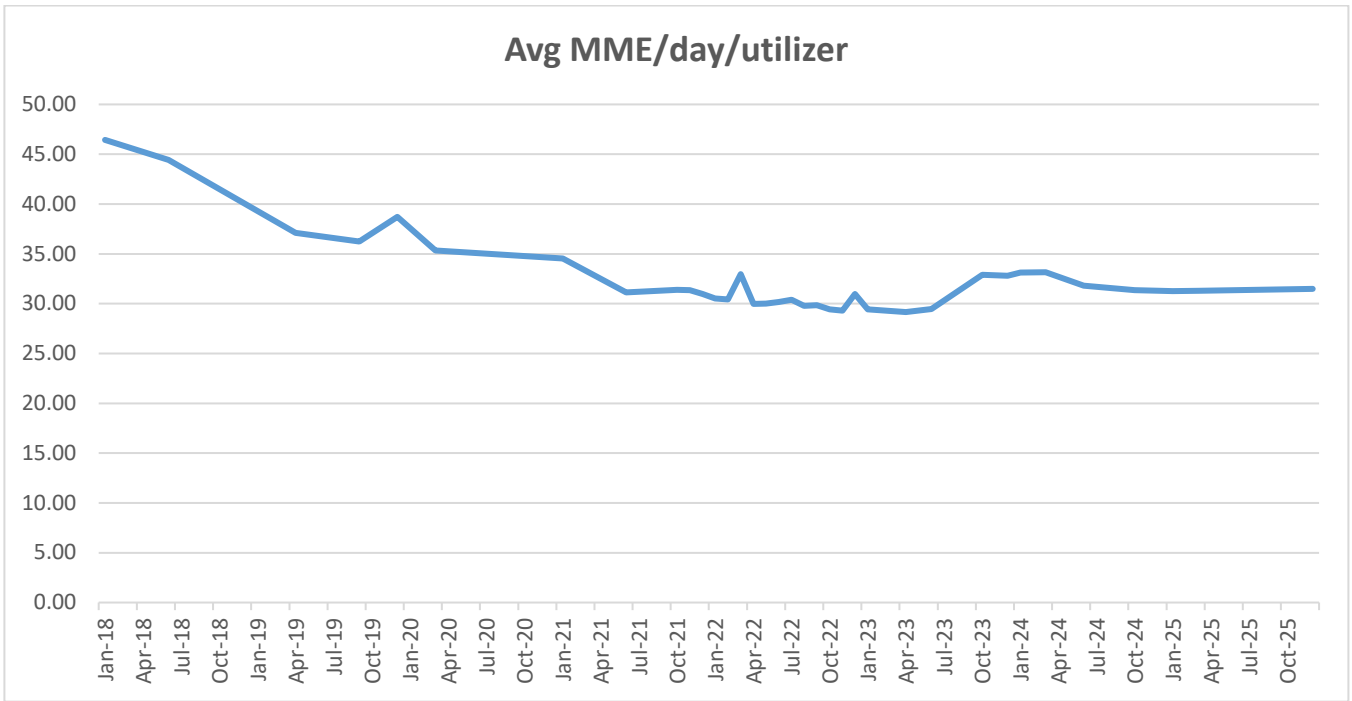
Commercial E
Approval Criteria
1. Diagnosis of Hyperphagia with Prader-Willi syndrome (PWS) Authorization of 12 months may be granted for treatment of hyperphagia with Prader-Willi syndrome (PWS) when all of the following criteria are met:
    - Member has diagnosis of Prader-Willi syndrome (PWS) confirmed by genetic testing demonstrating any of the following:
        - Deletion in the chromosomal 15q11-q13 region
        - Maternal uniparental disomy in chromosome 15
        - Imprinting defects, translocations, or inversions involving chromosome 15
    - Member has hyperphagia (e.g., food obsession, aggressive food seeking behavior, lack of satiety).
    - Member has been assessed for hyperglycemia prior to initiating treatment.
    - Member does not have clinically significant renal or hepatic impairment.
    - Member is 4 years of age and older with a weight greater than or equal to 20 kilograms (kg)

Continuation of Therapy
Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for hyperphagia with Prader-Willi syndrome (PWS) when the member has achieved or maintained a positive clinical response (e.g., reduction in hyperphagia, reduction in body fat mass, reduced levels of leptin).

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%

SDM 2Q2025
Mar 25 to Jun 25

Opioid Utilization Snapshot

3Q2025
Jun 25 to Sep 25

Opioid Claims **15,744**

3.3% prescription claims filled for an opioid

1.5% higher than Medicaid FFS benchmark

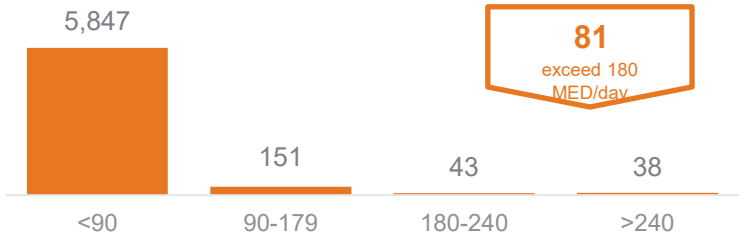
Utilizers **6,079**

32.4% are high utilizers [1]

6% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

88 opioid utilizing members with 3+ pharmacies

564 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

Opioid Claims **15,986**

3.3% prescription claims filled for an opioid

1.6% higher than Medicaid FFS benchmark

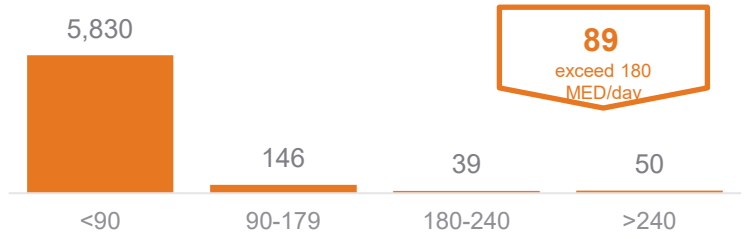
Utilizers **6,065**

32.3% are high utilizers [1]

6.3% higher than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

93 opioid utilizing members with 3+ pharmacies

646 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUMRx®

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

Opioid Utilization

SDM 3Q2025
Opportunities date range: Jun - Sep 2025
Benchmark: MEDICAID FEE FOR SERVICE

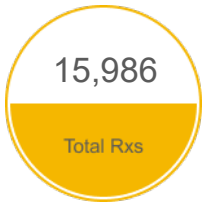
Utilizers: 6,065

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
- 1,957 high opioid utilizers were identified this period, which is 6.3% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
11.1%

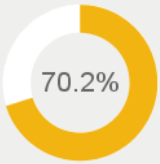
Opioid utilizers

HIGH UTILIZERS
32.3%
1,957 high utilizers

6.3% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

70.2% of all opioid Rxs were filled for short acting opioids. **3,754** Rxs were for medication assisted therapy (MAT) and **127** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

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

Utilizers by cumulative MED

89 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	5,830	146	39	50

MED – view definition

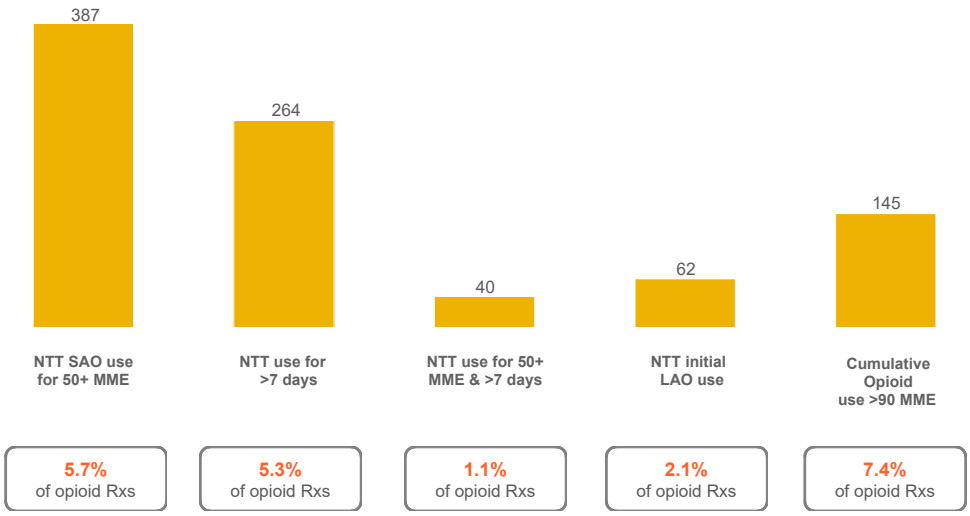
Opioid Opportunity Assessment

SDM 3Q2025
Opportunities date range: Jun - Sep 2025
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.1%

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?

93 opioid utilizing members use 3 or more pharmacies and 646 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
1,326	832	1,230	726	140

Anticonvulsants –view definition

New Business

Bimzelx Review

Classification	Drug Name	Total Rx	Paid Amount	Paid/Rx	Mbrs
Anti-IL17A/F/AF mAb	BIMZELX INJ 160MG/ML BIMZELX INJ 320MG/2ML	9 8	$158,552.67 $206,079.41	$17,616.96 $25,759.93	8
Human mAb to IL-17A	TALTZ INJ 80MG/ML	55	$450,863.94	$8,197.53	24
sTNFR fusion protein, TNFα inhibitor	ENBREL INJ 25MG ENBREL INJ 50MG/ML ENBREL MINI INJ 50MG/ML ENBREL SRCLK INJ 50MG/ML	6 6 4 75	$24,536.10 $55,531.45 $31,760.34 $482,888.18	$4,089.35 $9,255.24 $7,940.09 $6,438.51	43
TNFα inhibitor	HUMIRA INJ 20/0.2ML HUMIRA INJ 40/0.4ML HUMIRA PEN INJ 40/0.4ML HUMIRA PEN INJ 40MG/0.8ML HUMIRA PEN INJ 80/0.8ML HUMIRA PEN KIT CD/UC/HS HUMIRA PEN KIT PS/UV	3 14 182 23 20 5 1	$20,265.46 $127,972.26 $1,461,501.45 $181,897.42 $248,825.70 $101,049.04 $13,334.96	$6,755.15 $9,140.88 $8,030.23 $7,908.58 $12,441.29 $20,209.81 $13,334.96	91
	AMJEVITA INJ 40/0.4ML	3	$4,001.09	$1,333.70	1
	HADLIMA PUSH INJ 40/0.4ML HADLIMA PUSH INJ 40/0.8ML	14 10	$11,670.01 $9,539.01	$833.57 $953.90	11
	ADALIMU-ADAZ INJ 40/0.4ML	3	$3,977.55	$1,325.85	1

Drug	RA	NRAS	pJIA	PsO	PsA	AS	HS	UV	Cro	UC
Anti-IL17A/F/AF mAb										
Bimzelx (bimekizumab-bkzx)		✔		✔	✔	✔	✔			
Human mAb to IL-17A										
Taltz (ixekizumab)		✔		✔ (6+)	✔	✔				
sTNFR fusion protein, TNFα inhibitor										
Enbrel (etanercept)	✔		✔ (2+)	✔ (4+)	✔ (2+)	✔				
TNFα inhibitor										
Humira (adalimumab)	✔		✔ (2+)	✔	✔	✔	✔ (12+)	✔ (2+)	✔ (6+)	✔ (+5)
Abrilada* (adalimumab-afzb)	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔
Amjevita* (adalimumab-atto)	✔		✔ (2+)	✔	✔	✔	✔ (+12)	✔ (+2)	✔ (6+)	✔
Cyltezo* (adalimumab-adbm)	✔		✔ (2+)	✔	✔	✔	✔ (+12)	✔ (+2)	✔ (6+)	✔
Hadlima* (adalimumab-bwwd)	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔
Hulio* (adalimumab-fkjp)	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔
Hyrimoz* (adalimumab-adaz)	✔		✔ (2+)	✔	✔	✔	✔ (+12)	✔ (+2)	✔ (6+)	✔
Idacio (adalimumab-aacf)	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔
Simlandi* (adalimumab-ryvk)	✔		✔ (2+)	✔	✔	✔	✔ (+12)	✔ (+2)	✔ (6+)	✔
Yuflyma* (adalimumab-aaty)	✔		✔ (2+)	✔	✔	✔	✔ (+12)	✔ (+2)	✔ (6+)	✔
Yusimry* (adalimumab-aqvh)	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔
adalimumab-aacf	✔		✔ (2+)	✔	✔	✔	✔	✔	✔ (6+)	✔

*Designated as an interchangeable with the reference product.

Abbreviations: RA = rheumatoid arthritis; NRAS = non-radiographic axial spondyloarthritis; pJIA = polyarticular juvenile idiopathic arthritis; PsO = plaque psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; HS = hidradenitis suppurativa; UV = uveitis; Cro = Crohn's; UC = ulcerative colitis

Citeria for Consideration

1. Diagnosis
2. Patient's age
3. Prescribed by or in consultation with a dermatologist or rheumatologist
4. The medication will not be used in combination with another biologic agent
5. Patient has a documented 60-day or 90-day trial of all of the following:
    a. Enbrel or Humira or biosimilar
    b. Taltz

Dupixent (dupliumab) – new indications

- **Treatment of adult patients with bullous pemphigoid** (rare autoimmune skin condition characterized by large fluid-filled blisters that typically appear on areas of the skin that flex, such as the upper thighs and armpits)
- **Treatment of chronic spontaneous urticaria (CSU) in adults and pediatric patients ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment** (condition characterized by the recurrent appearance of hives and/or angioedema for six weeks or longer, without a known trigger)

Criteria Consideration for Bullous Pemphigoid (BP)

State A
Initial Authorization: 6 months
1. Diagnosis of bullous pemphigoid (BP) as confirmed by skin biopsy
2. Patient is ≥ 18 years of age
3. Inadequate response, intolerance, or contraindication to one of the following:
   a. Topical corticosteroid
   b. Oral corticosteroid
   c. Doxycycline
4. The medication must be prescribed by or in consultation with an allergist, immunologist, or dermatologist

Reauthorization: 12 months
1. Documentation of positive clinical response (e.g., improved symptoms, decreased blister formation and pruritis, improved healing of blisters and erosions)

State B
1. Does the member have a confirmed diagnosis based on clinical features of bullous pemphigoid (BP) (e.g., urticarial or eczematous or erythematous plaques, bullae, pruritus) AND histopathology, immunopathology, and serology?
2. Does the member have an active parasitic (helminth) infection?
   a. If YES = DENY
   b. If NO = APPROVE for 6 months for initial requests. APPROVE quantity sufficient for loading dose during 1st month for diagnosis of atopic dermatitis, asthma, bullous pemphigoid, and prurigo nodularis only. APPROVE for 1 year for reauthorization requests.

Commercial
Initial Authorization: 6 months
1. Diagnosis of bullous pemphigoid (BP) as confirmed by skin biopsy or serology
2. Will be used in combination with a tapering course of oral corticosteroids (e.g., prednisone) until disease control has occurred
3. Prescribed by or in consultation with one of the following:
   - Allergist/Immunologist
   - Dermatologist

Reauthorization: 12 months
1. Patient demonstrates positive clinical response to therapy (e.g., decreased pruritus severity from baseline, no new lesions or worsening of old lesions)

Criteria Consideration for Chronic Spontaneous Urticaria (CSU)

State A

1. Has the member remained symptomatic despite antihistamine therapy (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, diphenhydramine, hydroxyzine, chlorpheniramine, etc.)?
2. Will this medication be used in combination with another biologic for chronic spontaneous urticaria (e.g., Xolair)?
3. Does the member have an active parasitic (helminth) infection?
   a. If YES = DENY
   b. If NO = APPROVE for 6 months for initial requests. APPROVE quantity sufficient for loading dose during 1st month for diagnosis of atopic dermatitis, asthma, bullous pemphigoid, and prurigo nodularis only. APPROVE for 1 year for reauthorization requests.

State B

Initial Authorization: 3 months

1. Submission of documentation (e.g., chart notes) confirming diagnosis of chronic spontaneous urticaria
2. Persistent symptoms (itching and hives) for at least 4 consecutive weeks despite titrating to an optimal dose with a second generation H1 antihistamine (e.g., cetirizine, fexofenadine), unless there is a contraindication or intolerance to H1 antihistamines
3. Paid claims or submission of documentation (e.g., chart notes) confirming concurrent use with an H1 antihistamine, unless there is a contraindication or intolerance to H1 antihistamines
4. Paid claims or submission of documentation (e.g., chart notes) confirming patient has tried and had an inadequate response or intolerance to at least TWO of the following additional therapies:
   - Doxepin
   - H1 antihistamine
   - H2 antagonist (e.g., famotidine, cimetidine)
   - Hydroxyzine
   - Leukotriene receptor antagonist (e.g., montelukast)
5. Paid claims or submission of documentation (e.g., chart notes) demonstrating history of failure, contraindication, or intolerance to Xolair (omalizumab)
6. Prescribed by one of the following:
   - Allergist/immunologist
   - Dermatologist

Reauthorization: 6 months

1. Patient's disease status has been re-evaluated since the last authorization to confirm the patient's condition warrants continued treatment
2. Submission of documentation (e.g., chart notes) confirming patient has experienced at least one of the following:
   - Reduction in itching severity from baseline
   - Reduction in the number of hives from baseline
3. Paid claims or submission of documentation (e.g., chart notes) demonstrating history of failure, contraindication, or intolerance to Xolair (omalizumab)

State C

1. Diagnosis of chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment
2. Patient is ≥ 12 years of age
3. Has the member remained symptomatic despite antihistamine therapy (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, diphenhydramine, hydroxyzine, chlorpheniramine, etc.)?
4. Will this medication be used in combination with another biologic for chronic spontaneous urticaria (e.g., Xolair)?

Commercial

Initial Authorization: 6 months

1. Submission of medical records (e.g., chart notes) confirming a diagnosis of chronic spontaneous urticaria (CSU)
2. Both of the following:
   a. Persistent symptoms (itching and hives) for at least 6 consecutive weeks despite concurrent use of a second generation H1 antihistamine (e.g., cetirizine, fexofenadine), unless there is a contraindication or intolerance to H1 antihistamines
   b. Paid claims or submission of medical records (e.g., chart notes) confirming a minimum 2-week trial of up-dosing (e.g., up to 4x dose) of the second generation H1 antihistamine, unless there is a contraindication or intolerance to H1 antihistamines
3. Patient is 12 years of age or older
4. Will be used concurrently with a second generation H1 antihistamine, unless there is a contraindication or intolerance to H1 antihistamines
5. Prescribed by or in consultation with one of the following:
   - Allergist/Immunologist
   - Dermatologist

Reauthorization: 12 months

1. Patient demonstrates positive clinical response to therapy as evidenced by a reduction from baseline in itching severity or the number of hives

Neffy (epinephrine nasal spray)
Time frame: 7/1/2025 to 9/30/2025
Indication: for the treatment of anaphylaxis

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/Rx	Utilizers	Age Range
Auvi-Q inj 0.1mg	3	$1,329.46	$443.15	2	3	0 – 7
Auvi-Q inj 0.15mg	4	$1,447.47	$361.87	2	4	5 – 8
Auvi-Q inj 0.3mg	1	$606.31	$606.31	2	1	16
Epipen Jr 0.15mg	0					
Epipen 0.3mg	0					
Epinephrine inj 0.15mg	172	$51,262.32	$298.04	2.27	159	0 – 58
Epinephrine inj 0.3mg	344	$100,554.02	$292.31	2.15	310	5 – 64
Neffy NS 1mg/0.1ml	2	$1,378.60	$689.30	2	2	6
Neffy NS 2mg/0.1ml	7	$4,826.40	$689.49	2	5	9 – 14

*IHS excluded

AUVI-Q Auto-injector that offers retracting needle & audio cues
NEFFY epinephrine nasal spray

Criteria for Consideration

State A
Approval Criteria for Epipen/Epipen Jr and Auvi-Q: 12 months
1. The patient has experienced therapeutic failure to 2 preferred medications (please specify) OR
2. Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications

State B
Approval Criteria for Neffy: 12 months
1. Clinically valid reason why the patient cannot use an epinephrine auto-injector product

State C
Approval Criteria for Neffy: 6 months
1. There is a shortage on Epinephrine Pens manufactured by Mylan

Commercial
Approval Criteria for Epipen/Epipen Jr: 6 months
1. Requested drug is being used for a Food and Drug Administration (FDA)-approved indication
2. Trial and failure (within the past 180 days) or intolerance to generic epinephrine

Zilbrysq (zilucoplan) – treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive

Criteria for Consideration

State A
Initial Authorization: 6 months
1. Diagnosis of generalized myasthenia gravis (gMG)
2. Documented positive serology for acetylcholine receptor (AChR) autoantibodies
3. Patient has a baseline MG-Activities of Daily Living (MG-ADL) total score of ≥6
4. Patient has tried and failed, or has contraindication, or intolerance to TWO of the following:
    - Corticosteroids
    - Azathioprine
    - Cyclosporine
    - Mycophenolate mofetil
    - Methotrexate
    - Tacrolimus
5. Prescribed by, or in consultation with, a neurologist or neuromuscular specialist
6. Patient is not receiving Zilbrysq in combination with another complement inhibitor used for the treatment of gMG (e.g., Soliris, Ultomiris)

Reauthorization: 12 months
1. Submission of medical records (e.g., chart notes) documenting a positive clinical response to therapy (e.g. reduction in MG-ADL score or improvement in talking, chewing, swallowing, breathing, double vision, eyelid drop, movement)

Vyalev (foscaribidopa/foslevodopa) – for the treatment of motor fluctuations in people with advanced Parkinson disease

Foscaribidopa and foslevodopa are prodrugs of carbidopa/levodopa given via continuous subcutaneous infusion for the treatment of Parkinson's disease in adults. It is covered by South Dakota Medicaid following prior authorization when the patient meets the following criteria:

Criteria for Consideration

Initial Therapy (must meet all):

- Therapy must be prescribed by or in consultation with a neurologist
- Individual has a diagnosis of idiopathic Parkinson's disease
- Documentation is provided indicating that the individual is levodopa responsive
- Individual has an average "off time" of at least 3 hours per day and one of the following:
  - Individual is currently taking optimized treatment with oral carbidopa/levodopa dosed at least 4 times daily
  - Individual has documented intolerance or inability to take oral carbidopa/levodopa
- Individual is ≥ 18 years of age
- Approval duration: 6 months

Continuation of Therapy (must meet all):

- Documentation is provided indicating off time has reduced since starting therapy
- If patient met initial approval for therapy due to inability to take oral carbidopa/levodopa, this inability is still present
- Approval duration: 1 year

Anzupgo (delgocitinib) – for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable.

Criteria for Consideration

State A
Initial Authorization: 6 months
1. Diagnosis of moderate to severe chronic hand eczema (CHE)
2. Patient is 18 years of age or older
3. Prescribed by or in consultation with one of the following:
   - Dermatologist
   - Allergist/Immunologist
4. Trial and failure of a minimum 30-day supply (14-day supply for topical corticosteroids), contraindication, or intolerance to ALL of the following:
   - Medium or higher potency topical corticosteroid
   - One calcineurin inhibitor (e.g., tacrolimus ointment)
   - Eucrisa (crisaborole)
   - Opzelura (ruxolitinib)
   - Vtama (tapinarof)
   - Zoryve (roflumilast) 0.05% or 0.15% cream
   - Adbry (tralokinumab-ldrm)

Reauthorization: 12 months
1. Patient demonstrates positive clinical response to therapy (e.g., erythema, scaling, hyperkeratosis, fissures)
2. Not used in combination with other JAK inhibitors or potent immunosuppressants (e.g., azathioprine or cyclosporine)

Commercial B
Initial Authorization: 6 months
1. Diagnosis of moderate to severe chronic hand eczema (CHE)
2. Patient is 18 years of age or older
3. Prescribed by or in consultation with one of the following:
   - Dermatologist
   - Allergist/Immunologist
4. Trial and failure of a minimum 30-day supply (14-day supply for topical corticosteroids), contraindication, or intolerance to BOTH of the following:
   - Medium or higher potency topical corticosteroid
   - Generic calcineurin inhibitor (e.g., tacrolimus ointment)
5. Not used in combination with other Janus kinase (JAK) inhibitors or potent immunosuppressants (e.g., azathioprine or cyclosporine)

Reauthorization: 12 months
1. Patient demonstrates positive clinical response to therapy (e.g., erythema, scaling, hyperkeratosis, fissures)
2. Not used in combination with other JAK inhibitors or potent immunosuppressants (e.g., azathioprine or cyclosporine)

Optum Rx®

Therapeutic Class Overview

Epinephrine Products for Anaphylaxis

Introduction

- Anaphylaxis, a potentially fatal disorder, is a severe, acute, multisystem syndrome with rapid onset resulting from a sudden release of mast cell- and basophil-derived mediators into circulation. Most commonly, it results from immunologic reactions to foods, medications, and insect stings. In humans, the heart, vasculature system, and lungs are predominantly affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest. Symptoms consist of progressive swelling, difficulty breathing, and itchy rash, leading to shock and potentially death (*Sicherer et al 2017, Singletary et al 2015*).
- Anaphylaxis is unpredictable and variable, as it may be mild and resolve spontaneously, or it may be severe and progress to cardiovascular or respiratory compromise or death within minutes. Therefore, it is important to administer epinephrine early, as epinephrine can be lifesaving when administered as rapidly as possible once anaphylaxis is recognized. Delayed use of epinephrine is associated with increased mortality; therefore, epinephrine should also be administered to patients who have signs or symptoms of impending anaphylaxis or in whom suspicion of anaphylaxis is high, even when diagnostic criteria are not met (*Campbell and Kelso 2025*). Epinephrine is the treatment of choice and only first-line medication in the management of anaphylaxis because the benefits associated with epinephrine are greater than those associated with any other available pharmacologic intervention (eg, antihistamines, bronchodilators, glucocorticoids). Epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from alpha-1 (α1), beta-1 (β1), and beta-2 (β2) adrenergic receptor agonist effects and include increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2), and decreased release of mediators of inflammation from mast cells and basophils (β2) (*Brown et al 2020, Campbell et al 2014, Sicherer et al 2017*).
- In general, clinical data regarding the use of pharmacologic treatment of anaphylaxis are based upon extrapolation from therapies utilized in cardiac arrest and asthma, uncontrolled clinical trials with humans who develop anaphylaxis during insect sting challenges, randomized controlled trials of interventions such as epinephrine in patients not experiencing anaphylaxis at the time of administration, and animal anaphylaxis models. Randomized, placebo-controlled trials that meet current standards have not been performed for any pharmacologic intervention in humans experiencing anaphylaxis. Of note, placebo-controlled trials with epinephrine will never be performed due to ethical considerations in a disorder that can be fatal within minutes.
- Epinephrine products for anaphylaxis are all Food and Drug Administration (FDA)-approved for the emergency treatment of severe allergic reactions.
  - Injectable epinephrine products include Auvi-Q, epinephrine injection, EpiPen, and EpiPen Jr, with alternatives available for EpiPen and EpiPen Jr (see Table 1 below). An AB-rated (therapeutically equivalent) generic is available for EpiPen and EpiPen Jr (*Orange Book: Approved drug products with therapeutic equivalence evaluations 2025*). All of these agents are available as auto-injectors and administered as an intramuscular (IM) or subcutaneous (SC) injection into the anterolateral aspect of the thigh. Based on clinical trial data, IM administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine (*Campbell and Kelso 2025, Sicherer et al 2017, Simons et al 1998, Simons et al 2001*).
    - Differences among the various injectable epinephrine agents include specific packaging and administration requirements. These products are approved and/or available as a 0.15 and/or 0.3 mg injection, while Auvi-Q is also available as a 0.1 mg injection. Auvi-Q is the first epinephrine auto-injector with audio instructions that guide patients and caregivers through the injection process.
  - Neffy (epinephrine nasal spray) was FDA-approved on August 9, 2024, and is the first nasal spray formulation of epinephrine for treatment of severe allergic reactions, providing an alternative to auto-injectors. This formulation may be beneficial for patients who are unable to self-inject epinephrine (*FDA news release 2024*). Neffy is available as a 1 mg and 2 mg single-dose nasal spray, supplied in a carton containing 2 blister packages, each with a single-dose nasal spray for one-time use.
- The epinephrine products for anaphylaxis are designed for emergency supportive therapy and are not intended to substitute for immediate medical care. In conjunction with the administration of any of these agents, patients should seek appropriate medical care, though if epinephrine is used promptly and the patient experiences a prompt, complete, and durable response, immediate activation of emergency medical services may not be required (*Campbell and Kelso 2025, Golden et al 2024, Sicherer et al 2017*).

- In some patients, ≥ 1 dose of epinephrine may be required to treat anaphylaxis. A dose of epinephrine may be repeated 5-to-15 minutes after the first dose. Rarely, a third dose may also be necessary, particularly for patients with severe anaphylaxis and who cannot access prompt emergency care. Bronchodilators (and supplemental oxygen) should be administered to patients with respiratory signs or symptoms that persist after the administration of epinephrine (*Campbell and Kelso 2025*).
  - A systematic review and meta-analysis of 86 studies on the use of multiple epinephrine doses in anaphylaxis found that 7.7% (95% confidence interval [CI], 6.4 to 9.1) of anaphylaxis events from any cause were treated with ≥ 1 epinephrine dose (*Patel et al 2021*). Patients at risk for anaphylaxis should carry 2 epinephrine autoinjectors and be educated on their use (*Brown et al 2020*). It is also recommended that patients who are prescribed Neffy have immediate access to 2 epinephrine nasal sprays at all times.

- Medispan class: Anaphylaxis Therapy Agents

Table 1. Medications Included Within Class Review

Drug	Available Strength(s)	Alternative Available (same molecular entity)[a]
Auvi-Q (epinephrine injection)	0.3 mg[b], 0.15 mg[b], 0.1 mg	-
epinephrine injection [b]	0.3 mg, 0.15 mg	-
EpiPen (epinephrine injection)	0.3 mg	✔ [c]
EpiPen Jr (epinephrine injection)	0.15 mg	✔ [c]
Neffy (epinephrine nasal spray)	2 mg/0.1 mL, 1 mg/0.1 mL	-

[a] For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
[b] These products are BX-rated by the FDA and are not considered to be therapeutically equivalent to other pharmaceutically equivalent products due to insufficient data.
[c] These products are AB-rated by the FDA. Generics given an AB rating by the FDA are considered to be therapeutically equivalent to the reference drug, with *in vivo* and/or *in vitro* evidence supporting bioequivalence.

(*Drugs@FDA 2025, FDA listing of authorized generics 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Epinephrine injection[a]	Neffy (epinephrine nasal spray)
Emergency treatment of allergic reactions (Type 1) including anaphylaxis to stinging insects (eg, order Hymenoptera, which include bees, wasps, hornets, yellow jackets, and fire ants), biting insects (eg, triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (eg, radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis	✔	
Emergency treatment of Type 1 allergic reactions, including anaphylaxis, in adult and pediatric patients ≥ 4 years old who weigh ≥ 15 kg		✔

[a] Intended for immediate administration as emergency supportive therapy only and are not a substitute for immediate medical care.

(*Prescribing information: Auvi-Q 2025, epinephrine injection 2021, EpiPen/EpiPen Jr 2023, Neffy 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

- A thorough literature search failed to retrieve any clinical trials evaluating the epinephrine products for the treatment of anaphylaxis in their FDA-approved indications. It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can be fatal within minutes and mandates prompt epinephrine administration.
- Epinephrine is essential for the treatment of anaphylaxis as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts. Immediate pre-hospital administration of epinephrine is associated with a lower risk of hospitalization and death in patients with anaphylaxis (*Bock et al 2001, Bock et al 2007, Boyce et al 2010, Campbell et al 2014, Fineman et al 2015, Fleming et al 2015, Golden et al 2017, Kemp et al 2008, Lieberman et al 2015, Sampson et al 1992, Sampson et al 2014, Sicherer et al 2017, Simons et al 1998, Simons et al 2001*).
- A randomized crossover study in healthy adults revealed that Auvi-Q and EpiPen were bioequivalent and had similar peak, total epinephrine exposure, and safety profiles after a single injection of 0.3 mg (*Edwards et al 2013*).
- FDA-approval of Neffy was based on 4 studies in 175 healthy adults without anaphylaxis. These studies compared the effects of Neffy 2 mg to approved epinephrine injection products. Results demonstrated comparable epinephrine blood concentrations and blood pressure and heart rate effects between Neffy and approved epinephrine injection products. A study of Neffy in children weighing > 66 pounds showed that epinephrine concentrations in children were similar to adults who received Neffy (*FDA news release 2024*). The FDA approval of Neffy 1 mg in patients ≥ 4 years old weighing ≥ 15 kg was extrapolated from clinical pharmacology studies in adults that compared the pharmacokinetic and pharmacodynamic profiles of Neffy to epinephrine injection that has established safety and effectiveness for this patient population. A single arm study of Neffy 1 mg in 42 patients 4 to 17 years of age weighing 15 to < 30 kg found a lower median change blood pressure comparable heart rate effects to adults who received Neffy 2 mg (*Neffy prescribing information 2025*).

Clinical Guidelines

- Current clinical guidelines including those from the National Institute of Allergy and Infectious Diseases (NIAID), American Academy of Pediatrics, the World Allergy Organization, and the Joint Task Force for Practice Parameters representing the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) and/or and the Joint Council of Allergy, Asthma and Immunology recommend epinephrine as the first-line medication of choice for the treatment of anaphylaxis due to its life-saving effects. It is suggested that patients who have a history of anaphylaxis or systemic reaction to allergens, including insect stings or foods, be prescribed an injectable epinephrine agent and be advised to carry it with them at all times. Consideration may also be given to patients who do not have a history of anaphylaxis but are at high risk of an anaphylactic reaction. (*Boyce et al 2010, Campbell et al 2014, Cardona et al 2020, Golden et al 2017, Golden et al 2024, Kemp et al 2008, Lieberman et al 2015, Sampson et al 2014, Shaker et al 2020, Sicherer et al 2017 [reaffirmed 2024], Simons et al 2015*).
  - Auto-injectors are preferred over prefilled syringes in the community setting due to ease of use and accuracy of dosing, but guidelines do not differentiate between the individual auto-injector products. Choice of an epinephrine agent should be evaluated on an individual patient basis; some factors to consider are product size, ease of use, ease of carrying, needle protection, and cost.
  - It is suggested that in general, clinicians should counsel patients and caregivers not to administer epinephrine preemptively to an asymptomatic patient (*Golden et al 2024*).
  - It is suggested that clinicians counsel patients that emergency medical services may not be immediately required if the patient experiences prompt, complete, and durable response to treatment with epinephrine, provided that additional epinephrine and medical care are readily available, if needed. Patients should always activate emergency medical services after epinephrine use if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens after the first dose of epinephrine (*Golden et al 2024*).
- Antihistamines, glucocorticoids, and bronchodilators may be used as adjunctive therapy to epinephrine but should not be used as initial or sole therapy as these agents do not have any life-saving properties (*Lieberman et al 2015, Shaker et al 2020, Sicherer et al 2017 [reaffirmed 2024], Simons et al 2015*).

Safety Summary

- Contraindications:

- There are no contraindications to the use of the epinephrine products for anaphylaxis in a life-threatening allergic reaction.

- Warnings and precautions (all agents):
  - Epinephrine is not intended as a substitute for immediate medical care; in conjunction with its administration, patients should seek appropriate medical care. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.
  - Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, renal impairment, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms. The presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.
  - Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations. All forms of epinephrine used for anaphylaxis contain sulfites that may cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible patients. Because the alternatives to epinephrine in a life-threatening situation may not be satisfactory, the presence of a sulfite should not deter administration of the agent for the treatment of serious allergic or other emergency situations, even in a sulfite-sensitive patient.
- Additional warnings and precautions (epinephrine injection):
  - Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by *Clostridia* (gas gangrene) have been reported at the injection site following epinephrine injection for anaphylaxis. To decrease the risk of *Clostridium* infection, the drug should not be injected into the buttock. Should signs and symptoms of infection occur, patients should seek medical care.
  - Epinephrine should only be injected into the anterolateral aspect of the thigh. In children, the leg should be held firmly in place prior to and during injection to reduce injury, as lacerations, bent needles, embedded needles, and other injuries have been observed after epinephrine auto-injector administration on children. Accidental injection into the hands or feet should be avoided as this may result in loss of blood flow to the area. If an accidental injection occurs, patients should inform a health care provider when he/she goes to the nearest emergency room for further treatment of anaphylaxis. Possible inadvertent intravascular administration should also be avoided.
    - An analysis evaluated 22 cases of epinephrine auto-injector-related injuries including lacerations and embedded needles in children. In response, product warnings were updated to require immobilization of a child's leg prior to and during injection, and injection time for the EpiPen and EpiPen Jr was reduced from 10 to 3 seconds (*Brown et al 2016*).
- Additional warnings and precautions (epinephrine nasal spray):
  - There is a potential for altered absorption of epinephrine nasal spray in patients with underlying structural or anatomical nasal conditions (eg, polyps, history of nasal fractures/injuries/surgery). Use of epinephrine administered by other routes should be considered for these patients.

- Adverse Events
  - Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some patients receiving therapeutic doses of epinephrine but are more likely to occur in patients with hypertension or hyperthyroidism. Large doses of epinephrine can cause acute hypertension. Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse events does not contraindicate its use in an acute, life-threatening allergic reaction.
  - Additional adverse events in patients receiving epinephrine nasal spray in clinical trials included throat irritation, headache, nasal discomfort, rhinorrhea, nasal pruritus, sneezing, abdominal pain, gingival pain, hypoesthesia (oral), and nasal congestion. A greater number of adverse events were experienced when patients received 2 doses vs 1 dose.

- Drug Interactions
  - Several drug-drug interactions exist with epinephrine. Patients who receive epinephrine while concomitantly taking anti-arrhythmics, cardiac glycosides, or diuretics should be observed carefully for the development of cardiac arrhythmias. The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines. The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs. Ergot alkaloids may also reverse the pressor effects of epinephrine.
    - Because epinephrine nasal spray may alter nasal mucosa for up to 2 weeks after administration, there is a potential risk for increased exposure/increased systemic absorption of nasal products; this may increase the risk of adverse events associated with these products.
- Pregnancy
  - There are no adequate or well-controlled studies of the acute effect of epinephrine in pregnant women. Although animal reproductive studies have shown an adverse effect on the fetus, epinephrine is still considered the first-line medication of choice for anaphylaxis during pregnancy due to its life-saving effects.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epinephrine injection	Auto-injectors: Auvi-Q, epinephrine injection, EpiPen, EpiPen Jr	IM or SC	Single injection of 1 dose; an additional dose may be needed with severe persistent anaphylaxis More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.	Dosing is based on weight: • Patients 7.5 to 15 kg: 0.1 mg • Patients 15 to 30 kg: 0.15 mg • Patients ≥ 30 kg: 0.3 mg Each of the products are designed for single use. Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary. Injection should be administered into the anterolateral aspect of the thigh, through clothing if necessary; repeated injections should not be administered at the same site. Prior to injection, each product should be visually inspected for particulate matter and discoloration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epinephrine nasal spray	Neffy	Nasal	1 spray administered into 1 nostril; a second dose may be administered after 5 minutes in the same nostril with a second nasal spray More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.	Dosage is based on weight: • Patients ≥ 30 kg: 2 mg • Patients < 30 kg: 1 mg Each Neffy nasal spray is for single use and delivers the entire dose upon activation. Neffy should not be primed. The right hand should be used to administer epinephrine to the right nostril and he left hand should be used to administer epinephrine to the left nostril. The nasal spray should not be angled to the inside septum or outer wall of the nose as some medication may be lost.

See the current prescribing information for full details.

- Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be administered.

Conclusion

- Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into the circulation.
- Foods, medications, and insect stings that cause a subsequent immunologic reaction are the most common reason for an anaphylactic reaction to occur. In humans, the heart, vasculature system, and lungs are predominantly affected during anaphylaxis, and fatalities can result from circulatory collapse and respiratory arrest. Current clinical guidelines recommend prompt epinephrine injection for sudden onset of any anaphylaxis symptoms after exposure to an allergen that previously caused anaphylaxis in a patient.
- Epinephrine can be lifesaving when administered as rapidly as possible once anaphylaxis is recognized and is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts.
- Acting as an agonist at α1, β1, and β2 adrenergic receptors, epinephrine works in the emergency treatment of anaphylaxis by causing increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2) and decreased release of mediators of inflammation from mast cells and basophils (β2). Of note, clinical trials evaluating epinephrine for emergency anaphylaxis treatment will never be performed, due to ethical considerations in a disorder that can be fatal within minutes and mandates prompt epinephrine administration.
- Epinephrine injection, Auvi-Q, EpiPen, EpiPen Jr, and Neffy are all FDA-approved for the emergency treatment of Type 1 allergic reactions, including anaphylaxis. As noted in the FDA-approved package labeling, epinephrine products are essential for the treatment of anaphylaxis, and these agents are designed for emergency supportive therapy. These epinephrine products are not intended as a substitute for immediate medical care and in conjunction with the administration of any of these agents, patients should seek appropriate medical care if warranted. In some patients, treatment of the anaphylactic reaction may require an additional 1 to 2 doses of epinephrine for severe persistent anaphylaxis. Patients at risk for anaphylaxis should carry > 1 epinephrine autoinjector or nasal spray and be educated on their use. Bronchodilators (and supplemental oxygen) should be administered to patients with respiratory signs or symptoms that persist after the administration of epinephrine.
- All of the injectable epinephrine products for anaphylaxis are available as single use products to be administered by the patient or caregiver as an IM or SC injection into the anterolateral aspect of the thigh. IM administration is preferred to SC administration as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine. Epinephrine nasal spray is available as a single use product administered into 1 nostril.

- Differences among the various epinephrine agents include specific packaging and administration requirements. Epinephrine injection, Auvi-Q, EpiPen, and EpiPen Jr are available as auto-injectors; each agent is approved as a 0.15 and 0.3 mg injection, while Auvi-Q is also available as a 0.1 mg injection. Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary. Auvi-Q is the only epinephrine agent that contains audio instructions to guide patients and caregivers through the injection process. Neffy is the first nasal spray formulation of epinephrine, providing an alternative to auto-injectors and may be beneficial for patients who are unable to self-inject epinephrine. Neffy is available as a 1 mg dose (for patients weighing 15 kg to < 30 kg) and 2 mg dose (for patients weighing ≥ 30 kg).

References

- Auvi-Q. Package insert. Kaleo, Inc.; April 2025.
- Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol.* 2001;107(1):191-193.
- Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol*. 2007;119(4):1016-1018.
- Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6):S1-58.
- Brown JC, Simons E, Rudders SA. Epinephrine in the management of anaphylaxis. *J Allergy Clin Immunol Pract*. 2020;8(4):1186-1195.
- Brown JC, Tuuri RE, Akhter S, et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med*. 2016;67(3):307-315.
- Campbell RL, Kelso JM. Anaphylaxis: emergency treatment. UpToDate Web Site. Updated June 20, 2025. Accessed August 12, 2025. www.uptodate.com.
- Campbell RL, Li JT, Nicklas RA, et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol*. 2014;113:599-608.
- Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J*. 2020;13(10):100472.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed August 12, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Edwards ES, Gunn R, Simons ER, et al. Bioavailability of epinephrine from Auvi-Q compared with EpiPen. *Ann Allergy Asthma Immunol*. 2013;111(2):132-137.
- Epinephrine injection. Package insert. Amneal Pharmaceuticals; February 2021.
- EpiPen/EpiPen Jr. Package insert. Viatris Specialty; February 2023.
- FDA listing of authorized generics. Food and Drug Administration Web site. Accessed August 12, 2025. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm126391.htm.
- FDA news release. Food and Drug Administration Web site. August 9, 2024. Accessed August 12, 2025.. https://www.fda.gov/news-events/press-announcements/fda-approves-first-nasal-spray-treatment-anaphylaxis#:~:text=Today%2C%20the%20U.S.%20Food%20and%20Drug%20Administration%20approved,weigh%20at%20least%2030%20kilograms%20%28about%2066%20pounds%29.
- Fineman S, Bowman S, Campbell R, et al; for the American College of Allergy, Asthma & Immunology (in press). Addressing barriers to emergency anaphylaxis care: from emergency medical services to emergency department to outpatient follow-up. *Ann Allergy Asthma Immunol*. 2015;115(4):301-305.
- Fleming JT, Clark S, Camargo CA Jr, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *J Allergy Clin Immunol Pract*. 2015;3(1):57-62.
- Golden DB, Demain J, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol*. 2017;118(1):28-54.
- Golden DBK, Wang J, Waserman S, et al. Anaphylaxis: A 2023 practice parameter update. *Ann Allergy Asthma Immunol.* 2024;132(2):124-176.
- Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis-a statement of the World Allergy Organization. *World Allergy Organ J*. 2008;1(Suppl 2):S18-26.
- Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341-384.
- Neffy. Package insert. ARS Pharmaceuticals Operations, Inc. March 2025.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. Accessed August 12, 2025.. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
- Patel N, Chong KW, Yip AYG, et al. Use of multiple epinephrine doses in anaphylaxis: A systematic review and meta-analysis. *J Allergy Clin Immunol*. 2021;148(5):1307-1315.
- Sampson HA, Aceves S, Bock A, et al for the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology. Food allergy: a practice parameter update – 2014. *J Allergy Clin Immunol*. 2014;134(5):1016-1025.
- Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;327(6):380-384.
- Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. *J Allergy Clin Immunol.* 2020;145(4):1083-1123.
- Sicherer SH, Simons FER, AAP section on allergy and immunology. Epinephrine for first-aid management of anaphylaxis. *Pediatrics.* 2017 [reaffirmed 2024];139(3):e20164006.

- Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J*. 2015;8(1):32.
- Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular vs subcutaneous injection. *J Allergy Clin Immunol*. 2001;108(5):871-873.
- Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol*. 1998;101(1 pt 1):33-37.
- Singletary EM, Charlton NP, Epstein JL, et al. Part 15: First aid: 2015 American Heart Association and American Red Cross guidelines update for first aid. *Circulation.* 2015;132(18 Suppl 2):S574-S589.
- Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy*. 2014;69(8):983-991.

Publication Date: September 9, 2025

Optum Rx®

Therapeutic Class Overview

Myasthenia Gravis Agents

Introduction

- Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission. In the United States (U.S.), MG has a incidence of approximately 68 cases per million (per person-years) and a adjusted mean prevalence of 316 cases per million. Within the Medicaid-insured population, slightly lower numbers emerged with the adjusted incidence of 50 new cases per million person-years, and the adjusted prevalence rate of 203.7 cases per million (*Ye et al 2024*).
- Hallmark symptoms of MG include a fluctuating degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles. Weakness is the result of an antibody-mediated, T cell-dependent immunologic attack directed at proteins in the postsynaptic membrane; the majority of patients with MG have autoantibodies against the anti-acetylcholine receptor (AChR) (*Dresser et al 2021*). These autoantibodies are directly pathogenic at the postsynaptic membrane of the neuromuscular junction by accelerating endocytosis and degradation of AChRs, as well as inducing complement-mediated membrane damage and inflammation *(Howard et al 2017).*
- The goal of therapy for MG is to reduce patient symptoms while minimizing side effects (*Dellarocca 2024*). The acetylcholinesterase (AChE) inhibitor pyridostigmine is generally used as initial first-line treatment for symptomatic MG *(Sanders et al 2016).* Most patients will also require some form of immunotherapy, including prednisone or glucocorticoid-sparing therapies for long-term maintenance. Glucocorticoid alternatives include azathioprine, mycophenolate mofetil, tacrolimus, or biologic therapies (*Bird 2025[a]*)
  - Approximately 10% of patients with severe MG are refractory to, or intolerant of the first-line glucocorticoid-sparing therapies and may require ongoing rescue therapy with intravenous immunoglobulins (IVIG) or plasma exchange (PE), or experience frequent myasthenic crises while on immunosuppressive therapy.
  - For patients with refractory MG, the complement inhibitor eculizumab, rituximab, or cyclophosphamide may be treatment options; there is limited clinical experience with other biologic therapies (ie, ravulizumab, rozanolixizumab, zilucoplan) for refractory disease (*Bird 2025[a]*).
  - Thymectomy may also lead to clinically meaningful benefits in patients with AChR antibody-positive MG *(Gronseth et al 2020).*
- The focus of this overview will include the AChE inhibitor pyridostigmine and targeted biologic therapies including the neonatal Fc receptor blockers (FcRn) blockers and complement inhibitors.
  - The FcRn blockers are a class of antibody fragment that targets the neonatal FcRn, preventing it from recycling immunoglobulin G (IgG) back into the blood; this causes a reduction in overall IgG levels, including the abnormal AChR antibodies that are present in MG (*Vyvgart prescribing information 2025*). Agents include Vyvgart (efgartigimod alfa), Rystiggo (rozanolixizumab-noli) and Imaavy (nipocalimab). Of note, nipocalimab and rozanolixizumab-noli have also demonstrated reductions in the muscle-specific tyrosine kinase (MuSK) antibody.
  - The complement inhibitors work by binding to the terminal complement protein C5, preventing the formation of the membrane attack complex (MAC), that are known to causes damage to the postsynaptic membrane of the neuromuscular junction (*White et al 2025*). Agents include Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan).
- Only the MG indications will be reviewed in detail within this overview; other Food and Drug Administration (FDA)-approved indications are listed in the indications section.
- Medispan classes: Antimyasthenic/cholinergic agents (pyridostigmine); hematological agents, misc. - complement inhibitors (eculizumab, ravulizumab, zilucoplan); immunomodulators – neonatal FcRn antagonist (efgartigimod, nipocalimab, rozanolixizumab).

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*
Imaavy (nipocalimab)	-
Mestinon (pyridostigmine) tablet, oral solution, extended-release tablet	✔
Rystiggo (rozanolixizumab-noli)	-
Soliris (eculizumab) injection	-
Ultomiris (ravulizumab-cwvz) injection	-
Vyvgart (efgartigimod alfa-fcab) injection	-

Drug	Alternative Available (same molecular entity)*
Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc)	
Zilbrysq (zilucoplan)	-

*For example, authorized brand alternative, branded generic, generic, interchangeable biosimilar

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025, Purple Book: Database of Licensed Biological Products 2025*)

Indications

Table 2. FDA approved indications - pyridostigmine

Indication	Mestinon (pyridostigmine)
Treatment of MG	✔

(*Prescribing information: Mestinon 2020)*

Table 3. FDA approved indications – Complement inhibitors

Indication	Soliris (eculizumab) [a]	Ultomiris (ravulizumab-cwvz) [b]	Zilbrysq (zilucoplan)
Treatment of generalized MG (gMG) in adult patients who are AChR antibody-positive	✔	✔	✔

[a] Soliris (eculizumab) has 3 additional FDA-approved indications: 1) treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis; 2) for the treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy; and 3) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody-positive. For the indication of aHUS, there is a limitation of use: Soliris is not indicated for the treatment of patients with Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS).
[b] Ultomiris (ravulizumab-cwvz) has 3 additional FDA-approved indications: 1) treatment of PNH in patients ≥ 1 month of age; 2) treatment of aHUS to inhibit complement-mediated thrombotic microangiopathy in patients ≥ 1 month of age; and 3) treatment of NMOSD in adults who are anti-aquaporin-4 (AQP4) antibody-positive.

(*Prescribing information: Soliris 2025, Ultomiris 2025, Zilbrysq 2025*)

Table 4. FDA approved indications – FcRn receptor blockers

Indication	Imaavy (nipocalimab)	Rystiggo (rozanolixizumab-noli)	Vyvgart (efgartigimod alfa-fcab)	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) [a]
Treatment of gMG in adult patients who are AChR antibody-positive	✔ (12+)	✔	✔	✔
Treatment of gMG in adult patients who are MuSK antibody-positive	✔ (12+)	✔		

[a] Vyvgart Hytrulo has 1 additional FDA approved indication: treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).

(*Prescribing information: Imaavy 2025, Rystiggo 2025, Vyvgart 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

- For the assessment of patients with gMG, the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score and the Quantitative Myasthenia Gravis (QMG) scale are utilized (*ClinicalTrials.gov [NCT03669588], Howard et al 2021*).
  - The MG-ADL is an 8-item patient-reported outcome scale used to measure MG symptoms and effect on daily activities; each item is graded on a 4-point symptom severity scale from 0 (normal) to 3 (most severe), with a total score ranging from 0 to 24, with higher scores reflecting worse symptoms and greater functional impairment.
  - The QMG is a 13-item tool that measures disease severity based on bodily function impairment; providers rate items on a 4-point severity scale from 0 (no symptoms) to 3 (severe symptoms), with a total score ranging from 0 to 39, where higher scores indicate greater disease severity.
  - A clinically meaningful improvement is defined as a 2- or 3-point decrease in the MG-ADL total score or QMG score, respectively.

Pyridostigmine

- Pyridostigmine and other AChE inhibitors have been shown to be effective based on robust observation data and clinical experience. Randomized controlled trials (RCT) have not been conducted (*Bird 2025[b], Maggi and Mantegaza 2011*). Pyridostigmine only provides symptomatic relief of MG and may be adequate treatment for some patients, but those with gMG will require additional therapy.

Complement inhibitors

Soliris (eculizumab)

- The efficacy of eculizumab in adults with anti-AChR antibody-positive refractory gMG was evaluated in a 26-week, Phase 3, double-blind (DB), multicenter (MC), placebo-controlled (PC), RCT (REGAIN). Patients who had been previously treated with immunosuppressive therapies or chronic IVIG or PE without symptom control were randomized to receive eculizumab (n = 62) or placebo (n = 63). Patients receiving previous treatment with a AChE inhibitor, corticosteroid, or other immunosuppressive treatments were to maintain the dose and schedule of these therapies. For the primary endpoint, change from baseline to Week 26 in MG-ADL total score measured by worst-rank analysis of covariance (ANCOVA), the difference between groups in mean total score did not achieve statistical significance; however, in the responder analysis for the MG-ADL and the QMG scores, a higher proportion of patients achieved a clinically meaningful response with eculizumab than with placebo (*Howard et al 2017*).
  - In an open-label extension (OLE) of the REGAIN trial (N = 117) patients were treated with eculizumab 1200 mg every 2 weeks for up to 3 years (median 23 months). Results demonstrated that the exacerbation rate that was 75% lower than the 1-year before baseline (25 vs 102 events, respectively per 100 patient-years; p < 0.0001); functional gains (eg, activities of daily living [ADLs], muscle strength, functional ability and quality of life) were maintained over through 3 years (*Muppidi et al 2019*).

Ultomiris (ravulizumab-cwvz)

- A 26-week, DB, PC, MC, RCT established the efficacy and safety of ravulizumab-cwvz in 175 adults with anti-AChR antibody-positive gMG. Patients were randomized to ravulizumab-cwvz (n = 86) or placebo (n = 89) administered via IV administration and dosed based on body weight. Patients were also treated with AChE inhibitors (80%), corticosteroids (70%), and non-steroidal immunosuppressants (68%) at baseline and continued during the study. The primary endpoint, mean MG-ADL change from baseline at Week 26 was significantly improved with ravulizumab-cwvz (difference, -1.6; 95% confidence interval [CI], -2.6 to -0.7; p < 0.001) compared to placebo. Ravulizumab-cwvz also significantly improved the key secondary endpoint, change from baseline in QMG (difference, -2.0; 95% CI, -3.2 to -0.8; p < 0.001). Serious adverse effects (AEs; ie, infections, pneumonia) were reported in 23% of patients receiving ravulizumab-cwvz (*Ultomiris prescribing information 2025*).
  - Long-term efficacy was demonstrated in an OLE study, which reported sustained improvements across all metrics for up to 60 weeks (*Meisel et al 2023*).

Zilbrysq (zilucoplan)

- The efficacy of zilucopan in adults with anti-AChR antibody-positive gMG was evaluated in a 12-week, Phase 3, DB, MC, PC, RCT (RAISE). Patients with Myasthenia Gravis Foundation of America (MGFA) class II to IV, MG-ADL score of ≥ 6, and QMG ≥ 12 were included in this study. Patients were randomized to zilucoplan 0.3 mg/kg once daily by self-

injection (n = 86) or placebo (n = 88) for 12 weeks. The primary efficacy endpoint was change from baseline to week 12 in MG-ADL score in the modified intention-to-treat population (*Howard et al 2023*).
  - Overall, the patients in the zilucoplan showed a greater reduction in MG-ADL score from baseline to week 12, compared to those in the placebo group (least squares mean [LSM] change -4.39 vs -2.30; LSM difference, -2.09; p = 0.0004).

FcRn Blockers

Vyvgart (efgartigimod alfa-fcab)

- The efficacy and safety of efgartigimod alfa-fcab were established in the 26-week, Phase 3, DB, MC, PC, randomized controlled ADAPT trial (*Howard et al 2021*). The trial included 167 adults with gMG with anti-AChR antibody-positive or negative status with a baseline MG-ADL total score of ≥ 5, with > 50% related to non-ocular symptoms. Patients were on stable doses of AChE inhibitors, corticosteroids, or nonsteroidal immunosuppressives (in combination or as monotherapy) at baseline. Patients were randomized to placebo or efgartigimod alfa-fcab 10 mg/kg administered IV weekly for 4 weeks. Repeated cycles were initiated depending on clinical response with MG-ADL scores ≥ 5 and no earlier than 8 weeks after the initiation of the previous cycle. The primary endpoint was the proportion of MG-ADL responders, defined as ≥ 2-point MG-ADL improvement sustained for ≥ 4 weeks in anti-AChR antibody-positive patients in cycle 1. Key secondary endpoints were the proportion of QMG responders, defined as ≥ 3-point improvement over 4 consecutive weeks starting by week 4, and the proportion of MG-ADL responders in cycle 1 in the overall population.
  - The proportion of MG-ADL responders in cycle 1 in the anti-AChR antibody-positive patients were significantly higher in the efgartigimod alfa-fcab group (44/65 [68%]) compared with placebo (19/64 [30%]) (odds ratio [OR], 4.95; 95% CI, 2.21 to 11.53; p < 0.0001).
  - Patients in the efgartigimod alfa-fcab group had a higher rate of response on QMG in cycle 1 compared with the placebo group (41/65 [63%] vs 9/64 [14%], respectively; OR, 10.84; 95% CI, 4.18 to 31.20; p < 0.0001).
  - The proportion of MG-ADL responders in cycle 1 in the overall population were significantly higher in the efgartigimod alfa-fcab group (57/84 [68%]) compared with placebo (31/83 [37%]; OR, 3.70; 95% CI, 1.85 to 7.58; p < 0.0001).
- The ADAPT-SC trial was a 10 week non-inferiority trial that compared the efficacy of subcutaneous (SC) efgartigimod to IV efgartigimod in patients with gMG for 1 treatment cycle (4 once-weekly administrations of either formulation); SC efgartigimod was shown to be noninferior to IV efgartigimod in lowering total IgG at 4 weeks. Interim open-label extension results (up to 6 cycles) confirmed consistent IgG reduction (*Howard et al 2024*).

Imaavy (nipocalimab)

- The efficacy of nipocalimab in adults with antibody-positive refractory gMG was evaluated in a 24-week, DB, MC, PC, RCT (VIVACITY-MG3 trial). In this study, 88% of patients were AChR-positive, 11% were MuSK-positive. Included patients were on a stable dose of standard of care therapy prior to baseline (ie, AChE inhibitor, steroids or non-steroidal immunosuppressive therapies with suboptimal response), were MGFA class II to IV, and had a MG-ADL score of ≥ 6. A total of 196 patients were randomized to receive nipocalimab or placebo (n = 98 for both groups). The primary efficacy endpoint was the difference in the mean change from baseline over weeks 22, 23, and 24 on the MG-ADL total score (*Antozzi et al 2025*).
  - Treatment with nipocalimab demonstrated a statistically significant difference in the primary end point (-4.70 with nipocalimab vs -3.25 with placebo; difference, -1.45; 95% CI, -2.38 to -0.52; p = 0.0024). An OLE study is underway.
  - An ongoing, Phase 2/3, open label, single arm study in pediatric patients ≥ 12 years of age demonstrated reduced serum immunoglobulin G (IgG) levels at 24 weeks (primary endpoint) and improvements in MG-ADL and QMC scales (*Strober et al 2024*).

Rystiggo (rozanolixizumab)

- Efficacy and safety of rozanolixizumab in adults with anti-AChR or anti-MuSK antibody-positive gMG was evaluated in the Phase 3, DB, PC, MC, RCT (MycarinG). Included patients were diagnosed as MGFA class II to IV, had a MG-ADL ≥ 3 from non-ocular symptoms, and QMG ≥ 11. A total of 200 patients were randomized to receive rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo. The primary endpoint was Change in MG-ADL from baseline through day 43 (*Bril et al 2023*).
  - Overall, reductions in MG-ADL score from baseline to day 43 were greater in both the rozanolixizumab 7 mg/kg and rozanolixizumab 10 mg/kg groups compared to placebo (LSM, -3.37 vs -3.40 vs -0.78, respectively; p < 0.0001 for both); rozanolixizumab was effective in patients with AChE and MuSK autoantibody-positive gMG types.

- A pooled analysis of MycarinG and 2 OLE studies demonstrated consistent and clinically meaningful improvements in MG-ADL, myasthenia gravis composite (MGC), and QMG scores at the end of the first cycle (day 43) and subsequent cycles (*Bril et al 2025*).

Systematic Review and meta-analyses (MA)

- Three MAs evaluating FcRn blockers (+/- other targeted therapies) in adult patients with gMG have been published (*Gu et al 2024, Zhong et al 2024,* and *Ma et al 2024*). Overall, authors concluded that FcRn blockers were effective therapies for gMG, ranking above complement inhibitors and off-label targeted therapies (eg, rituximab) in efficacy as measured by MG-ADL and/or QMG. In all MAs, rozanolixizumab and efgartigimod were among the most effective therapies (data from VIVACITY-MG3 [nipocalimab] data were not incorporated into these MAs).
- Another systematic review and MA of 8 RCTs evaluated the efficacy of various FcRn blockers (ie, efgartigimod, rozanolixizumab, satralizumab [not FDA approved for MG], batoclimab [not available in the U.S.], and nipocalimab) in MG patients. Key findings included significantly improved clinical outcomes with FcRn inhibitors compared to placebo across several MG-specific scales including MD-ADL (mean difference [MD], -1.45) and QMG (MD, -2.33). In terms of safety, rozanolixizumab was associated with higher rates of AEs (*Ahktar et al 2025*).

- The Institute for Clinical and Economic Review (ICER) evaluated the Phase 3 studies supporting eculizumab in the REGAIN study and efgartigimod alfa-fcab in the ADAPT study for the treatment of gMG (*Howard et al 2017, Howard et al 2021, Tice et al 2021*). Evidence supporting rituximab and IVIG were also reviewed. See Table 5.
  - A network MA comparing eculizumab, efgartigimod alfa-fcab, and placebo at 4 weeks in patients with refractory anti-AChR antibody-positive gMG showed that both eculizumab and efgartigimod alfa-fcab significantly improved MG-ADL and QMG. At 4 weeks, efgartigimod alfa-fcab had significantly greater improvements compared with eculizumab. At 8 weeks, the results for efgartigimod alfa-fcab had returned to near baseline due to the dosing schedule and were lower than those for eculizumab.

Table 5. Pivotal trial results in anti-AChR antibody-positive populations

Trial	Treatment Arms	MG-ADL			QMG		
		Baseline	Mean Δ MG-ADL		Baseline	Mean Δ QMG	
			4 weeks	8 weeks		4 weeks	8 weeks
REGAIN	Eculizumab (n = 62)	10.5	-3.5; p = 0.0008	-3.7; p = 0.0046	17.3	-3.3; p = 0.0256	-4.0; p = 0.0021
	Placebo (n = 63)	9.9	-1.5	-1.8	16.9	-1.5	-1.4
ADAPT anti-AChR antibody-positive	Efgartigimod (n = 65)	9.0	-4.6; p < 0.05	-2.2; NS	16.0	-6.2; p < 0.05	-2.9; p < 0.05
	Placebo (n = 64)	8.6	-1.7	-1.7	15.2	-1.0	-1.2

Abbreviations: Δ = change from baseline; AChR = acetylcholine receptor; MG-ADL = Myasthenia Gravis-Activities of Daily Living; NS = not significant; QMG = Quantitative Myasthenia Gravis

- In adults with gMG positive for anti-AChR antibodies refractory to conventional therapy, ICER concluded:
  - There is moderate certainty of a small or substantial net health benefit with high certainty of at least a small benefit for eculizumab added to conventional therapy compared to conventional therapy alone (Evidence Rating B+).
  - There is moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod alfa-fcab added to conventional therapy with high certainty of at least comparable net health benefit (Evidence Rating C++).
  - Given uncertainties about dosing and long-term benefits and safety of efgartigimod alfa-fcab and the limitations of indirect comparisons, evidence was insufficient (Evidence Rating I) to distinguish the net health benefits of efgartigimod alfa-fcab from eculizumab.
  - Evidence was insufficient (Evidence Rating I) to distinguish the net health benefits of rituximab and IVIG from placebo, eculizumab, and efgartigimod alfa-fcab.
- In adults with gMG negative for anti-AChR antibodies, ICER concluded:

- Evidence was insufficient (Evidence Rating I) to distinguish the net health benefits of efgartigimod alfa-fcab added to conventional therapy from conventional therapy alone.

Clinical Guidelines

- MG is a heterogeneous disease state with no internationally accepted standard of care. Due to the heterogenous nature of the disease, no one treatment approach is best for all patients (*Sanders et al 2016*).
- International consensus guidance for the management of MG recommends pyridostigmine as initial symptomatic treatment in most patients with MG. The dose of pyridostigmine should be titrated and individualized based on symptoms (*Narayanaswami et al 2020, Sanders et al 2016*).
  - Pyridostigmine should be part of the initial treatment in most patients and adjusted as needed based on symptoms.
  - Corticosteroids and/or nonsteroidal immunosuppressive therapy (eg, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used in all patients who have not met treatment goals after an adequate trial of pyridostigmine.
    - A nonsteroidal immunosuppressant agent should be added to corticosteroids when: steroid AEs are deemed significant by the patient or physician, response to adequate trial of corticosteroids is inadequate, or the corticosteroid dose cannot be reduced due to symptom relapse.
    - Nonsteroidal immunosuppressant agents should be used alone when corticosteroids are contraindicated or refused. If corticosteroids and a nonsteroid immunosuppressant agent are being used together, the corticosteroid should be gradually tapered off once treatment goals are met; If a relapse occurs while tapering, the dose should be adjusted upward. A majority of patients will continue nonsteroidal immunosuppressant therapy for many years or for life. An alternative nonsteroidal immunosuppressant agent should be considered if a patient has significant AEs or complications.
  - Patients with refractory MG, defined as patients who do not achieve treatment goals despite an adequate trial of corticosteroids and ≥ 2 other non-steroidal immunosuppressants, should be referred to as physician specialists for management. The following may be used in refractory gMG:
    - IVIG and/or plasma exchange: appropriate for short-term treatment in patients with life-threatening signs and symptoms, when rapid response is needed, as perioperative SOC, prior to beginning steroids, or when other therapy is insufficiently effective.
    - Cyclophosphamide
    - Rituximab: should be considered as an early therapeutic option in patients with MuSK antibody-positive disease with an unsatisfactory response to initial immunotherapy.
      - The efficacy of rituximab in refractory AChR antibody-positive gMG is uncertain.
    - Eculizumab: should be considered for the treatment of severe, refractory, AChR antibody-positive gMG after an adequate trial of alternative immunotherapies have been unsuccessful.
- In non-thymomatous, AChR antibody-positive gMG patients 18 to 50 years of age, The American Academy of Neurology (AAN) recommends that thymectomy should be considered early in the disease to improve clinical outcomes and to minimize immunotherapy requirements and the need for hospitalizations for disease exacerbations. Thymectomy should be strongly considered for patients with gMG who fail to respond to an initial trial of immunotherapy or have intolerable AEs from that therapy (*Gronseth et al 2020*).
- These society guidelines were published prior to the approval of FcRn blockers, ravulizumab, and zilucoplan for the indication of gMG.

Safety Summary

Pyridostigmine (oral)

- Contraindication: Patients with bronchial asthma and urinary or intestinal obstruction.
- Warning and precaution: cholinergic crisis
- Common AEs are usually related to overdosage and fall into 2 categories, muscarinic and nicotinic.
  - Muscarinic AEs: Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, and diaphoresis
  - Nicotinic AEs: Muscle cramps, fasciculation, weakness
  - Skin rash may occur due to the bromide radical but usually subside after discontinuation of medication.

Imaavy (nipocalimab)
- Contraindicated in patients with history of serious hypersensitivity reaction to nipocalimab or any of its excipients.
- Warnings and precautions
  - Infections: Delay treatment in patients with an active infection; increased risk of activation of latent viral infections (eg, herpes zoster); administration of live vaccines is not recommended due to reduced immunoglobulin (Ig) G from nipocalimab therapy.
  - Risk of hypersensitivity reactions such as angioedema, anaphylaxis, rash, urticaria, or eczema.
  - Increased risk of infusion related reactions: If severe, discontinue and administer appropriate therapy; consider risk vs benefit before readministering. If mild to moderate reaction occurs, may rechallenge with close observation, slower infusion rate, and premedication.
- The most common AEs (≥ 10%) included respiratory tract infections, peripheral edema, and muscle spasms
- Drug interactions: Concomitant use of nipocalimab with other medications that bind to FcRn (eg, immunoglobulins, monoclonal antibodies, antibody derivatives containing the human Fc domain of the IgG subclass) may lower systemic exposures and reduce effectiveness of these agents; consider alternatives.

Rystiggo (rozanolixizumab-noli)
- Warnings and precautions: Delay treatment in patients with active infections, risk of hypersensitivity reactions, serious aseptic meningitis has been reported; monitor for symptoms and initiate treatment according to standard of care.
- The most common (≥ 10%) AEs included headache, infections, diarrhea, pyrexia, hypersensitivity reactions, and nausea.
- Drug interactions: Concomitant use of rozanolixizumab with other medications that bind to FcRn is not recommended.

Vyvgart (efgartigimod alfa-fcab) and **Vyvgart Hytrulo** (efgartigimod alfa and hyaluronidase-qvfc)
- Warnings and precautions: Delay treatment in patients with active infections, risk of hypersensitivity reactions.
  - Vyvgart Hytrulo carries an additional warning for an increased risk of infusion-related reactions (if severe, discontinue and administer appropriate therapy; consider risk vs benefit before readministering. If mild to moderate reaction occurs, may rechallenge with close observation, slower infusion rate, and premedication).
- The most common (≥ 10%) AEs included respiratory tract infections, headache, and urinary tract infection.
  - Vyvgart Hytrulo is also associated with injection site reactions (≥ 15%).
- Drug interactions: Concomitant use of efgartigimod with other medications that bind to FcRn is not recommended.

Soliris (eculizumab) and **Ultomiris** (ravulizumab-cwvz)
- **Boxed warning:** Serious meningococcal infections; all patients should receive meningococcal vaccines ≥ 2 weeks prior to first dose; Patients are at an increased risk for invasive disease causes by *Neisseria* (*N.*) *meningitidis*. Both agents are available only through risk evaluation and mitigation strategy (REMS) program.
- Contraindications: Unresolved *N. meningitidis* infection, patients not currently vaccinated against *N. meningitidis*
- Warnings and precautions*:* patients being treated for serious meningococcal infections, patients with other systemic infections, infusion related reactions.
- The most common (≥ 10%) AE in the gMG trial of eculizumab was musculoskeletal pain.
- The most common (≥ 10%) AEs in the gMG trial of ravulizumab-cwvz were diarrhea and upper respiratory tract infection.

Zilbrysq (zilucoplan)
- **Boxed warning:** Serious meningococcal infections; all patients should receive meningococcal vaccines ≥ 2 weeks prior to first dose. Patients receiving zilucoplan are at an increased risk for invasive disease causes by *N. meningitidis*. Monitor patients for early signs and symptoms of meningococcal infections regardless of vaccination.
- Contraindications: Unresolved *N. meningitidis* infection, patients not currently vaccinated against *N. meningitidis*.
- Warnings and precautions*:* patients with other systemic infections, risk of pancreatitis and pancreatic cysts.
- The most common (≥ 10%) AEs in patients with gMG were injection site reactions, upper respiratory tract infection, and diarrhea.

Dosing and Administration

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Imaavy (nipocalimab)	Injection; single dose vial	IV	One time initial dose of 30 mg/kg, followed by 15 mg/kg ever 2 weeks.	Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation. Live vaccines are not recommended during treatment due to transient reductions in IgG levels.
Mestinon (pyridostigmine)	Tablet, extended release tablet, oral solution	Oral	Solution and immediate-release tablets: Once daily (administration may be spaced throughout the day) Timespan extended-release tablets: Once or twice daily	Dosage and frequency must be individualized. The oral solution formulation allows dosage adjustment for children and “brittle” MG patients who require fractional dosing. Timespan extended-release tablets: interval between doses should be ≥ 6 hours.
Rystiggo (rozanolixizumab-noli)	Injection; single dose vial	SC	Once weekly for 6 weeks. Administer subsequent treatment cycles based on clinical evaluation.	Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation. The safety of initiating subsequent cycles < 63 days from the start of the previous treatment cycle has not been established.
Soliris (eculizumab)	Injection; single dose vial	IV	Initial dose weekly for the first 4 weeks, followed by a lower dose 1 week later, then a higher maintenance dose every 2 weeks thereafter	Patients should be vaccinated against meningococcal infections according to ACIP recommendations ≥ 2 weeks prior to initiation; If urgent therapy is indicated in a patient not up to date with vaccines, antibacterial drug

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				prophylaxis should be given. Supplemental dosing is required for patients with MG in cases of concomitant plasmapheresis or PE, or fresh frozen plasma infusion.
Ultomiris (ravulizumab-cwvz)	Injection; single-dose vial	IV	Maintenance doses administered every 4 or 8 weeks (depending on indication and body weight), starting 2 weeks after loading dose.	Patients should be vaccinated against meningococcal infections according to ACIP recommendations ≥ 2 weeks prior to initiation; If urgent therapy is indicated in a patient not up to date with vaccines, antibacterial drug prophylaxis should be given. Supplemental dosing is required for patients with MG in cases of concomitant plasmapheresis or PE, or fresh frozen plasma infusion.
Vyvgart (efgartigimod alfa-fcab)	Injection; single-dose vial	IV	Dose of 10 mg/kg once weekly for 4 weeks. In patients weighing ≥ 120 kg, the recommended dose is 1200 mg per infusion. Administer subsequent treatment cycles based on clinical evaluation.	Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle. Patients should be monitored during administration and for 1 hour after for hypersensitivity reactions.
Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc)	Injection; prefilled syringe and single-dose vial	SC	Administer in cycles of once weekly injections for 4 weeks. Administer subsequent treatment cycles based on clinical evaluation.	Evaluate the need to administer age-appropriate vaccines according to immunization guidelines before initiation of a new treatment cycle.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Prefilled syringe can be administered by patients and/or caregivers.
Zilbrysq (zilucoplan)	Injections; prefilled syringe	SC	Once daily; weight-based dosing.	Obtain baseline amylase and lipase. Pregnancy: may cause fetal harm.

See the current prescribing information for full details.

Conclusion

- Generalized MG is a rare disorder of neuromuscular transmission that results in variable degrees of weakness impacting activities of daily living due to autoantibodies. The majority of patients have antibodies targeting AChR.
- The treatment goal of treatment MG is to reduce patient symptoms while minimizing side effects. Treatment guidelines recommend pyridostigmine as the first-line therapy for symptomatic relief; however, most patients with generalized MG will require additional immunotherapy, including corticosteroids and glucocorticoid-sparing agents. For those unresponsive to conventional treatments, targeted biologic therapies such as FcRn blockers and complement inhibitors have demonstrated significant clinical efficacy, particularly in anti-AChR antibody-positive populations.
- Recent clinical trials and MAs demonstrate the efficacy of FcRn blockers (efgartigimod, rozanolixizumab, nipocalimab) and complement inhibitors (eculizumab, ravulizumab, zilucoplan) in improving functional outcomes and quality of life for patients with MG.
- FcRn inhibitors are given parenterally. Efgartigimod (IV), efgartigimod PH20 (SC; can be self-administered), and rozanolixizumab (SC) are administered in symptom-driven treatment cycles while nipocalimab (IV) is administered on an every 2-week schedule.
  - Only nipocalimab and rozanolixizumab are indicated in anti-MuSK positive disease.
  - The safety profiles of these agents are similar; rozanolixizumab carries a warning for aseptic meningitis.
  - Common AEs observed with FcRn inhibitors included infection, headache, hypersensitivity, and infusion-related reactions; nipocalimab is associated with the unique AEs of peripheral edema and total cholesterol elevations.
- The complement inhibitors are also given parenterally; eculizumab (IV) is dosed every 2 weeks, ravulizumab (IV) every 4 to 8 weeks, and zilucoplan (SC) daily. All 3 agents carry a Boxed Warning for the risk of serious meningococcal infections, including invasive disease causes by *N. meningitidis;* all patients should receive meningococcal vaccines ≥ 2 weeks prior to first dose. The most common AEs included respiratory infections, diarrhea, and injection site reactions (zilucoplan).

References

- Akhtar M, Akhtar M, Farooqi HA, et al. Efficacy and safety of FcRn inhibitors in patients with Myasthenia gravis: An updated systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2025:254:108910. doi: 10.1016/j.clineuro.2025.108910.
- Antozzi C, Vu T, Ramchandren S, et al. Safety and efficacy of nipocalimab in adults with generalised myasthenia gravis (Vivacity-MG3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2025;24(2):105-116. doi: 10.1016/S1474-4422(24)00498-8.
- Bird SJ. Chronic immunosuppressive therapy for myasthenia gravis. UpToDate Web site. Updated March 24, 2025[a]. Accessed October 23, 2025. http://www.uptodate.com.
- Bird SJ. Overview of the treatment of myasthenia gravis. UpToDate Web site. Updated September 26, 2025[b]. Accessed October 23, 2025. http://www.uptodate.com.
- Bril V, Drużdż A, Grosskreutz J, et al. Rozanolixizumab in generalized myasthenia gravis: Pooled analysis of the Phase 3 MycarinG study and two open-label extensions. *J Neuromuscul Dis*. 2025;12(2):218-230. doi:10.1177/22143602241305511
- Bril V, Drużdż A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. *Lancet Neurol*. 2023;22(5):383-394. doi:10.1016/S1474-4422(23)00077-7
- ClinicalTrials.gov Web site. Accessed October 23, 2025.http://www.clinicaltrials.gov
- Dellarocca MA. The treatment of myasthenia gravis. *US Pharm*. 2024;49(1):4-8.
- Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. *J Clin Med*. 2021;10(11):2235.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed October 23, 2025.
- Gronseth GS, Barohn R, Narayanaswami P. Practice advisory: thymectomy for myasthenia gravis (practice parameter update). Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2020;94:705-709. doi: 10.1212/WNL.0000000000009294

- Gu J, Qiao Y, Huang R, Cong S. Efficacy and safety of immunosuppressants and monoclonal antibodies in adults with myasthenia gravis: a systematic review and network meta-analysis. *J Transl Med*. 2024;22(1):955. Published 2024 Oct 21. doi:10.1186/s12967-024-05751-1
- Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurology*. 2023;22:395-406.
- Howard JF, Bril V, Karam C, et al for the ADAPT Investigator Study Group. Safety, efficacy, and tolerability of efgartigimod in patients with generalized myasthenia gravis (ADAPT): a multcentre, randomized, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2021;20:526-536.
- Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol.* 2017;16(12):976-986
- Howard JF, Vu T, Li G, et al. Subcutaneous efgartigimod PH20 in generalized myasthenia gravis: A phase 3 randomized noninferiority study (ADAPT-SC) and interim analyses of a long-term open-label extension study (ADAPT-SC+). *Neurotherapeutics*. 2024;21(5):e00378. doi:10.1016/j.neurot.2024.e00378.
- Imaavy. Package insert. Johnson & Johnson. April 2025.
- Ma Y, Nie X, Zhu G, Qi W, Hao L, Guo X. The Efficacy and Safety of Different Targeted Drugs for the Treatment of Generalized Myasthenia Gravis: A Systematic Review and Bayesian Network Meta-analysis. *CNS Drugs*. 2024;38(2):93-104. doi:10.1007/s40263-024-01062-7
- Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. *Clin Drug Investig*. 2011;31(10):691-701.
- Meisel A, Annane D, Vu T, et al. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. *J Neurol.* 2023;270(8):3862-3875. doi: 10.1007/s00415-023-11699-x.
- Mestinon. Package insert. Bausch Health US, LLC; December 2020.
- Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. 2019;60(1):14. Epub 2019 Mar 8.
- Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: focused update. *Neurology*. 2021;96:114-122.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed October 23, 2025.
- Purple Book: Database of licensed biological products. Food and Drug Administration Web site. https://purplebooksearch.fda.gov/. Accessed July 27, 2022.
- Rystiggo. Package insert. UCB, Inc.; March 2025.
- Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016;87(4):419-425.
- Soliris. Package insert. Alexion Pharmaceuticals, Inc.; February 2025.
- Strober J, et al. Safety and effectiveness of nipocalimab in adolescent participants in the open label Phase 2/3 Vibrance-MG clinical study. Presentation at American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting. October 2024. Accessed October 23, 2025. https://www.mdaconference.org/abstract-library/safety-and-effectiveness-of-nipocalimab-in-adolescent-participants-in-the-open-label-phase-2-3-vibrance-mg-clinical-study/
- Tice JA, Touchette DR, Nikitin D, et al. Eculizumab and efgartigimod for the treatment of myasthenia gravis: Effectiveness and value; final report. Institute for Clinical and Economic Review, October 20, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Final-Report_102021-1.pdf. Accessed October 23, 2025.
- Ultomiris. Package insert. Alexion Pharmaceuticals, Inc.; September 2025.
- Vyvgart. Package insert. Argenx US, Inc.; October 2025.
- White LM, Clay FJ, Forbes AM, et al. Complement inhibitors for myasthenia gravis in adults. *Cochrane Database Syst Rev*. 2025;7(7):CD016098. doi: 10.1002/14651858.CD016098.
- Ye Y, Murdock DJ, Chen C, Liedtke Knox CA, et al. Epidemiology of myasthenia gravis in the United States. *Front Neurol.* 2024:15:1339167. doi: 10.3389/fneur.2024.1339167.
- Zhong H, Li Z, Li X, et al. Initiation response, maximized therapeutic efficacy, and post-treatment effects of biological targeted therapies in myasthenia gravis: a systematic review and network meta-analysis. *Front Neurol*. 2024;15:1479685. doi:10.3389/fneur.2024.1479685
- Zilbrysq. Package insert. UCB, Inc.; February 2025.

Publication Date: November 14, 2025

Optum Rx®

Therapeutic Class Overview

Atopic dermatitis agents

Introduction

- Atopic dermatitis (AD), also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus. It is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). It is one of the most common skin disorders in the United States, affecting 13% of pediatrics and 7% of adults (*Berke et al 2012, Eichenfield et al 2014[a], Food and Drug Administration [FDA] presentation 2015, Silverberg and Howe 2025*).
- The pathogenesis of AD is complex and attributed to a complex interplay of epidermal barrier dysfunction, cutaneous inflammation, and environmental factors. Manifestations vary by age and AD severity, but hallmark features include dry skin and pruritis (*Castro 2006, Eichenfield et al 2014[a], Silverberg and Howe 2025, Sidbury et al 2023*).
- There is no cure for AD. Goals of treatment are to improve symptoms, prevent flares, and improve quality of life. The general approach to the treatment of AD involves eliminating exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical and/or systemic agents (*Eichenfield et al 2014[b], Schneider et al 2013, Sidbury et al 2023, Tollefson et al 2014*).
- Topical corticosteroids (TCS) are first-line treatments for AD in patients who do not respond to non-pharmacologic measures (eg, emollients). Nonsteroidal topical treatments are also an option; these agents include topical calcineurin inhibitors (TCIs), topical phosphodiesterase-4 (PDE-4) inhibitors, topical aryl hydrocarbon receptor (AHR) agonists, and topical Janus kinase (JAK) inhibitors. These agents are used in the acute setting to resolve flares, and may be applied intermittently to reduce the risk of relapse (*Clinical Pharmacology 2025, Davis et al 2025, Eichenfield et al 2014[b], Schneider et al 2013, Sidbury et al 2023, Tollefson et al 2014*).
  - TCSs are associated with tolerability and safety concerns, including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents (*Eichenfield et al 2014[b], Krakowski et al 2008, Schneider et al 2013, Sidbury et al 2023*).
  - TCIs (ie, Elidel [pimecrolimus], tacrolimus) inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in AD. These agents are associated with stinging/burning, which may limit use.
  - Eucrisa (crisaborole) and Zoryve (roflumilast) inhibit PDE-4 to suppress the release of pro-inflammatory cytokines. Crisaborole is available as an ointment, which may be difficult to apply, while Zorvye is available as a cream.
  - Opzelura (ruxolitinib) and Anzupgo (delgocitinib) are topical JAK inhibitors. Opzelura is highly effective for AD but has several associated Boxed Warnings. Anzupgo does not have Boxed Warnings but is approved for a limited population.
  - Vtama (tapinarof) is an AHR agonist that regulates gene expression in immune and epithelial cells to maintain skin homeostasis.
- Use of systemic therapies in AD is typically reserved for patients with moderate to severe disease, or for those with mild to moderate disease who do not respond to topical therapy alone. FDA-approved systemic medications include subcutaneous (SC) biologic interleukin (IL) inhibitors and oral JAK inhibitors. Phototherapy is a non-pharmacologic systemic option that is highly effective but difficult to administer. (*Berger 2025, Davis et al 2025, Eichenfield et al 2014[b], Schneider et al 2013, Sidbury et al 2023, Gonzalez 2025, Tollefson et al 2014*).
  - Monoclonal antibodies for AD include Dupixent (dupilumab), Adbry (tralokinumab-ldrm [ie, tralokinumab]), Ebglyss (lebrikizumab-lbkz [ie, lebrikizumab]), and Nemluvio (nemolizumab-lbkz [ie, nemolizumab]). These agents modulate AD-related inflammation by inhibiting IL-13 (Adbry, Ebglyss, Dupixent), IL-4 (Dupixent), and/or IL-31 (Nemluvio).
  - Systemic JAK inhibitors indicated for AD include Cibinqo (abrocitinib) and Rinvoq (upadacitinib). These agents block JAK1 and 2 to inhibit the inflammatory cascade. Systemic JAK inhibitors are more effective than monoclonal antibodies for the treatment of AD but are associated with several Boxed Warnings, which may limit use.
  - Off-label systemic options for AD include cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. These are less effective than monoclonal antibodies and systemic JAK inhibitors for the treatment of AD.
- The scope of this review includes agents FDA-approved for the treatment of AD. General anti-inflammatory agents such as systemic or topical corticosteroids are not included.
  - Although some products in this review have additional FDA-approved indications, only information pertaining to the indication of AD is included within this document.
- Medispan Class: Immunosuppressive Agents – Topical; PDE-4 Inhibitors – Topical; Macrolide Immunosuppressants – Topical; Atopic dermatitis – Monoclonal Antibodies; Atopic dermatitis – JAK Inhibitors

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)[a]
Topical agents	
Anzupgo (delgocitinib) cream	-
Elidel (pimecrolimus) cream	✔
Eucrisa (crisaborole) ointment	-
Opzelura (ruxolitinib) cream	-
tacrolimus ointment	✔
Vtama (tapinarof) cream	-
Zoryve (roflumilast) cream[b]	-
Systemic agents	
Adbry (tralokinumab-ldrm) injection	-
Cibinqo (abrocitinib) tablet	-
Dupixent (dupilumab) injection	-
Ebglyss (lebrikizumab-lbkz) injection	-
Nemluvio (nemolizumab-ilto) injection	-
Rinvoq (upadacitinib) extended-release tablets	-

[a] For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
[b] Only Zoryve (roflumilast) 0.15% cream is indicated for AD; Zoryve (roflumilast) 0.3% cream, not included in this review, is indicated for psoriasis.

(*Drugs@FDA 2025, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2025, Purple Book: Database of Licensed Biological Products 2025*)

Indications

Table 2. Food and Drug Administration Approved Indications – topical agents

Indication	Anzupgo	Elidel	Eucrisa	Opzelura	tacrolimus	Vtama	Zoryve
Treatment of mild to moderate AD[a] in those who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable		✔ (≥ 2 years)		✔ b (≥ 12 years)			
Treatment of moderate to severe AD[a] in those who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable					✔ (≥ 2 years [0.03%]) (≥ 18 years [0.1%])		
Treatment of mild to moderate AD			✔ (≥ 3 months)				✔ c (≥ 6 years)
Treatment of AD						✔ (≥ 2 years)	
Treatment of moderate to severe chronic hand eczema in adults who have had an inadequate response to, or for whom topical corticosteroids are not advisable	✔ d						

[a] Second-line treatment indicated for short-term, non-continuous use in non-immunocompromised individuals

[b] Limitation of use: Use of Opzelura in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended
[c] 0.15% cream
[d] Limitation of use: Use of Anzupgo in combination with other JAK inhibitors or potent immunosuppressants is not recommended

Table 3. Food and Drug Administration Approved Indications – systemic agents

Indication	Adbry	Cibinqo	Dupixent	Ebglyss	Nemluvio	Rinvoq
Treatment of patients with moderate to severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable	✔ a (≥ 12 years)		✔ a (≥ 6 months)	✔ a,b (≥ 12 years)		
Treatment of patients with moderate to severe AD in combination with TCSs and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies					✔ (≥ 12 years)	
Treatment of patients with refractory, moderate to severe AD not adequately controlled with other systemic drug products, including biologics, or when those therapies are not advisable		✔ c (≥ 12 years)				✔ c (≥ 12 years)

[a] Can be used with or without TCSs.
[b] Ebglyss is indicated for use in adults and pediatric patients ≥ 12 years of age weighing ≥ 40 kg.
[c] Limitation of use: Use in combination with therapeutic biologics, other JAK inhibitors, or other immunosuppressants is not recommended.

(*Prescribing information: Adbry 2024, Anzupgo 2025, Cibinqo 2025, Dupixent 2025, Ebglyss 2024, Elidel 2020, Eucrisa 2025, Nemluvio 2025, Opzelura 2024, Rinvoq 2025 Tacrolimus ointment 2023, Vtama 2025, Zoryve cream 2024*)

- 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

Topical agents

Pimecrolimus and tacrolimus

- The approval of pimecrolimus cream was based on 3 randomized, double-blind (DB), vehicle-controlled (VC), Phase 3 studies in patients 3 months to 17 years of age with mild to moderate AD (N = 589). Two of these 3 trials supported the use of pimecrolimus cream in patients 2 years of age and older with mild to moderate AD. Two other identical, 6-week, VC, Phase 3 trials were conducted in pediatric patients 2 to 17 years of age (N = 403). These studies showed significant clinical response based on physician's global evaluation for pimecrolimus-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.
- The approval of tacrolimus ointment was based on 3 randomized, DB, VC, Phase 3 studies in patients with moderate to severe AD. One of the studies was conducted in pediatric patients (N = 351), 2 to 15 years of age, and the other 2 studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the tacrolimus group compared to the vehicle group ($p < 0.001$). There was some evidence that tacrolimus 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the tacrolimus strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Pimecrolimus and tacrolimus have been directly compared in clinical trials. One trial compared pimecrolimus 1% to tacrolimus 0.03% in patients 2 to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study (*Kempers et al 2004*). However, itching was reported at a significantly higher rate in the tacrolimus group. In 2 other clinical trials, tacrolimus 0.1% was compared to

pimecrolimus in adult patients over 6 weeks. Patients treated with tacrolimus had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with pimecrolimus. The success of therapy based on the Investigator Global AD Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of AD in face and neck were all statistically significant for the tacrolimus group in both studies. There were no differences in adverse effects (AEs) between the groups *(Abramovits et al 2008, Fleischer et al 2007)*.

- These agents have been evaluated in several meta-analyses (MAs) that concluded tacrolimus and pimecrolimus were effective alternatives to TCSs in short-term studies (*Ashcroft 2005, Chen et al 2010, El-Batawy et al 2009)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A Cochrane review published in 2007 summarized the efficacy of pimecrolimus 1% cream vs topical comparators (vehicle or active treatment). The review included 31 RCTs enrolling a total of 8019 patients (*Ashcroft et al 2007*).
  - Compared to vehicle in short-term trials (≤ 6 weeks), pimecrolimus was demonstrated to have superior efficacy based on the investigator's global assessment (IGA). More pimecrolimus-treated patients achieved mild or absent pruritus at the 1-week and subsequent assessments. Longer-term trials (6 to 12 months) demonstrated a lower incidence of flares in pimecrolimus-treated patients.
  - In comparative trials to TCSs, pimecrolimus was significantly less effective vs triamcinolone acetonide 0.1% (a mid-potency TCS) based on IGA and vs betamethasone valerate 0.1% (a potent TCS) based on participant's global assessments. Pimecrolimus was also associated with significantly more overall withdrawals and skin burning.
  - In head-to-head trials comparing the TCIs, pimecrolimus was significantly less effective than tacrolimus 0.1% for IGA at 6 weeks (risk ratio [RR], 0.58; 95% confidence interval [CI], 0.46 to 0.74) and led to more withdrawals due to lack of efficacy (RR, 2.37; 95% CI, 1.10 to 5.08) based on 2 trials involving 639 patients. There was no significant difference in proportions of patients experiencing any AEs.
- A Cochrane review published in 2015 summarized the efficacy of tacrolimus ointment compared to other active treatments. The review included 20 RCTs enrolling a total of 5885 patients (*Cury Martins et al 2015*).
  - In comparative trials of tacrolimus ointment (0.03% and 0.1% strengths) to TCSs, tacrolimus was demonstrated to have greater efficacy vs low-potency TCSs, and comparable efficacy vs mid-potency TCSs, based on the physician's global assessment. Tacrolimus was associated with a higher rate of application site burning sensation compared to TCSs of various potencies.
  - In head-to-head trials comparing the TCIs, the physician's global assessment demonstrated significantly more improvement for tacrolimus 0.1% vs pimecrolimus 1% (RR, 1.80; 95% CI, 1.35 to 2.42). Two studies enrolling 506 patients, which reported results at 6 weeks, found no significant differences in the overall occurrence of AEs between the groups. One study comparing tacrolimus 0.03% vs pimecrolimus 1% in 139 patients demonstrated a significant difference favoring tacrolimus in the physician's global assessment (RR, 1.42; 95% CI, 1.02 to 1.98). No significant difference was demonstrated in application site reactions between tacrolimus 0.03% and pimecrolimus 1%.
- Another systematic review (SR) and MA evaluated published data from 13 RCTs enrolling a total of 6954 patients comparing TCIs (n = 3492) to TCSs (n = 3462). The mean follow-up of the trial was 101 weeks, with a range of 2 to 260 weeks. Tacrolimus 0.03% was evaluated in 5 trials, tacrolimus 0.1% in 5 trials, and pimecrolimus 1% in 3 trials. Potencies of the TCSs were as follows: low or least potency, 4 trials; least potency (face) and lower-mid potency (other body areas), 4 trials; lower-mid potency, 4 trials; mid potency, 1 trial (*Broeders et al 2016*).
  - Improvement of AD and treatment success were generally similar between groups, slightly favoring TCIs vs TCSs. The percentage of patients with improvement of AD was 81% vs 71% (RR, 1.18; 95% CI, 1.04 to 1.34; p = 0.01), and the percentage with treatment success was 72% vs 68% (RR, 1.15; 95% CI, 1.00 to 1.31; p = 0.04).
  - The number of AEs (74% vs 64%; RR, 1.28; 95% CI, 1.05 to 1.58; p = 0.02) and AEs related to treatment (11% vs 8%; RR, 1.45; 95% CI, 1.15 to 1.83; p = 0.002) were higher in the topical calcineurin group compared with the TCS group, including higher rates of skin burning and pruritus.
- A 5-year, open-label (OL), multicenter (MC) study evaluated the use of pimecrolimus in 2418 infants compared to TCSs. The primary endpoint was safety; the secondary endpoint was long-term efficacy, defined as a score of 0 to 5 on the IGA. TCSs included low-potency products such as hydrocortisone 1% or medium-potency products such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More pimecrolimus-treated patients reported bronchitis (p = 0.02), infected eczema (p < 0.001), impetigo (p = 0.045), and nasopharyngitis (p = 0.04). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the

pimecrolimus-treated group. Over the 5-year period, 88.7% and 92.3% of the pimecrolimus- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of pimecrolimus- and corticosteroid-treated patients, respectively, completing the study *(Sigurgeirsson et al 2015)*.

- Some studies have identified a potential risk of malignancy with TCI use:
  - A retrospective cohort study evaluated initial cancer diagnosis in patients with a diagnosis of AD or eczema and found that while exposure to pimecrolimus or tacrolimus was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician-suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to tacrolimus and not pimecrolimus ($p < 0.001$, $p = 0.086$, respectively) (*Hui et al 2009*).
  - An MA of observational studies (N = 11 studies, including 8 cohort studies in which 408,366 patients were treated with TCIs) published up to October 2020, evaluated the association between TCI use and risk of malignant neoplasms vs controls (non-active comparator or TCSs). There was no association between TCI use and cancer overall vs non-active comparators (RR, 1.03; 95% CI, 0.92 to 1.16). However, the lymphoma risk was elevated with TCIs compared to both the non-active comparators (RR, 1.86; 95% CI, 1.39 to 2.49) and the TCSs (RR, 1.35; 95% CI, 1.13 to 1.61). No significant association was found between TCI use and increased skin cancer (melanoma and keratinocyte carcinoma) (*Lam et al 2021*).
  - An MA of 110 studies (52 RCTs and 69 non-randomized studies) examined the risk of cancer with TCIs and found that the absolute risk of any cancer was not different with TCIs vs controls (odds ratio [OR], 1.03; 95% credible interval [CrI], 0.94 to 1.11) (*Devasenapathy et al 2023*).

Crisaborole

- The safety and efficacy of crisaborole were demonstrated in 2 identically designed, randomized, Phase 3, DB, VC trials (CrisADe CORE 1 and 2) in patients (N = 1527) with mild to moderate AD and ≥ 5% treatable BSA. The primary endpoint of IGA success was defined as the proportion of subjects at Day 29 who were clear or almost clear (IGA 0 or 1) with a ≥ 2-grade improvement from baseline (*Paller et al 2016).*
  - More patients receiving crisaborole vs vehicle achieved the primary endpoint of IGA success (CORE 1: 32.8% vs 25.4%, $p = 0.038$; CORE 2: 31.4% vs 18.0%, $p < 0.001$), with a greater percentage of crisaborole-treated patients achieving clear/almost clear skin overall (51.7% vs 40.6%, $p = 0.005$; 48.5% vs 29.7%, $p < 0.001$).
  - An OL extension trial of CORE 1 and CORE 2 evaluated the safety of crisaborole in 517 patients with mild to moderate AD for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs (TEAEs) were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with crisaborole (93.1%). The most commonly observed AEs (≥ 1% of patients) included AD flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications (*Eichenfield et al 2017*).
- The CrisADe CARE trial (N = 137) was a Phase 4, OL trial that demonstrated crisaborole was tolerated and effective in children aged 3 to 24 months with mild to moderate AD. Crisaborole systemic exposure in infants was comparable with that of patients aged ≥ 2 years. TEAEs were reported for 88 (64.2%) patients (98.9% were mild/moderate). The most frequently reported TEAEs were application site pain (3.6%), application site discomfort (2.9%), and erythema (2.9%). IGA clear/almost clear scores with ≥ 2-grade improvement at day 29 were achieved by 30.2% of patients. From baseline to day 29, mean percentage change in EASI score was -57.5%, and mean change in Patient-Oriented Eczema Measure (POEM) total score was -8.5 (*Schlessinger et al 2020*).
- The CrisADe CONTROL study was a Phase 3, randomized, DB, OL, VC, 52-week study of 270 patients aged 3 months and older with mild to moderate AD involving 5% or more of treatable BSA. Patients in the crisaborole group had a longer median time until first flare compared to those receiving vehicle (111 vs 30 days; $p = 0.0034$). The mean number of flare-free days was also higher in the treatment arm compared to placebo (234.0 vs 199.4; $p = 0.00346$), and the total number of flares was lower in the treatment arm (0.95 vs 1.36; $p = 0.0042$) (*Eichenfield et al 2023*).
- There are limited data on the relative efficacy of crisaborole ointment compared to other active topical therapies, as no head-to-head trials have been conducted. In a 2017 review from the Institute for Clinical and Economic Review (ICER), there was a trend suggesting that pimecrolimus was superior to crisaborole based on the IGA score, but findings were not statistically significant (*ICER 2017*).

- A subsequent network meta-analysis (NMA) including a total of 9 trials found that crisaborole appeared to be superior to pimecrolimus and comparable to tacrolimus for achieving IGA. In this NMA, patients were more likely to achieve IGA 0 to 1 with crisaborole than with pimecrolimus 1% cream (hazard ratio [HR], 1.62; 95% CrI, 1.04 to 2.48). There was weak evidence of a difference between crisaborole and tacrolimus 0.03% (HR, 1.35; 95% CrI, 0.95 to 1.84) and no evidence of a difference vs tacrolimus 0.1% (HR, 1.18; 95% CrI, 0.64 to 1.96). The NMA for safety was not feasible due to data limitations. This analysis was sponsored by the manufacturer of crisaborole, and several additional limitations were noted (*Fahrbach et al 2020*).

Delgocitinib

- The safety and efficacy of delgocitinib cream were demonstrated in 2 randomized, Phase 3, DB, VC trials (DELTA 1 and DELTA 2) in a total of 960 adults with moderate to severe hand eczema, recent (ie, within 1 year) inadequate response to contraindication TCS, a baseline IGA chronic hand eczema (IGA-CHE) score of 3 or 4, and a Hand Eczema Symptom Diary (HESD) itch score of ≥ 4 at baseline. The primary endpoint was defined as the proportion of patients at week 16 with an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline. Patients were randomized (2:1) to delgocitinib 20 mg/g or vehicle cream twice daily for 16 weeks.
  - At week 16, more delgocitinib-treated patients achieved IGA-CHE treatment success (19.7% in DELTA 1 and 29.1% in DELTA 2) vs the vehicle (9.9% in DELTA 1 and 6.9% in DELTA 2); the difference was statistically significant in both trials. In addition, delgocitinib demonstrated significant reductions in itch and pain as measured by HESD itch and pain rating scale scores.
  - Similar rates of AEs were reported in the delgocitinib vs placebo groups in DELTA 1 (45% vs 51%) and DELTA 2 (46% vs 45%). Compared to the delgocitinib group, a higher percentage of patients in the placebo group discontinued the trial due to AEs (DELTA 1; 1% vs 4%, respectively; DELTA 2, < 1% vs 3%, respectively) (*Bissonnette et al 2024*).
- The long-term safety and efficacy of delgocitinib were examined in a 36-week extension study of DELTA 1 and DELTA 2 (DELTA 3); delgocitinib demonstrated effective disease control and was well-tolerated (*Gooderham et al 2025*).

Roflumilast

- The safety and efficacy of roflumilast 0.15% cream were demonstrated in 2 MC, randomized, DB, VC trials (INTEGUMENT-1 and INTEGUMENT-2). The trials enrolled a total of 1337 patients aged ≥ 6 years with mild to moderate AD. Patients were randomized 2:1 to receive roflumilast 0.15% cream or vehicle cream once daily for 4 weeks. The primary endpoint was the proportion of patients who achieved treatment success at week 4, defined as a validated Investigator Global Assessment for AD (vIGA-AD) score of 0 or 1 (clear or almost clear) plus a 2-grade improvement from baseline. In INTEGUMENT-1, treatment success at week 4 was achieved in 32% of patients receiving roflumilast 0.15% cream and 15.2% of patients receiving vehicle (treatment difference, 17.4%; $p < 0.001$). In INTEGUMENT-2, treatment success at week 4 was achieved in 28.9% of patients receiving roflumilast 0.15% cream and 12% of patients receiving vehicle (treatment difference, 16.5%; $p < 0.001$) (*Simpson et al 2024*).
- An open-label extension study (INTEGUMENT-OLE) examined the long-term safety and efficacy of roflumilast 0.15% cream in patients who successfully completed INTEGUMENT-1 or INTEGUMENT-2 (N = 657). For the first 4 weeks of the open-label extension, patients applied roflumilast cream once daily. At week 4, patients who achieved vIGA-AD of 0 (clear) switched from daily application to proactive twice-weekly application; if AD worsened (ie, worsening symptoms for 1 week, vIGA-AD ≥ 2 or signs/symptoms uncontrolled at any clinic visit), patients resumed daily application. Roflumilast cream was well-tolerated for up to 56 weeks; at week 56, 56.6% of patients treated with continuous roflumilast (ie, during the parent trial and in INTEGUMENT-OLE) had a vIGA-AD score of 0 or 1. Among patients who achieved vIGA-AD of 0 and switched to twice-weekly application, vIGA-AD of 0 or 1 was maintained for a median of 281 days (*Simpson et al 2025*).

Ruxolitinib

- The safety and efficacy of ruxolitinib cream were demonstrated in 2 identically designed, randomized, Phase 3, DB, VC trials (TRuE-AD1 and TRuE-AD2) in a total of 1249 patients aged ≥ 12 years with AD, 3% to 20% affected BSA, and a baseline IGA score of 2 or 3. The primary endpoint was defined as the proportion of patients at week 8 with an IGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline. Patients were randomized (2:2:1) to ruxolitinib 0.75% cream twice daily (n = 500), ruxolitinib 1.5% cream twice daily (n = 499; FDA-approved dose), or vehicle cream twice daily (n = 250) for 8 weeks.

  - In TRuE-AD1 and TRuE-AD2, more ruxolitinib-treated patients achieved IGA treatment success with ruxolitinib 0.75% (50.0% and 39.0%, respectively) and ruxolitinib 1.5% (53.8% and 51.3%, respectively), vs the vehicle (15.1% and 7.6%, respectively; p < 0.0001) at week 8. In addition, both ruxolitinib strengths demonstrated significant reductions in itch (as measured by daily itch numerical rating scale scores) and an increase in patients achieving a 75% improvement in EASI (EASI-75) compared to the vehicle. A larger proportion of vehicle-treated patients reported TEAE(s) vs patients treated with the ruxolitinib 1.5% cream (33.2% vs 26.5%, respectively). A total of 15 patients discontinued from both studies due to TEAEs (n = 8 [3.2%] with vehicle and 7 with ruxolitinib [0.6% in the ruxolitinib 1.5% cream group]) (*Papp et al 2021*).
  - The long-term safety and efficacy of ruxolitinib were examined in a 44-week extension study of TRuE-AD1 and TRuE-AD2; ruxolitinib demonstrated effective disease control and was well-tolerated (*Papp et al 2023*).
- One dose-ranging, DB/OL, Phase 2 trial evaluated the effectiveness of ruxolitinib vs triamcinolone. The DB phase evaluated ruxolitinib (doses ranging from 0.15% to 1.5% once to twice daily) cream (n = 50 administered ruxolitinib 1.5% twice daily cream) vs triamcinolone 0.1% cream twice daily (n = 51) vs a vehicle cream twice daily (n = 52) in 307 adults with AD, an IGA score of 2 or 3 (mild to moderate disease), and 3% to 20% affected BSA at baseline. Treatment continued for 8 weeks, except for the triamcinolone group, which was treated for only 4 weeks. Therapeutic benefit was demonstrated with ruxolitinib as early as week 4, regardless of dose. Ruxolitinib 1.5% twice daily cream demonstrated the greatest improvement in IGA responses vs the vehicle at week 4 (38.0% vs 7.7%, respectively; p < 0.001) and week 8 (48.0% vs 9.6%, respectively; p < 0.001). Ruxolitinib 1.5% twice daily cream was not statistically different from the triamcinolone 0.1% twice daily cream for IGA responses at week 4 (38.0% vs 25.5%, respectively). Of note, no comparisons between ruxolitinib and triamcinolone could be made at week 8, because triamcinolone treatment was stopped at week 4 (*Kim et al 2020*).

Tapinarof

- The safety and efficacy of tapinarof cream were demonstrated in 2 identically designed, randomized, Phase 3, DB, VC trials (ADORING 1 and ADORING 2) in patients aged ≥ 2 years with AD, vIGA-AD score ≥ 3, EASI score ≥ 6, and 5% to 35% affected BSA. Patients were randomized in a 2:1 ratio to receive tapinarof cream 1% or vehicle cream daily for 8 weeks; the primary endpoint was the proportion of patients with a vIGA-AD response at week 8 (defined as a vIGA-AD score of 0 [clear] or 1 [almost clear] with a ≥ 2-point improvement from baseline). In both trials, more patients receiving tapinarof achieved vIGA-AD response at week 8 (ADORING 1: 45.4% vs 13.9%, p < 0.0001; ADORING 2: 46.4% vs 18%, p < 0.0001). Tapinarof-treated patients were also more likely to achieve EASI-75 responses than vehicle-treated patients (*Silverberg et al 2024[a]*).
- The long-term safety and efficacy of tapinarof cream were examined in ADORING 3, a 48-week extension study of patients who completed ADORING 1 or ADORING 2; tapinarof cream demonstrated effective disease control and was well-tolerated (*Bissonnette et al 2025*).

Systematic Reviews and Meta-analyses

- A Cochrane NMA of 291 studies (N = 45,846) compared the efficacy and safety of topical anti-inflammatory treatments (including TCSs, TCIs, PDE-4 inhibitors, and JAK inhibitors) in patients with AD of any severity. The primary outcomes examined were patient-reported symptoms, clinician-reported symptoms, and IGA. Most trials looked at short-term outcomes, with a median treatment duration of 21 days across studies. Potent TCSs, JAK inhibitors (eg, ruxolitinib 1.5%), and tacrolimus 0.1% consistently ranked among the most effective topical anti-inflammatory agents, while PDE-4 inhibitors (eg, crisaborole 2%, roflumilast 0.15%) consistently ranked among the least effective. TCIs and crisaborole 2% were ranked most likely to cause local application site reactions, while TCSs were ranked least likely to cause such reactions (*Lax et al 2024*).

Systemic agents

Monoclonal antibodies

Dupilumab

- The efficacy and safety of dupilumab compared to placebo in adults with moderate to severe AD were evaluated in two Phase 3 trials, SOLO 1 (N = 671) and SOLO 2 (N = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to placebo, dupilumab 300 mg SC weekly, or dupilumab 300 mg

SC every other week for 16 weeks. The proportion of patients with an IGA score of 0 or 1 and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome (*Simpson et al 2016*).
  - In both studies, between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo ($p < 0.001$ for all comparisons). Significantly more patients who received dupilumab achieved EASI-75 compared to those who received placebo ($p < 0.001$). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common AEs with dupilumab compared to placebo were conjunctivitis and injection-site reactions.
  - Patients who completed dupilumab treatment in SOLO-1 or SOLO-2 could continue into the SOLO-CONTINUE trial, in which patients were randomized to a continuation of their original regimen of dupilumab (300 mg weekly or every other week), dupilumab 300 mg every 4 weeks, dupilumab every 8 weeks, or placebo for an additional 36 weeks. Results demonstrated that patients who continued treatment with dupilumab once weekly or every 2 weeks maintained IGA and EASI endpoints more than patients who switched to placebo. Post hoc analyses showed no apparent difference between dupilumab once weekly and every 2 weeks in maintenance of EASI response. No new safety signals were identified (*Worm et al 2020*).
- The long-term efficacy and safety of dupilumab were compared to placebo in 740 patients with moderate to severe AD not adequately controlled with TCSs in the LIBERTY AD CHRONOS study. Patients received dupilumab 300 mg once weekly, dupilumab 300 mg once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and ≥ 2-point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group ($p < 0.0001$). Similar efficacy results were reported at week 52. At 1 year, the most common AEs associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab, while herpes zoster and eczema herpeticum were more common in the placebo group (*Blauvelt et al 2017*).
  An OL extension study (LIBERTY AD OLE) evaluated the long-term use of dupilumab in adults who had previously participated in Phase 1 through Phase 3 clinical trials of dupilumab for AD. In this study, patients received dupilumab weekly (rather than the FDA-approved every-2-week dosing). Patients could continue treatment for up to 3 years, although a relatively small number of patients completed the study through 3 years of treatment. Based on available data, the safety profile of dupilumab was consistent with previously reported trials, with no new safety signals, and efficacy was maintained (*Beck et al 2020, Deleuran et al 2020*). At the final 5-year analysis, 326 patients completed treatment up to 260 weeks. Overall, 220/326 (67.5%) of patients achieved an IGA score of 0 or 1, and 288/326 (88.9%) achieved 75% or greater improvement in EASI (mean EASI at baseline, 16.39; mean EASI at end of study, 2.75) (*Beck et al 2024*).
- Pediatric studies
  - The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate to severe AD in a DB, MC, RCT, LIBERTY AD ADOL. Patients < 60 kg received dupilumab 400 mg initially, then 200 mg every 2 weeks, and patients ≥ 60 kg received 600 mg initially, then 300 mg every 2 weeks for 16 weeks. Compared with placebo, dupilumab resulted in significantly higher proportions of patients achieving EASI-75 at week 16 (41.5% vs 8.2%; $p < 0.001$) and IGA score of 0 or 1 with 2 or more points improvement at week 16 (24.4% vs 2.4%; $p < 0.001$) *(Dupixent prescribing information 2025, Simpson et al 2020[a]).*
    - In an ongoing OL extension study, LIBERTY AD PED-OLE, adolescent patients with moderate to severe AD who had previously participated in dupilumab trials received dupilumab 300 mg every 4 weeks, which could be titrated to 200 mg (for body weight < 60 kg) or 300 mg (for body weight ≥ 60 kg) every 2 weeks due to inadequate response. Concomitant topical therapies were allowed. Of 294 analyzed patients, 102 patients completed the week 52 visit, 43 patients had discontinued the study prematurely, and 253 patients were continuing therapy. The majority of patients (70.9%) required titration to the approved every-2-week dosage. At the time of database lock, the proportions of patients achieving IGA 0/1 and EASI-75 by week 52 were 42.7% and 81.2%, respectively. The long-term safety profile in adolescents was comparable to that seen in adults and consistent with the known dupilumab safety profile (*Blauvelt et al 2022[a]*).
  - The efficacy of dupilumab plus TCSs was compared to TCSs alone in 367 patients 6 to 11 years of age with moderate to severe AD in a 16-week DB, MC, RCT, LIBERTY AD PEDS. Patients < 30 kg received dupilumab 200 mg initially, then 100 mg every 2 weeks, and patients ≥ 30 kg received 400 mg initially, then 200 mg every 2 weeks. Patients in a third group were dosed regardless of weight at 600 mg initially and 300 mg every 4 weeks thereafter. The primary endpoint was the proportion of patients with an IGA score of 0 or 1 at Week 16. In patients who received dupilumab 300 mg every 4 weeks plus TCSs, 30% achieved the primary outcome vs 13% with TCSs alone.

In patients who received dupilumab 200 mg every 2 weeks, 39% achieved the primary outcome vs 10% with TCSs alone (*Dupixent prescribing information 2025, Paller et al 2020*).
  - An OL extension in 33 children aged 6 to 11 years with severe AD evaluated dupilumab 2 mg/kg or 4 mg/kg for a duration of 16 weeks. TEAEs were mostly mild to moderate in nature, and none led to treatment discontinuation. The most commonly reported TEAEs for the 2 mg/kg and 4 mg/kg doses were nasopharyngitis (47% and 56%, respectively) and AD exacerbation (29% and 13%, respectively). Single-dose dupilumab improved AD, with further improvements with continued treatment through week 52 in children with severe disease (*Cork et al 2021*).
  - The LIBERTY AD PRESCHOOL trial was a 16-week, DB, MC, RCT that evaluated the use of dupilumab vs placebo, each in combination with TCSs, in 162 patients 6 months to 5 years of age with moderate to severe AD. The dupilumab dose was 200 mg every 4 weeks in patients weighing ≥ 5 to < 15 kg and 300 mg every 4 weeks in patients weighing ≥ 15 to < 30 kg. The primary endpoint, the proportion of patients with an IGA score of 0 or 1 at week 16, was achieved by 28% of patients treated with dupilumab plus TCSs vs 4% of those treated with TCSs alone, for a difference of 24% (95% CI, 13 to 34). Improvements favoring dupilumab were also demonstrated for EASI-75, EASI-90, and pruritus scores (*Dupixent prescribing information 2025, Paller et al 2022).*
  - An OL extension in 142 patients 6 months to 5 years of age with moderate to severe AD evaluated weight-based dupilumab every 4 weeks for up to 1 year. By week 52, 36.2% of patients had achieved an IGA score of 0 or 1. EASI-50, EASI-75, and EASI-90 responses were achieved in 96.6%, 79.3%, and 58.6% of patients, respectively (*Paller et al 2024[a]*).
- An NMA of 74 studies (N = 8177), with 11 trials comparing dupilumab vs placebo, examined the comparative effectiveness of systemic immunosuppressive treatments for moderate to severe AD. Many of the interventions included in the NMA are not FDA-approved for the treatment of AD. Results for dupilumab vs placebo are provided below (*Sawangjit et al 2020*).
  - Dupilumab was associated with an increased proportion of patients achieving EASI-75 at ≤ 16 weeks vs placebo (RR, 3.04; 95% CI, 2.53 to 3.65; 8 trials; n = 3150) and at > 16 weeks (RR, 2.59; 95% CI, 1.87 to 3.60; 2 trials; n = 1162). An EASI-75 was achieved by 18% to 20% of placebo-treated patients.
  - An increased proportion of dupilumab-treated patients vs placebo had an IGA score of 0 to 1 point at ≤ 16 weeks (RR, 3.58; 95% CI, 3.00 to 4.26; 10 trials; n = 3634).
  - Dupilumab was more effective than placebo in achieving improvement in POEM score (mean difference [MD], 7.30; 95% CI, 6.61 to 8.00) at short-term follow-up.
  - Dupilumab had a decreased risk of serious AEs at ≤ 16 weeks vs placebo (RR, 0.35; 95% CI, 0.19 to 0.64; 9 trials; n = 2628), but no significant difference in serious AEs at > 16 weeks (3 trials; n = 1541).
- Another MA of 50 RCTs (n = 6681) examined systemic agents for AD. Dupilumab demonstrated superiority vs placebo for EASI-75 at 12 to 16 weeks of treatment (risk difference, 0.37; 95% CI, 0.32 to 0.42; I^2 = 19%) (*Siegels et al 2021*).

Lebrikizumab

- The efficacy and safety of lebrikizumab compared to placebo in patients aged ≥ 12 years with moderate to severe AD were evaluated in 3 randomized, DB, placebo-controlled, Phase 3 trials: ADvocate 1 (N = 424), ADvocate 2 (N = 427), and ADhere (N = 211).
  - ADvocate 1 and ADvocate 2 were identically designed trials enrolling adults and adolescents aged ≥ 12 years weighing ≥ 40 kg with moderate to severe AD for whom topical treatments were inadequate or inadvisable; patients had to have a baseline EASI score ≥ 16, an IGA score ≥ 3, and an affected BSA ≥ 10% to be eligible for enrollment. Patients were randomized in a 2:1 ratio to receive lebrikizumab 250 mg SC every 2 weeks with loading doses of 500 mg at baseline and week 2 (ADvocate 1, n = 283; ADvocate 2, n = 281) or placebo (ADvocate 1, n = 141; ADvocate 2, n = 146) for 16 weeks. Topical treatments were not allowed during this period. At week 16, patients who responded to lebrikizumab were re-randomized to receive lebrikizumab every 2 weeks, lebrikizumab every 4 weeks, or placebo for an additional 36 weeks. The primary endpoint was the proportion of patients achieving an IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at week 16 (*Blauvelt et al 2023*).
    - In both trials, lebrikizumab was superior to placebo for achievement of the primary endpoint. In ADvocate 1, a primary outcome response occurred in 43.1% and 12.7% of patients in the lebrikizumab and placebo groups, respectively (treatment difference, 29.7%; 95% CI, 21.6 to 37.8; p < 0.001). In ADvocate 2, a primary outcome response occurred in 33.2% and 10.8% of patients in the lebrikizumab and placebo groups, respectively (treatment difference, 21.9%; 95% CI, 14.2 to 29.6; p < 0.001).
    - During the 36-week maintenance phase, lebrikizumab every 2 weeks and lebrikizumab every 4 weeks maintained similar improvements in AD symptoms; in a pooled analysis of data from ADvocate 1 and 2, an IGA

score of 0 or 1 with a ≥ 2-point improvement from baseline was maintained in 71.2%, 76.9%, and 47.9% of patients rerandomized to lebrikizumab every 2 weeks, lebrikizumab every 4 weeks, or placebo, respectively.
  - The ADhere trial was a 16-week trial enrolling adults and adolescents aged ≥ 12 years weighing ≥ 40 kg with moderate to severe AD for whom topical treatments were inadequate; patients had to have a baseline EASI score ≥ 16, an IGA score ≥ 3, and an affected BSA ≥ 10% to be eligible for enrollment. Patients were randomized in a 2:1 ratio to receive lebrikizumab 250 mg SC every 2 weeks with loading doses of 500 mg at baseline and week 2 (n = 145) or placebo (n = 66) for 16 weeks. All patients received concomitant TCSs; TCIs were also permitted. The primary endpoint was the proportion of patients achieving an IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline at week 16. The primary endpoint was achieved in 41.2% of patients receiving lebrikizumab and 22.1% of patients receiving placebo (treatment difference, 18.3%; 95% CI, 5.1 to 31.5; p = 0.01). The percentage of patients achieving EASI-75 was also greater among patients treated with lebrikizumab (*Simpson et al 2023*).
- The long-term safety and efficacy of lebrikizumab were examined in a 100-week extension study of ADvocate 1, ADvocate 2, and ADhere (ADjoin); lebrikizumab demonstrated effective disease control and was well-tolerated for up to 104 weeks of treatment (*Guttman-Yassky et al 2025*).
- An additional Phase 3 OL study (ADore) examined the safety and efficacy of lebrikizumab in adolescents aged ≥ 12 years weighing ≥ 40 kg with moderate to severe AD (N = 206); patients had to have a baseline EASI score ≥ 16, an IGA score ≥ 3, and an affected BSA ≥ 10% to be eligible for enrollment. All patients received lebrikizumab 250 mg SC every 2 weeks with loading doses of 500 mg at baseline and week 2; treatment continued for 52 weeks. Topical therapies (corticosteroids, calcineurin inhibitors, PDE-4 inhibitors) were only permitted as rescue therapy. The primary endpoint was discontinuation due to AEs; efficacy endpoints included the percentage of patients achieving an EASI-75 response and the percentage of patients achieving an IGA response (IGA score of 0 or 1 with a reduction of ≥ 2 points from baseline). By the end of the 52-week trial period, 2.4% of patients had discontinued treatment due to AEs; 62.6% achieved an IGA response, and 81.9% achieved an EASI-75 response (*Paller et al 2023[a]*).

Nemolizumab

- The efficacy and safety of nemolizumab compared to placebo in patients aged ≥ 12 years with moderate to severe AD were evaluated in 2 identically designed, randomized, DB, placebo-controlled, Phase 3 trials: ARCADIA 1 (N = 941) and ARCADIA 2 (N = 787). Patients were eligible for enrollment if they had an IGA score ≥ 3, an EASI score ≥ 16, BSA involvement of ≥ 10%, pruritus, and documented history of inadequate response to TCSs (with or without TCIs). Patients were randomized 2:1 to receive nemolizumab 30 mg SC once every 4 weeks following a 60 mg loading dose (ARCADIA 1, n = 620; ARCADIA 2, n = 522) or placebo (ARCADIA 1, n = 321; ARCADIA 2, n = 265) for 16 weeks; all patients continued to receive background therapy with TCSs (with or without a TCI). The coprimary endpoints were IGA success at week 16 (defined as IGA score of 0 [clear] or 1 [almost clear] with a ≥ 2-point improvement from baseline) and EASI-75 response at week 16 (*Silverberg et al 2024[b]*).
  - In ARCADIA 1, IGA success at week 16 was achieved in 36% and 25% of patients treated with nemolizumab and placebo, respectively (treatment difference, 11.5%; 97.5% CI, 4.7 to 18.3; p = 0.0003); EASI-75 response at week 16 was achieved in 44% and 29%, respectively (treatment difference, 14.9%; 97.5% CI, 7.8 to 22.0; p < 0.0001).
  - In ARCADIA 2, IGA success at week 16 was achieved in 38% and 26% of patients treated with nemolizumab and placebo, respectively (treatment difference, 12.2%; 97.5% CI, 4.6 to 19.8; p = 0.0006); EASI-75 response at week 16 was achieved in 42% and 30%, respectively (treatment difference, 12.5%; 97.5% CI, 4.6 to 20.3; p = 0.0006). Similar response rates were observed among the subgroup of patients with severe pruritus at baseline. Significant improvements were also noted in secondary endpoints, such as improvement in pruritus and reduced sleep disturbance.

Tralokinumab

- FDA approval of tralokinumab was supported by 2 placebo-controlled monotherapy trials, ECZTRA 1 and ECZTRA 2 (*Wollenberg et al 2021*), and 1 trial in combination with topical steroids, ECZTRA 3 (*Silverberg et al 2021[a]*). Each of these trials enrolled adults with moderate to severe AD having a baseline EASI score ≥ 16, IGA score of ≥ 3, affected BSA ≥ 10%, and an inadequate response to topical medications. In all 3 trials, patients were randomized to receive placebo or tralokinumab 600 mg by SC injection on day 0, followed by 300 mg injected every other week for the first 16 weeks of treatment. Co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and the proportion of patients achieving an EASI-75 response, each assessed at week 16.

  - In ECZTRA 1 (N = 802), an IGA response was achieved by 15.8% and 7.1% of patients in the tralokinumab and placebo groups, respectively, for a difference of 8.6 (95% CI, 4.1 to 13.1; p = 0.002). An EASI-75 response was achieved by 25.0% and 12.7%, respectively, for a difference of 12.1 (95% CI, 6.5 to 17.7; p < 0.001).
  - In ECZTRA 2 (N = 794), an IGA response was achieved by 22.2% and 10.9% of patients in the tralokinumab and placebo groups, respectively, for a difference of 11.1 (95% CI, 5.8 to 16.4; p < 0.001). An EASI-75 response was achieved by 33.2% and 11.4%, respectively, for a difference of 21.6 (95% CI, 15.8 to 27.3; p < 0.001).
  - In ECZTRA 3 (N = 380), an IGA response was achieved by 38.9% and 26.2% of patients in the tralokinumab and placebo groups, respectively, for a difference of 12.4 (95% CI, 2.9 to 21.9; p = 0.015). An EASI-75 response was achieved by 56.0% and 35.7%, respectively, for a difference of 20.2 (95% CI, 9.8 to 30.6; p < 0.001).
- An additional trial, ECZTRA 7, was a randomized, DB, placebo-controlled trial that evaluated the use of tralokinumab plus TCSs in 277 adults with severe AD and an inadequate response or intolerance/contraindication to cyclosporine. Patients received tralokinumab 600 mg followed by 300 mg every 2 weeks, or placebo (*Gutermuth et al 2022*).
  - The primary endpoint, EASI-75 at week 16, was achieved by 64.2% and 50.5% of patients in the tralokinumab and placebo groups, respectively (difference, 14.1%; 95% CI, 2.5 to 25.7; p = 0.018). The first secondary endpoint, achievement of a ≥ 4-point reduction in the peak pruritus numeric rating scale (PP-NRS) at week 16, was numerically but not statistically significantly better for tralokinumab (45.5%) than placebo (35.6%) (p = 0.106). Most of the additional secondary endpoints were nominally significant based on the testing hierarchy.
- Data beyond 16 weeks:
  - In ECZTRA 1 and ECZTRA 2, tralokinumab-treated patients who achieved the prespecified criteria for clinical response of IGA score of 0 or 1 or EASI-75 were re-randomized to receive tralokinumab every 2 weeks, tralokinumab every 4 weeks, or placebo for a 36-week maintenance period. Of patients achieving an IGA of 0 or 1 at week 16, 51% (ECZTRA 1) to 59% (ECZTRA 2) who continued every-2-week treatment maintained this response at week 52 without use of rescue medication. Of patients achieving EASI-75 at week 16, 56% (ECZTRA 2) to 60% (ECZTRA 1) maintained this response without rescue medication (*Wollenberg et al 2021*).
  - In ECZTRA 3, tralokinumab-treated patients who achieved the prespecified criteria for clinical response of an IGA score of 0 or 1 or an EASI-75 were re-randomized to receive tralokinumab every 2 weeks or tralokinumab every 4 weeks for an additional 16 weeks. In the every-2-week maintenance group, of patients who had an IGA response at week 16, 89.6% (95% CI, 77.8 to 95.5) maintained their response at week 32; of patients who had an EASI-75 response at week 16, 92.5% (95% CI, 83.7 to 96.8) maintained their response at week 32 (*Silverberg et al 2021[a]*).
  - Two-year interim results from an ongoing 5-year OL extension trial, ECZTEND, evaluated the use of tralokinumab plus optional TCSs in patients previously treated in one of the tralokinumab parent trials. In ECZTEND, patients received one dose of tralokinumab 600 mg, followed by 300 mg every 2 weeks. Patients treated with tralokinumab for 2 years (n = 345) maintained high EASI-75, EASI-90, and IGA response rates (82.5%, 59.8%, and 48.1%, respectively). Long-term use of tralokinumab was well tolerated, with a safety profile consistent with the parent trials. In the safety analysis set (n = 1174), participants receiving tralokinumab had an exposure-adjusted rate of 237.8 AEs/100 patient-years exposure (*Blauvelt et al 2022[b]*).
- The efficacy and safety of tralokinumab in pediatric patients 12 to 17 years of age were evaluated in ECZTRA 6. Patients (N = 289) with moderate-to-severe AD were randomized to receive either tralokinumab (150 or 300 mg) or placebo every 2 weeks for a total of 16 weeks. At week 16, there were more patients in the tralokinumab groups, 150 mg (n = 98) and 300 mg (n = 97) who achieved a statistically significant IGA score of 0 or 1 without rescue medication (21 [21.4%] and 17 [17.5%], respectively) compared to placebo (n = 94; 4 [4.3%]). A greater proportion of patients receiving tralokinumab 150 mg (28 [28.6%]) and 300 mg (27 [27.8%]) also achieved EASI-75 without rescue medication at week 16 compared to placebo (6 [6.4%]) (*Paller et al 2023[b]*).

JAK inhibitors

Abrocitinib

- FDA approval of abrocitinib was supported by 2 placebo-controlled monotherapy trials, JADE MONO-1 (*Simpson et al 2020[b]*) and JADE MONO-2 (*Silverberg et al 2020*), and 1 trial in combination with topical steroids, JADE COMPARE (*Bieber et al 2021*). Each of these trials enrolled patients with moderate to severe AD having a baseline EASI score ≥ 16, IGA score of ≥ 3, affected BSA ≥ 10%, and an inadequate response to topical medications. JADE MONO-1 and JADE MONO-2 enrolled adults and adolescents, and JADE COMPARE was limited to adults. Patients received abrocitinib 100 mg daily, abrocitinib 200 mg daily, or placebo; JADE COMPARE also included a group who received

dupilumab at its FDA-approved dosing. Co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and the proportion of patients achieving an EASI-75 response, each assessed at week 12.
  - In JADE MONO-1 (N = 387):
    - An IGA response was achieved by 44%, 24%, and 8% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. Both strengths were significantly more effective than placebo (200 mg, $p < 0.0001$; 100 mg; $p = 0.0037$).
    - An EASI-75 response was achieved by 63%, 40%, and 12% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. Both strengths were significantly more effective than placebo ($p < 0.0001$).
  - In JADE MONO-2 (N = 391):
    - An IGA response was achieved by 38.1%, 28.4%, and 9.1% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. Both strengths were significantly more effective than placebo (200 mg, $p < 0.0001$; 100 mg; $p = 0.0008$).
    - An EASI-75 response was achieved by 61.0%, 44.5%, and 10.4% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. Both strengths were significantly more effective than placebo ($p < 0.0001$).
  - In JADE COMPARE (N = 838):
    - An IGA response was achieved by 48.4%, 36.6%, 36.5%, and 14.0% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively. Both strengths of abrocitinib were significantly more effective than placebo ($p < 0.001$).
    - An EASI-75 response was achieved by 70.3%, 58.7%, 58.1%, and 27.1% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo groups, respectively. Both strengths of abrocitinib were significantly more effective than placebo ($p < 0.001$).
    - The study was not formally designed to evaluate the superiority of abrocitinib vs dupilumab.
- JADE EXTEND was a long-term extension study in which patients who were randomized to receive dupilumab in JADE COMPARE were re-randomized to receive abrocitinib 100 mg (n = 130) or 200 mg (n = 73) daily for 12 weeks. Among prior dupilumab responders, EASI-75 was achieved in 93.5% and 90.2% of patients who received 12 weeks of abrocitinib 200 mg or 100 mg, respectively. Among dupilumab non-responders, EASI-75 was achieved in 80.0% and 67.7% of patients who received 12 weeks of abrocitinib 200 mg or 100 mg, respectively (*Shi et al 2022*).
- JADE REGIMEN (N = 798) evaluated the ability to withdraw abrocitinib therapy in responders and reinstitute treatment if the patient experienced a flare, defined as a ≥ 50% loss of initial EASI response with a new IGA score of ≥ 2. Patients with moderate to severe AD who had responded to a 12-week course of OL abrocitinib 200 mg daily were randomized to DB abrocitinib 200 mg, abrocitinib 100 mg, or placebo for 40 weeks. Patients experiencing a flare received rescue treatment with abrocitinib 200 mg plus topical therapy (*Blauvelt et al 2022[c]*).
  - A total of 18.9%, 42.6%, and 80.9% of patients experienced a flare in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. The risk of flare was significantly reduced with abrocitinib 200 mg vs placebo, abrocitinib 100 mg vs placebo, and abrocitinib 200 mg vs abrocitinib 100 mg ($p < 0.001$ for each comparison).
  - At week 12 of rescue with abrocitinib 200 mg and TCSs in patients who had experienced a flare, the EASI-75 response recapture rates were 55.0%, 74.5%, and 91.8% in the groups who had received maintenance with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively.
- JADE DARE (N = 727) was a randomized, DB, Phase 3 trial conducted to compare the efficacy and safety of the higher dose of abrocitinib (n = 362) to dupilumab (n = 365), each given concomitantly with background topical therapy (ie, low to mid-potency TCSs, TCIs, or topical PDE-4 inhibitor), in adults with moderate to severe AD. Trial participants were randomized to receive abrocitinib 200 mg orally once daily through week 26, or one dose of dupilumab 600 mg followed by 300 mg SC every other week with the last injection given at week 24 (*Reich et al 2022*).
  - Co-primary endpoints were achievement of a ≥ 4-point improvement in the PP-NRS score at week 2 and EASI-90 at week 4. The proportions of patients achieving the PP-NRS endpoint at week 2 were 48% and 26% in the abrocitinib and dupilumab groups, respectively, and the proportions achieving EASI-90 at week 4 were 29% and 15%, respectively ($p < 0.0001$ for both comparisons). A key secondary endpoint of EASI-90 at week 16 was achieved by 54% and 42% of patients treated with abrocitinib and dupilumab, respectively ($p = 0.0008$ for superiority).
  - The incidence of AEs was higher in the abrocitinib group (74%) vs the dupilumab group (65%). Nausea, acne, headache, herpes simplex, and herpes zoster were more frequent with abrocitinib, and conjunctivitis was more frequent with dupilumab. The proportions of patients who had AEs that were serious, severe, or led to study discontinuation were similar between the 2 groups.

- JADE TEEN (N = 285) was a randomized, DB, placebo-controlled study in patients 12 to 17 years of age with moderate to severe AD and an inadequate response to topical medications or a need for systemic therapy. Patients received abrocitinib 200 mg, abrocitinib 100 mg, or placebo for 12 weeks in combination with topical therapy (ie, low to mid-potency TCSs, TCIs, or topical PDE-4 inhibitor) (*Eichenfield et al 2021*).
  - Results for the co-primary endpoints at week 12 were as follows:
    - IGA response, defined as a score of 0 or 1 and a ≥ 2-point improvement from baseline, was achieved by 46.2%, 41.6%, and 24.5% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively ($p < 0.05$ for both abrocitinib doses vs placebo).
    - EASI-75 was achieved by 72.0%, 68.5%, and 41.5% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively ($p < 0.05$ for both abrocitinib doses vs placebo).
  - Overall, 62.8%, 56.8%, and 52.1% of patients in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively, experienced TEAEs. The most common TEAEs were nausea in the abrocitinib 200 mg group (18.1%) and upper respiratory tract infection in the abrocitinib 100 mg (9.5%) and placebo (10.4%) groups. TEAEs of special interest (herpes zoster, herpes simplex, oral herpes, eczema herpeticum, and conjunctivitis) were infrequent.

Upadacitinib

- The efficacy and safety of upadacitinib compared to placebo in adults and adolescent patients aged 12 years and older with moderate to severe AD were evaluated in two Phase 3 monotherapy trials, Measure Up 1 and Measure Up 2 (*Guttman-Yassky et al 2021*), and one Phase 3 trial in combination with TCSs, AD Up (*Reich et al 2021*). Co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and the proportion of patients achieving an EASI-75 response, each assessed at week 16. Both co-primary endpoints were met vs placebo in all 3 studies ($p < 0.0001$ vs placebo on all endpoints).
  - In Measure Up 1 (N = 847):
    - An IGA response was achieved by 62.0%, 48.1%, and 8.4% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
    - An EASI-75 response was achieved by 79.7%, 69.6%, and 16.3% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
  - In Measure Up 2 (N = 836):
    - An IGA response was achieved by 52.0%, 38.8%, and 4.7% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
    - An EASI-75 response was achieved by 72.9%, 60.1%, and 13.3% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
  - In AD Up (N = 901):
    - An IGA response was achieved by 58.6%, 39.6%, and 10.9% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
    - An EASI-75 response was achieved by 77.1%, 64.6%, and 26.4% of patients in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.
- Data through 52 weeks of treatment are also available from the AD Up study described above. Efficacy was maintained for all endpoints in patients continuing therapy through this time frame. At week 52, EASI-75 was achieved by 69.0% and 50.8% of patients treated with upadacitinib 30 mg and 15 mg, respectively, and an IGA of 0 or 1 was achieved by 45.2% and 33.5%, respectively. No new important safety risks were observed (*Silverberg et al 2022*).
- Data through 76 weeks of treatment are available for adolescent patients enrolled in Measure Up 1, Measure Up 2, and AD Up. Efficacy was maintained in adolescents continuing therapy through this time frame based on EASI-75 rates and vIGA-AD scores (*Paller et al 2024[b]*).
- An additional trial, Heads Up (N = 692), was a randomized, DB, Phase 3b trial conducted to compare the efficacy and safety of the higher dose of upadacitinib to dupilumab, each given as monotherapy, in adults with moderate to severe AD. Patients were randomized to receive upadacitinib 30 mg orally once daily or dupilumab 600 mg x 1 dose followed by 300 mg SC every other week for 24 weeks, with the primary endpoint evaluated at week 16 (*Blauvelt et al 2021*).
  - At week 16, the primary outcome of EASI-75 was achieved by 71.0% and 61.1% of patients in the upadacitinib and dupilumab groups, respectively (adjusted difference, 10.0%; 95% CI, 2.9 to 17.0; $p = 0.006$). IGA response was not reported. The overall rate of TEAEs was higher with upadacitinib (71.6%) than with dupilumab (62.8%). Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related AEs were higher for patients who

received upadacitinib; rates of conjunctivitis and injection-site reactions were higher for patients receiving dupilumab.

- An OL Phase 3b/4 randomized trial (Level Up) compared the efficacy and safety of upadacitinib and dupilumab in patients aged ≥ 12 years with moderate to severe AD for whom systemic treatment was inadequate or inadvisable. Upadacitinib was initiated at 15 mg once daily and increased to 30 mg once daily if adequate response was not achieved; dupilumab was dosed according to the FDA-approved labeling. At week 16, the primary outcome of simultaneous EASI-90 and Worst Pruritus Numerical Rating Scale (WP-NRS) score of 0 or 1 was achieved in 19.9% of patients treated with upadacitinib vs 8.9% of patients treated with dupilumab ($p < 0.001$) (*Silverberg et al 2024[c]*).

Systematic Reviews and Meta-analyses

- An NMA of 19 trials comparing efficacy and safety of systemic treatments for moderate to severe AD found that the following agents (listed in order of efficacy) were associated with the highest efficacy based on EASI-50 response when used as monotherapy: upadacitinib 30 mg, abrocitinib 200 mg daily, upadacitinib 15 mg daily, dupilumab 300 mg every 2 weeks, and abrocitinib 100 mg daily. Results for comparisons of EASI-75 and -90 responses were similar. In trials assessing systemic therapies as combination therapy, abrocitinib 200 mg daily, dupilumab 300 mg every 2 weeks, and abrocitinib 100 mg daily (in order) had the highest EASI-50 response rates (of note, the combination therapy study for upadacitinib was not captured in this analysis). AE rates were generally higher among systemic therapies compared to placebo but were similar between active treatments (*Silverberg et al 2021[b]*).
- An ICER evidence report included an MA that evaluated the efficacy of the systemic products for AD (*Atlas et al 2021*).
  - Results of the MA demonstrated that, based on trials in adults, there was a higher likelihood of achieving each reported endpoint with dupilumab compared to tralokinumab when used as either monotherapy or in combination with TCS. These endpoints included EASI-50, EASI-75, EASI-90, IGA response, and improvement in PP-NRS.
  - JAK inhibitor comparisons within the class were dose dependent. When used as either monotherapy or combination therapy, the higher and lower doses of upadacitinib generally had numerically higher responses compared to the higher and lower doses, respectively, of abrocitinib, with some CrI that included 1.
  - When used as monotherapy, upadacitinib 30 mg had a higher likelihood of reaching each outcome compared to the monoclonal antibodies, with the exception of the pruritus response. For pruritus response, results were comparable between upadacitinib 30 mg and dupilumab. As combination therapy with TCS, upadacitinib 30 mg had a higher likelihood of reaching each outcome compared to the monoclonal antibodies, and upadacitinib 15 mg and abrocitinib 200 mg each had a higher likelihood of reaching each outcome compared to tralokinumab.
- An updated SR and MA evaluated continuous outcomes in the efficacy and safety of systemic treatments for moderate to severe AD. A total of 60 randomized trials with 16,579 patients were included (*Drucker et al 2022*).
  - Based on comparisons to FDA-approved dosing of dupilumab up to 16 weeks of treatment, results showed:
    - Abrocitinib 200 mg daily (MD, 2.2; 95% CrI, 0.2 to 4.0) and upadacitinib 30 mg daily (MD, 2.7; 95% CrI, 0.6 to 4.7) were associated with reduced EASI scores slightly more than dupilumab (high certainty for both).
    - Abrocitinib 100 mg daily (MD, -2.1; 95% CrI, -4.1 to -0.3), and tralokinumab 600 mg then 300 mg every 2 weeks (MD, -3.5; 95% CrI, -5.8 to -1.3) reduced EASI slightly less than dupilumab (high certainty for both).
    - There was no difference between upadacitinib 15 mg and dupilumab (MD, 0.2; 95% CrI, -1.9 to 2.2) (high certainty).
    - The pattern of results was similar for additional endpoints, including the change in POEM, PP-NRS, and Dermatology Life Quality Index.
    - Subgroup analyses limited to trials with and without concomitant use of topical anti-inflammatory treatment did not substantially alter effect estimates or conclusions.
  - Abrocitinib 100 mg daily was associated with more serious AEs than dupilumab (OR, 2.6; 95% CrI, 1.1 to 6.4; low certainty) and dupilumab was associated with fewer serious AEs than placebo (OR, 0.5; 95% CrI, 0.3 to 0.8; moderate certainty). No significant differences in the rate of serious AEs were demonstrated for other comparisons, including abrocitinib 200 mg daily vs dupilumab (OR, 1.4; 95% CrI, 0.5 to 3.6). For the analysis of withdrawals due to AEs, CrIs were wide, and the authors were not able to make clinically useful conclusions.
  - An update to this SR and MA, including data on lebrikizumab, evaluated 97 trials enrolling 24,679 patients (*Drucker et al 2024[a]*). Based on comparisons to FDA-approved dosing of dupilumab up to 16 weeks of treatment, lebrikizumab (500 mg at weeks 0 and 2 followed by 250 mg every 2 weeks) was probably associated with no important difference in reductions in EASI (MD, -2.0; 95% CrI, -4.5 to 0.3; moderate certainty). The pattern of results

was similar for additional endpoints, including the change in POEM, PP-NRS, and Dermatology Life Quality Index. The relative efficacy of other approved systemic medications was similar to that found by the previous update.

- An NMA assessing binary outcomes of systemic treatments for AD was also conducted. A total of 83 randomized trials with 22,122 patients were included (*Drucker et al 2024[b]*).
  - Based on comparisons to FDA-approved dosing of dupilumab up to 16 weeks of treatment, efficacy results demonstrated the following:
    - Abrocitinib 200 mg daily (OR 1.5; 95% CrI, 1.1 to 2.2) and upadacitinib 15 mg daily (OR, 1.7; 95% CrI, 0.9 to 3.3) and 30 mg daily (OR, 2.5; 95% CrI, 1.3 to 5.0) were associated with greater odds of achieving EASI 50 compared to dupilumab
    - Abrocitinib 100 mg daily (OR, 0.7; 95% CrI, 0.5 to 1.0), baricitinib 4 mg daily (OR, 0.5; 95% CrI, 0.3 to 0.7) and 2 mg daily (OR, 0.4; 95% CrI, 0.3 to 0.5), and tralokinumab 600 mg then 300 mg every 2 weeks (OR, 0.4; 95% CrI, 0.3 to 0.6) were associated with lower odds of achieving EASI 50 compared to dupilumab
    - A similar pattern of results was seen for EASI-75, EASI-90, and IGA success.

Clinical Guidelines

- The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) joint task force issued recommendations for managing AD using both topical and systemic approaches. There are 25 total recommendations (*AAAAI/ACAAI et al 2024*).
  - For topical agents, TCS and TCIs are recommended, while PDE-4 inhibitors (crisaborole) are suggested for use if patients are refractory to moisturizers. The panel conditionally recommends against topical JAK inhibitors (ie, ruxolitinib) due to safety concerns; similarly, adjunct topical antimicrobials are not recommended due to a poor risk:benefit profile.
  - For systemic agents, dupilumab and tralokinumab are recommended for use if patients are refractory or intolerant to mid to high potency topical treatment, while JAK inhibitors (abrocitinib, baricitinib, upadacitinib) and small molecular immunosuppressants (cyclosporine) are suggested for patients refractory or intolerant to mid to high potency topical treatment and systemic treatment inclusive of a recommended biologic agent. Baricitinib 1 mg daily, azathioprine, methotrexate, mycophenolate, and systemic corticosteroids are not recommended.
  - This guideline does not provide recommendations pertaining to the use of Vtama, Zoryve, Adbry, or Nemluvio.

- The American Academy of Dermatology (AAD) released guidelines for AD in 2014 which are being systematically updated to incorporate new agents and modalities (*Davis et al 2024, Eichenfield et al 2014[a], Eichenfield et al 2014[b], Sidbury et al 2023)*. In 2025, the AAD published a focused update with additional recommendations for agents not included in the previous version of the guideline (ie, Vtama, Zoryve, Ebglyss, and Nemluvio) (*Davis et al 2025*).
  - AAD strongly recommends TCS, TCIs, PDE4, or topical JAK inhibitors as first- or second-line topical pharmacotherapy in patients with mild to moderate AD who fail nonpharmacologic measures alone. The AAD panel does not indicate a preference for one agent over another except in specific scenarios.
    - The use of a TCI is recommended for flares associated with specific clinical situations, including recalcitrance to steroids, sensitive areas (face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use (*Eichenfield et al 2014[b]).*
    - For patients with recurrent flares, proactive maintenance treatment with TCS (1 to 2 times per week) or TCI (2 to 3 times per week) at sites that typically flare is recommended to help prevent relapses, and is more effective than emollients alone. Combination TCS plus TCI, concomitantly or sequentially, may be considered as a steroid-sparing regimen (*Eichenfield et al 2014[b]*). Updated guidance recommends intermittent use of medium potency TCSs as maintenance therapy (2 times per week) to reduce flares and relapse (*Sidbury et al 2023*).
    - Topical agents can be used concomitantly with phototherapy or systemic agents for maintenance or rescue therapy or treatment of flares.
    - Tapinarof cream is recommended for topical pharmacotherapy in patients with moderate to severe AD.
  - Biologics (dupilumab, tralokinumab, lebrikizumab, nemolizumab) are strongly recommended in patients with moderate to severe AD. Nemolizumab should be used with concomitant topical therapy. The group also strongly recommends JAK inhibitors (upadacitinib, abrocitinib, baricitinib) in patients with moderate to severe AD, but only in those who have failed alternate systemic therapy (eg, monoclonal antibodies).
  - Methotrexate and immunosuppressants (systemic corticosteroids, mycophenolate, azathioprine, cyclosporine) are conditionally recommended therapies with very low to low certainties of evidence.

  - This guideline does not provide recommendations pertaining to the use of Anzupgo.
- In 2025, the American Academy of Pediatrics (AAP) published a clinical report to review treatment recommendations for AD in pediatric patients, given the recent advancements in this area since their previous clinical report in 2014 (*Schoch et al 2025*).
  - TCSs are safe and effective treatment options when used with appropriate supervision.
  - TCIs (ie, tacrolimus and pimecrolimus) are effective for the treatment of mild to moderate AD, although tacrolimus is more effective than pimecrolimus. They are particularly useful in those with AD affecting areas where long-term steroid application is not desirable, such as the eyelids or face. However, TCIs are rarely effective in cases of AD that are recalcitrant to TCS.
  - Crisaborole has been shown to be safe and effective for mild to moderate AD; however, its specific place in therapy compared to TCS or TCIs is difficult to determine due to a lack of head-to-head comparisons.
  - Consider proactive treatment (TCS or tacrolimus has shown efficacy) in pediatric patients with recurrent flares in similar locations of involvement; individualize medication choice based on factors such as patient age, location of disease, and cost.
  - When topical therapies fail to control AD, systemic therapies can be considered. While the clinical report mentions several systemic agents that are approved for treatment of AD in pediatric patients (ie, dupilumab, tralokinumab, upadacitinib, and abrocitinib), no specific recommendations are made.
- A 2018 European consensus guideline from a variety of organizations on treatment of AD included dupilumab as a treatment option for patients with moderate to severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on pediatric treatment was provided due to lack of data (*Wollenberg et al 2018*).
- The International Eczema Council has released several guidance documents.
  - In 2017, recommendations pertaining to topical and systemic treatment of AD were released. Recommendations aligned closely with those from AAD and AAAI/ACAAI (*Simpson et al 2017*).
  - A 2019 position statement addressed conjunctivitis in AD with and without dupilumab therapy. Following panel discussion, the consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior to treatment, and treatment should be continued after referral to an ophthalmologist should new-onset conjunctivitis occur *(Thyssen et al 2019)*.
  - An additional consensus expert opinion statement from this group provides recommendations for the use of oral JAK inhibitors in AD; the statement concludes that the decision to initiate oral JAK inhibitor treatment should be shared between the patient and provider, accounting for disease severity and personal risk-benefit assessment (including consideration of baseline health risk factors, monitoring requirements, and treatment costs) (*Haag et al 2024*).

Safety Summary

Pimecrolimus and tacrolimus

- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with TCIs.
  - This warning was assigned in 2006 in an FDA labeling update, although a definitive causal link between TCIs and malignancy has not been established (*FDA press release 2006, Hui et al 2009, Lam et al 2021, Sigurgeirsson et al 2015*).
  - Avoid continuous long-term use in any age group, and limit application to areas of involvement with AD.
- Key warnings and precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - Avoid exposure to sunlight during treatment.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash.

Crisaborole

- Contraindications: Known hypersensitivity to crisaborole or any component of the formulation.
- Key warnings and precautions:

- Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with crisaborole.

- AEs:
  - In pivotal studies CORE 1 and 2, the AE reported by ≥ 1% of crisaborole-treated patients (45/1012 [4%] vs 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with crisaborole included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Paller et al 2016)*.

Ruxolitinib

- Boxed warnings: Serious infections; mortality; malignancy; major adverse cardiovascular events (MACE); thrombosis.
- Key warnings and precautions:
  - Serious infections have been reported with the oral JAK inhibitors (including tuberculosis, bacterial, mycobacterial, invasive fungal, viral, or opportunistic infections). Serious lower respiratory tract infections have been reported with topical ruxolitinib. Avoid ruxolitinib in cases of active, serious infections, including localized infections. Herpes viral reactivations have been reported with ruxolitinib; discontinue treatment until the episode resolves. Do not use ruxolitinib in patients with active hepatitis B or C.
  - Thrombocytopenia, anemia, and neutropenia have been reported with ruxolitinib cream.
  - The following events have been observed with JAK inhibitors prescribed for inflammatory conditions:
    - Mortality, including a higher rate of all-cause mortality and sudden cardiovascular (CV) death, was observed with an oral JAK inhibitor compared with tumor necrosis factor (TNF) inhibitors in a large, randomized, post-marketing safety study in patients with rheumatoid arthritis ≥ 50 years of age with ≥ 1 CV risk factor.
    - Malignancy and lymphoproliferative disorders, with an increased risk in patients who are past or current smokers.
      - A higher rate of malignancies (excluding non-melanoma skin cancer) was observed in patients treated with an oral JAK inhibitor compared to those treated with TNF inhibitors.
      - Malignancies were also reported in patients treated with ruxolitinib cream. Non-melanoma skin cancers have occurred.
    - MACE, defined as CV death, non-fatal myocardial infarction, and non-fatal stroke, has been observed at a higher rate with an oral JAK inhibitor compared with TNF inhibitors.
    - Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, has been observed at a higher rate with an oral JAK inhibitor compared with TNF inhibitors; some cases resulted in death. Thromboembolic events were also observed in trials with ruxolitinib cream. Ruxolitinib cream should be avoided in patients who may be at an increased risk of thrombosis.
  - Lipid elevations (eg, total cholesterol, triglycerides) have been reported with oral ruxolitinib.
- AEs: The most common AEs (incidence ≥ 1%) were nasopharyngitis (13%), diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea (1% for each).

Delgocitinib

- Key warnings and precautions:
  - Serious infections have been reported with oral JAK inhibitors; eczema herpeticum has been reported with delgocitinib. Viral reactivation has also been reported.
  - Non-melanoma skin cancers including basal cell carcinoma have been reported; periodic skin examinations are recommended for all patients.
  - Avoid vaccination with live vaccines immediately prior to, during, and after treatment.
  - Additional risks related to JAK inhibition as observed in patients with rheumatoid arthritis (ie, higher rates of all-cause mortality [including sudden CV death], MACE, thrombosis including DVT and PE, and malignancies (excluding non-melanoma skin cancer). Lipid elevations (eg, total cholesterol, low-density lipoprotein, and triglycerides) have also been reported with oral and topical JAK inhibitors.
- AEs: The most common AEs were application site pain, paresthesia, pruritus, erythema, bacterial skin infections (eg, finger cellulitis, paronychia, others), leukopenia, and neutropenia.

Roflumilast

- Contraindications: moderate to severe liver impairment (Child-Pugh class B or C).
- AEs:

- The most common adverse reactions in patients with AD treated with roflumilast 0.15% cream included headache, nausea, application site pain, diarrhea, and vomiting.

Tapinarof
- Tapinarof has no contraindications or warnings/precautions.
- AEs: The most common AEs (incidence ≥ 1%) in patients with AD were upper respiratory tract infection, folliculitis, lower respiratory tract infection, headache, asthma, vomiting, ear infection, pain in extremity, and abdominal pain.

Tralokinumab, dupilumab, and lebrikizumab
- Contraindications: Known hypersensitivity to the drug or any component of the formulation
- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis and angioedema with tralokinumab; anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash with dupilumab; angioedema and urticaria with lebrikizumab) have occurred.
  - Conjunctivitis and keratitis occurred more often with tralokinumab, dupilumab, and lebrikizumab than placebo in AD clinical trials; conjunctivitis was the most frequently reported eye disorder. New or worsening eye symptoms should be reported to a healthcare provider.
  - New-onset psoriasis has been reported in AD patients treated with dupilumab, including those without a family history of psoriasis. A population-based, retrospective cohort study of nearly 20,000 patients with AD found a 58% higher incidence of new-onset psoriasis among patients treated with dupilumab compared to a control group of other systemic agents (ie, corticosteroids, methotrexate, cyclosporine, azathioprine, or mycophenolate; 3-year cumulative incidence, 2.86% vs 1.79%; HR, 1.58; 95% CI, 1.25 to 1.99) (*Lin et al 2025*). Patients should report new-onset symptoms to their provider.
  - Arthralgia, sometimes resulting in hospitalization, has been reported in patients treated with dupilumab. Cases of new-onset psoriatic arthritis have also been reported with dupilumab. Patients should report new onset or worsening joint symptoms to their provider.
  - Pre-existing helminth infections should be treated before therapy with tralokinumab, dupilumab, or lebrikizumab. If a patient becomes infected while receiving tralokinumab, dupilumab, or lebrikizumab and does not respond to anti-helminth treatment, discontinue treatment until the parasitic infection resolves.
  - Complete all age-appropriate vaccinations before initiating therapy with tralokinumab, dupilumab, or lebrikizumab. Avoid live vaccines in patients treated with these drugs.
- AEs:
  - The most common adverse reactions in patients with AD treated with dupilumab included injection-site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
  - The most common AEs (incidence ≥ 1%) in patients with AD treated with tralokinumab were respiratory tract infections (24%), conjunctivitis (7%), injection-site reactions (7%), and eosinophilia (1%).
  - The most common AEs (incidence ≥ 1%) in patients with AD treated with lebrikizumab were conjunctivitis, injection site reactions, and herpes zoster.

Nemolizumab
- Contraindications: Known hypersensitivity to the drug or any component of the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (eg, facial angioedema) have occurred after administration.
  - Complete all age-appropriate vaccinations before initiating therapy with nemolizumab. Avoid live vaccines in patients treated with nemolizumab.
- AEs: The most common AEs (incidence ≥ 1%) in patients with AD treated with nemolizumab included headache (including migraine), arthralgia, urticaria, and myalgia.

Abrocitinib and upadacitinib
- Boxed warnings: serious infection; mortality; malignancy; MACE; thrombosis.
- Contraindications:
  - Upadacitinib is contraindicated in patients with a known hypersensitivity to upadacitinib or any component of the formulation.

- Abrocitinib is contraindicated in patients taking antiplatelet therapies (with the exception of low-dose aspirin) during the first 3 months of therapy.

- Key warnings and precautions:
  - Serious infections, including fatal infections, have been reported with the oral JAK inhibitors (including tuberculosis, bacterial, mycobacterial, invasive fungal, viral, or opportunistic infections), especially in those taking concomitant immunosuppressants. Avoid abrocitinib and upadacitinib in cases of active, serious infections, including localized infections. Herpes viral reactivations have been reported with abrocitinib and upadacitinib; discontinue treatment until the episode resolves. Hepatitis B virus reactivations have also occurred in patients receiving JAK inhibitors.
  - Laboratory abnormalities, including thrombocytopenia and lymphopenia, have occurred in patients receiving abrocitinib. Lymphopenia, neutropenia, elevated hepatic enzymes, and anemia have also been reported with upadacitinib.
  - The following events have been observed with JAK inhibitors prescribed for inflammatory conditions, with a higher risk compared with TNF inhibitors:
    - Mortality, including a higher rate of all-cause mortality and sudden CV death.
    - Malignancy and lymphoproliferative disorders.
    - MACE, defined as CV death, non-fatal myocardial infarction, and non-fatal stroke.
    - Thrombosis, including DVT, PE, and arterial thrombosis; some cases resulted in death. Avoid use of abrocitinib and upadacitinib in patients at an increased risk of thrombosis.
  - Hypersensitivity reactions (eg, anaphylaxis and angioedema) have occurred after administration of upadacitinib.
  - Gastrointestinal perforations have occurred after administration of upadacitinib.
  - Upadacitinib may cause fetal harm if administered to a pregnant woman. Verify pregnancy status prior to initiation of treatment and advise females of reproductive potential to use effective contraception during treatment and for 4 weeks after completion.
  - Complete all age-appropriate vaccinations before initiating therapy with abrocitinib or upadacitinib. Avoid live vaccines in patients treated with either drug.
- AEs:
  - Abrocitinib: The most common AEs (incidence ≥ 1%) in patients receiving 100 mg and 200 mg doses are nasopharyngitis, nausea, headache, herpes simplex, herpes zoster, increased blood creatine phosphokinase (CPK), dizziness, urinary tract infection, fatigue, acne, vomiting, oropharyngeal pain, influenza, gastroenteritis, impetigo, hypertension, contact dermatitis, upper abdominal pain, abdominal discomfort, and thrombocytopenia.
  - Upadacitinib: The most common AEs (incidence ≥ 1%) in patients with AD are upper respiratory tract infection, acne, herpes simplex, headache, increased CPK, cough, hypersensitivity, folliculitis, nausea, abdominal pain, pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza-like illness.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Topical agents				
Anzupgo (delgocitinib)	Cream (2%)	Topical	Two times daily	Do not use > 30 grams per 2 weeks or > 60 grams per month. Apply to affected areas only on the hands and wrists
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily	Do not use with occlusive dressings. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Continuous long-term use should be avoided, and application limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily	Once clinical effect is achieved, consider reducing to once daily.
Opzelura (ruxolitinib)	Cream (1.5%)	Topical	Two times daily	Do not use > 60 grams per week or > 100 grams per 2 weeks. Apply only up to 20% of body surface area. If signs and symptoms persist beyond 8 weeks, patients should be re-examined by their health care provider to confirm the diagnosis.
tacrolimus	Ointment (0.03% and 0.1%)	Topical	Two times daily	Do not use with occlusive dressings. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application limited to areas of involvement.
Vtama (tapinarof)	Cream (1%)	Topical	Once daily	--
Zoryve (roflumilast)	Cream (0.15%)*	Topical	Once daily	--
Systemic agents – monoclonal antibodies				
Adbry (tralokinumab)	Single-dose pre-filled syringe (150 mg), single-dose autoinjector (300 mg)	SC	Adults: one-time loading dose, then every 2 weeks Pediatric (12 to 17 years): one-time loading dose (lower dose vs adults), then every 2 weeks	Adults with weight < 100 kg: at week 16 or later, when clinical effect is achieved, consider every-4-week dosing. May be self-administered; administration under the supervision of an adult is recommended for pediatric patients. The autoinjector is only for use in adults; the pre-filled syringe is for use in adults and pediatric patients aged ≥ 12 years.
Dupixent (dupilumab)	Single-dose pre-filled syringe (200 mg, 300 mg), single-dose pre-filled pen (200 mg, 300 mg)	SC	Adults: one-time loading dose, then every 2 weeks Pediatric (6 months to 5 years): Weight-based dosing every 4 weeks (5 to < 30 kg) Pediatric (6 years to 17 years): Weight-based dosing every 4 weeks (15 to < 30 kg) or every 2 weeks (≥ 30 kg)	May be self-administered. In pediatric patients 6 months to 11 years of age, dupilumab should be administered by a caregiver. The pre-filled pen is only for use in adults and pediatric patients aged ≥ 2 years; the pre-filled syringe is for use in adults and pediatric patients aged ≥ 6 months.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ebglyss (lebrikizumab)	Single-dose pre-filled pen (250 mg), single-dose pre-filled syringe (250 mg)	SC	Loading dose at weeks 0 and 2, then every 2 weeks	At week 16 or later, when clinical effect is achieved, consider every-4-week dosing. May be self-administered. In pediatric patients, lebrikizumab should be administered by a caregiver. Safety and efficacy in pediatric patients < 40 kg have not been established.
Nemluvio (nemolizumab)	Single-dose pre-filled dual-chamber pen (30 mg)	SC	One-time loading dose, then every 4 weeks	At week 16 or later, when clinical effect is achieved, consider every-8-week dosing. May be self-administered. In pediatric patients, nemolizumab should be administered by or under the supervision of a caregiver. Reconstitution is required prior to administration.
Systemic agents – JAK inhibitors				
Cibinqo (abrocitinib)	Tablet (50 mg, 100 mg, 200 mg)	Oral	Once daily with or without food	May increase dosage to 200 mg once daily (maximum) if adequate response is not achieved. A reduced dose is recommended in certain patients based on drug interactions, renal function, and metabolizer status.
Rinvoq (upadacitinib)	Extended-release tablet (15 mg, 30 mg, 45 mg)	Oral	Once daily with or without food	May increase dosage to 30 mg once daily (maximum) in patients < 65 years of age if adequate response is not achieved. Patients ≥ 65 years of age, with severe renal impairment, or taking certain interacting medications should not increase the dose.

* Zoryve is also available as a 0.3% cream, but this formulation is not indicated for AD.
See the current prescribing information for full details.

Conclusion

- AD is a common dermatologic disease characterized by pruritic lesions. Topical pharmacotherapy is first-line for patients with mild to moderate disease; systemic therapies are reserved for patients with moderate to severe disease or in those who do not respond to topical agents alone.
- TCSs are a first-line topical option for patients with AD but are associated with skin atrophy and other AEs with long-term use. TCIs are similarly effective but associated with a higher risk of application site reactions. Tacrolimus ointment 0.1% is more effective than tacrolimus ointment 0.03% and pimecrolimus cream 1%.
- Newer nonsteroidal topical agents include JAK inhibitors (ie, delgocitinib, ruxolitinib), PDE4 inhibitors (ie, crisaborole, roflumilast), and aryl hydrocarbon receptor agonists (ie, tapinarof). They have demonstrated efficacy and safety vs vehicle in Phase 3 trials. These agents have not been directly compared against TCS or TCI in well-designed trials.
  - Crisaborole ointment 2% has demonstrated superior efficacy vs vehicle in patients ≥ 3 months of age with mild to moderate AD. NMA results suggest it is among the least effective topical interventions. Crisaborole use is associated with application site pain and burning.
  - Roflumilast cream 0.15% is approved for the treatment of mild to moderate AD in patients ≥ 6 years of age. It has demonstrated efficacy vs vehicle in large, well-designed Phase 3 trials and is one of 2 agents that are administered once daily.

  - Tapinarof cream was recently approved for the treatment of AD in patients ≥ 2 years of age. It has demonstrated superior efficacy vs vehicle in large, well-designed Phase 3 trials and is administered once daily.
  - Ruxolitinib cream demonstrated superior efficacy vs vehicle in patients ≥ 12 years of age with mild to moderate AD. NMAs have ranked it as among the most effective topical interventions for mild to moderate AD, but direct comparative efficacy is lacking. It has several Boxed Warnings and precautions that may limit use.
  - Delgocitinib cream demonstrated superior efficacy vs vehicle in adults with moderate to severe chronic hand eczema with an inadequate response to or inability to use TCS.
- Systemic agents for AD are indicated in patients with moderate to severe disease, or in patients with mild to moderate disease who fail topical monotherapy (of note, topical agents are often continued in patients who receive systemic medication to control or treat flares). Anti-IL-17, IL-4, and IL-31 monoclonal antibodies are available as a first-line systemic option. Systemic JAK inhibitors are also indicated for AD.
  - Dupilumab, lebrikizumab, nemolizumab, and tralokinumab block cytokine-mediated signaling to improve the signs and symptoms of moderate-to-severe AD. Specific indications vary among products with respect to age (dupilumab: ≥ 6 months of age, other monoclonal antibodies: ≥ 12 years of age) and use of concomitant therapy (nemolizumab: in combination with TCS or TCI; other monoclonal antibodies: with or without TCS).
    - These agents carry a warning for increased risk of serious infections. With the exception of nemolizumab, these agents are also associated with ocular AEs (eg, keratitis).
    - These agents have not been compared with one another, but indirect comparison via NMAs indicates that dupilumab and lebrikizumab are similarly effective to one another, while tralokinumab and nemolizumab are modestly less effective.
  - Abrocitinib and upadacitinib are JAK inhibitors that block intracellular cytokine-induced signaling to improve the signs and symptoms of AD. These agents are approved for use in patients ≥ 12 years of age with moderate to severe AD who have had an inadequate response to both topical and systemic therapies for AD.
    - These agents have not been compared against each other, but they have each been compared with dupilumab in monotherapy RCTs. Both agents have demonstrated superior efficacy vs dupilumab in direct comparisons, and vs lebrikizumab and tralokinumab in indirect comparisons.
    - JAK inhibitors have several Boxed Warnings, which include malignancy, thromboembolism, serious infection, MACE, and death. Additional warnings include laboratory abnormalities and recommendations pertaining to immunization.
- Clinical guidelines recommend the use of TCS and TCIs for both short-term induction and long-term maintenance treatment of AD. Guidelines from AAD and the AAAAI/ACAAI differ in their recommendations pertaining to JAK and PDE4 inhibitors. The former strongly recommends the use of these agents in their FDA-approved populations, while the latter conditionally recommends crisaborole and conditionally recommends *against* ruxolitinib. The guidelines from the AAAAI/ACAAI do not address the use of roflumilast cream 0.15% or tapinarof in the management of AD. A recent focused update of the AAD guidelines recommends roflumilast 0.15% cream for adults with mild to moderate AD and tapinarof for adults with moderate to severe AD.
- Guidelines recommend the use of monoclonal antibodies as a first-line option in patients with moderate to severe AD who have an inadequate response to topical agents alone. These products are well-tolerated with a positive efficacy profile. Guidelines recommend that JAK inhibitors be reserved for patients who do not respond to monoclonal antibody biologics given their AE profile. All patients should be offered topical pharmacotherapy for use in conjunction with systemic treatment to control signs and symptoms.

References

- AAAAI/ACAAI JTF Atopic Dermatitis Guideline Panel, Chu DK, Schneider L, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on practice parameters GRADE- and Institute of Medicine-based recommendations. *Ann Allergy Asthma Immunol*. 2024;132(3):274-312. doi:10.1016/j.anai.2023.11.009
- Abramovits W, Fleischer Jr AB, Jaracz E, et al. Adult patients with moderate atopic dermatitis: Tacrolimus ointment versus pimecrolimus cream. *J Drugs Dermatol.* 2008;12(7):1153-1158.
- Adbry. Package insert. Leo Pharma Inc.; June 2024.
- Anzupgo. Package insert. Leo Pharma Inc.; July 2025.
- Ashcroft DM, Chen LC, Garside R, Stein K, Williams HC. Topical pimecrolimus for eczema. *Cochrane Database Syst Rev*. 2007(4):CD005500.
- Ashcroft D, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. *BMJ*. 2005;330(7490):516-524.

- Atlas SJ, Brouwer E, Fox G, et al. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value; evidence report. Institute for Clinical and Economic Review (ICER). August 17, 2021. Accessed August 4, 2025. https://icer.org/wp-content/uploads/2021/08/Atopic-Dermatitis_Final-Evidence-Report_081721.pdf.
- Beck LA, Bissonnette R, Deleuran M, et al. Dupilumab in adults with moderate to severe atopic dermatitis: A 5-year open-label extension study. *JAMA Dermatol*. 2024; 160(8): 805–812.
- Beck LA, Thaçi D, Deleuran M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2020;21(4):567-577.
- Berger TG. Evaluation and management of severe refractory atopic dermatitis (eczema) in adults. UpToDate Web site. Updated June 9, 2025. Accessed August 4, 2025. www.uptodate.com.
- Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician*. 2012;86(1):35-42.
- Bieber T, Simpson EL, Silverberg JI, et al; JADE COMPARE Investigators. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384(12):1101-1112. doi: 10.1056/NEJMoa2019380.
- Bieber T, Vick K, Fölster-Holst R, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy*. 2007;62(2):184-189.
- Bissonnette R, Stein Gold L, Kircik L, et al. Skin clearance, duration of treatment-free interval, and safety of tapinarof cream 1% once daily: Results from ADORING 3, a 48-week phase 3 open-label extension trial in adults and children down to 2 years of age with atopic dermatitis. *J Am Acad Dermatol*. Published online May 16, 2025. doi:10.1016/j.jaad.2025.05.1391
- Bissonnette R, Warren RB, Pinter A, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema (DELTA 1 and DELTA 2): results from multicentre, randomised, controlled, double-blind, phase 3 trials. *Lancet*. 2024;404(10451):461-473. doi:10.1016/S0140-6736(24)01027-4
- Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389 (10086):2287-2303.
- Blauvelt A, Guttman-Yassky E, Paller AS, et al. Long-term efficacy and safety of dupilumab in adolescents with moderate-to-severe atopic dermatitis: Results through week 52 from a Phase III open-label extension Trial (LIBERTY AD PED-OLE). *Am J Clin Dermatol*. 2022[a];23(3):365-383.
- Blauvelt A, Langley RG, Lacour JP, et al. Long-term 2-year safety and efficacy of tralokinumab in adults with moderate-to-severe atopic dermatitis: Interim analysis of the ECZTEND open-label extension trial. *J Am Acad Dermatol*. 2022[b];87(4):815-824. doi: 10.1016/j.jaad.2022.07.019.
- Blauvelt A, Silverberg JI, Lynde CW, et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. *J Am Acad Dermatol*. 2022[c];86(1):104-112.
- Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2021;157(9):1047-1055. doi: 10.1001/jamadermatol.2021.3023.
- Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. *Br J Dermatol*. 2023;188(6):740-748. doi: 10.1093/bjd/ljad022.
- Broeders JA, Ahmed Ali U, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience. *J Am Acad Dermatol*. 2016;75(2):410-419.e3.
- Castro AP. Calcineurin inhibitors in the treatment of allergic dermatitis. *J Pediatr (Rio J)*. 2006;82(5):166-172.
- Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat*. 2010;21:144-156.
- Cibinqo. Package insert. Pfizer; January 2025.
- Clinical Pharmacology [database online]. Tampa, FL: Elsevier; 2025. Accessed August 4, 2025. http://www.clinicalpharmacology.com.
- Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *Br J Dermatol*. 2021;184(5):857-870.
- Cury Martins J, Martins C, Aoki V, Gois AF, Ishii HA, da Silva EM. Topical tacrolimus for atopic dermatitis. *Cochrane Database Syst Rev*. 2015;2015(7):CD009864.
- Davis DMR, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *J Am Acad Dermatol*. 2024;90(2):e43-e56. doi:10.1016/j.jaad.2023.08.102
- Davis DMR, Frazer-Green L, Alikhan A, et al. Focused update: Guidelines of care for the management of atopic dermatitis in adults. *J Am Acad Dermatol*. Published online June 17, 2025. doi:10.1016/j.jaad.2025.05.1386
- Deleuran M, Thaçi D, Beck LA, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol*. 2020;82(2):377-388.
- Devasenapathy N, Chu A, Wong M, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. *Lancet Child Adolesc Health*. 2023;7(1):13-25. doi:10.1016/S2352-4642(22)00283-8.
- Doss N, Kamoun M-R, Dubertret L, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate to severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs fluticasone 0.005% ointment. *Pediatr Allergy Immunol*. 2010;21:321-329.
- Doss N, Reitamo S, Dubertret L, et al. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol*. 2009;161:427-434.
- Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic immunomodulatory treatments for atopic dermatitis: Update of a living systematic review and network meta-analysis. *JAMA Dermatol*. 2022;158(5):523-532.
- Drucker AM, Lam M, Prieto-Merino D, et al. Systemic immunomodulatory treatments for atopic dermatitis: living systematic review and network meta-analysis update. *JAMA Dermatol*. 2024[a];160(9):936-944. doi: 10.1001/jamadermatol.2024.2192.
- Drucker AM, Lam M, Elsawi R, et al. Comparing binary efficacy outcomes for systemic immunomodulatory treatments for atopic dermatitis in a living systematic review and network meta-analysis. *Br J Dermatol*. 2024[b];190(2):184-190. doi:10.1093/bjd/ljad393
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed August 4, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.

- Dupixent. Package insert. Sanofi-Aventis US, LLC; June 2025.
- Ebglyss. Package insert. Eli Lilly; November 2024.
- Eichenfield LF, Call RS, Forsha DW, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol*. 2017;77(4):641-649.e5.
- Eichenfield LF, Flohr C, Sidbury R, et al. Efficacy and safety of abrocitinib in combination with topical therapy in adolescents with moderate-to-severe atopic dermatitis: The JADE TEEN randomized clinical trial. *JAMA Dermatol*. 2021;157(10):1165-1173.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014[a];70(2):338-351.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014[b];71:116-132.
- Eichenfield LF, Gower RG, Xu J, et al. Once-daily crisaborole ointment, 2%, as a long-term maintenance treatment in patients aged ≥ 3 months with mild-to-moderate atopic dermatitis: A 52-week clinical study. *Am J Clin Dermatol*. 2023;24(4):623-635.
- El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Science*. 2009;54(2):76-87.
- Elidel. Package insert. Bausch Health US, LLC; September 2020.
- Eucrisa. Package insert. Pfizer, Inc.; January 2025.
- Fahrbach K, Tarpey J, Washington EB, et al. Crisaborole ointment, 2%, for treatment of patients with mild-to-moderate atopic dermatitis: systematic literature review and network meta-analysis. *Dermatol Ther (Heidelb)*. 2020;10(4):681-694.
- FDA presentation. Dermatologic and Ophthalmic Drugs Advisory Committee Meeting: Atopic Dermatitis. March 2015. Accessed August 4, 2025. https://web.archive.org/web/20170304160918/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM439354.pdf.
- FDA press release. FDA approves updated labeling with boxed warning and medication guide for two eczema drugs, Elidel and Protopic. January 19, 2006. Accessed August 4, 2025. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/pimecrolimus-marketed-elidel-cream-information.
- Fleischer Jr AB, Abramovits W, Breneman D, et al. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. *J Dermatolog Treat*. 2007;18:151-157.
- Gonzalez ME. Management of severe, refractory atopic dermatitis (eczema) in children. UpToDate Web site. Updated June 2, 2025. Accessed August 4, 2025. www.uptodate.com.
- Gooderham M, Molin S, Bissonnette R, et al. Long-term safety and efficacy of delgocitinib cream for up to 52 weeks in adults with chronic hand eczema: Results of the phase 3 open-label extension DELTA 3 trial following the DELTA 1 and 2 trials. *J Am Acad Dermatol*. 2025;93(1):95-103. doi:10.1016/j.jaad.2025.03.008
- Gutermuth J, Pink AE, Worm M, et al. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). *Br J Dermatol*. 2022;186(3):440-452.
- Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. 2021;397(10290):2151-2168. doi: 10.1016/S0140-6736(21)00588-2.
- Guttman-Yassky E, Weidinger S, Simpson EL, et al. Two-year efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis: a long-term extension (ADjoin). *Dermatol Ther (Heidelb)*. 2025;15(8):2217-2232. doi:10.1007/s13555-025-01452-9
- Haag C, Alexis A, Aoki V, et al. A practical guide to using oral Janus kinase inhibitors for atopic dermatitis from the International Eczema Council. *Br J Dermatol*. 2024;192(1):135-143. doi: 10.1093/bjd/ljae342.
- Hui RL, Lide W, Chan J, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother*. 2009;43:1956-63.
- Institute for Clinical and Economic Review (ICER). Dupilumab and crisaborole for atopic dermatitis: effectiveness and value. Final evidence report and meeting summary. June 8, 2017. Accessed August 4, 2025. https://icer.org/wp-content/uploads/2020/10/MWCEPAC_ATOPIC_FINAL_EVIDENCE_REPORT_060717.pdf.
- Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol*. 2004;51(4):515-525.
- Kim BS, Howell MD, Sun K, et al. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145(2):572-582.
- Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics*. 2008;122(4):812-824.
- Lam M, Zhu JW, Tadrous M, et al. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: A systematic review and meta-analysis. *JAMA Dermatol*. 2021;157(5):549-558.
- Lax SJ, Van Vogt E, Candy B, et al. Topical anti-inflammatory treatments for eczema: network meta-analysis. *Cochrane Database Syst Rev*. 2024;8(8):CD015064. Published 2024 Aug 6. doi:10.1002/14651858.CD015064.pub2
- Lin TL, Fan YH, Fan KS, Juan CK, Chen YJ, Wu CY. Psoriasis risk in patients with atopic dermatitis treated with dupilumab. *JAMA Dermatol*. Published online June 18, 2025. doi:10.1001/jamadermatol.2025.1578
- Nemluvio. Package insert. Galderma Laboratories, LP; June 2025.
- Opzelura. Package insert. Incyte Corporation, Inc.; August 2024.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. Accessed August 4, 2025. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
- Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016;75(3):494-503.e4.
- Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol.* 2020;83(5):1282-1293.

- Paller AS, Simpson EL, Siegfried EC, et al. Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2022;400(10356):908-919. doi:10.1016/S0140-6736(22)01539-2.
- Paller AS, Flohr C, Eichenfield LF, et al. Safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis: a 52-week, open-label, phase 3 study. *Dermatol Ther (Heidelb)*. 2023[a];13(7):1517-1534. doi: 10.1007/s13555-023-00942-y.
- Paller AS, Flohr C, Cork M, et al. Efficacy and safety of tralokinumab in adolescents with moderate to severe atopic dermatitis: The phase 3 ECZTRA 6 randomized clinical trial. *JAMA Dermatol*. 2023[b];159(6):596-605. doi:10.1001/jamadermatol.2023.0627
- Paller AS, Siegfried EC, Simpson EL, et al. Dupilumab safety and efficacy up to 1 year in children aged 6 months to 5 years with atopic dermatitis: results from a phase 3 open-label extension study. *Am J Clin Dermatol*. 2024[a];25(4):655-668. doi:10.1007/s40257-024-00859-y
- Paller AS, Mendes-Bastos P, Siegfried E, et al. Upadacitinib in adolescents with moderate to severe atopic dermatitis: analysis of 3 phase 3 randomized clinical trials through 76 weeks. *JAMA Dermatol*. 2024[b];160(12):1304-1313. doi: 10.1001/jamadermatol.2024.3696.
- Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol*. 2021;85(4):863-872.
- Papp K, Szepietowski JC, Kircik L, et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: results from two phase 3 studies. *J Am Acad Dermatol*. 2023;88:1008-16. doi:10.1016/j.jaad.2022.09.060.
- Purple Book: Database of licensed biological products. Food and Drug Administration Web site. Accessed August 4, 2025. https://purplebooksearch.fda.gov/.
- Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10290):2169-2181. doi: 10.1016/S0140-6736(21)00589-4.
- Reich K, Thyssen JP, Blauvelt A, et al. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. *Lancet*. 2022;400(10348):273-282.
- Rinvoq. Package insert. AbbVie Inc.; April 2025.
- Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, et al. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev*. 2020 Sep 14;9:CD013206.
- Schlessinger J, Shepard JS, Gower R, et al. Safety, effectiveness, and pharmacokinetics of crisaborole in infants aged 3 to < 24 months with mild-to-moderate atopic dermatitis: A phase IV open-label study (CrisADe CARE 1). *Am J Clin Dermatol*. 2020;21(2):275-284.
- Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2):295-9.e1-27.
- Schoch JJ, Anderson KR, Jones AE, Tollefson MM; Section on Dermatology. Atopic dermatitis: update on skin-directed management: clinical report. *Pediatrics*. Published online May 19, 2025. doi:10.1542/peds.2025-071812
- Shi VY, Bhutani T, Fonacier L, et al. Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). *J Am Acad Dermatol*. 2022;87(2):351-358. doi:10.1016/j.jaad.2022.04.009.
- Sidbury R, Alikhan A, Bercovitch L, et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. *J Am Acad Dermatol*. 2023;89(1):e1-e20. doi:10.1016/j.jaad.2022.12.029.
- Siegels D, Heratizadeh A, Abraham S, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. *Allergy*. 2021;76(4):1053-1076.
- Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135(4):597-606.
- Silverberg JI, de Bruin-Weller M, Bieber T, et al. Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. *J Allergy Clin Immunol*. 2022;149(3):977-987.
- Silverberg JI, Howe W. Atopic dermatitis (eczema): pathogenesis, clinical manifestations, and diagnosis. UpToDate Web site. Updated July 17, 2025. Accessed August 4, 2025. www.uptodate.com.
- Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: A randomized clinical trial. *JAMA Dermatol*. 2020;156(8):863-873. doi: 10.1001/jamadermatol.2020.1406.
- Silverberg JI, Thyssen JP, Fahrbach K, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *J Eur Acad Dermatol Venereol*. 2021[b];35(9):1797-1810. doi: 10.1111/jdv.17351.
- Silverberg JI, Toth D, Bieber T, et al; ECZTRA 3 study investigators. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *Br J Dermatol*. 2021[a];184(3):450-463. doi: 10.1111/bjd.19573.
- Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. *N Engl J Med*. 2023;388(12):1080-1091. doi: 10.1056/NEJMoa2206714
- Silverberg JI, Eichenfield LF, Hebert AA, et al. Tapinarof cream 1% once daily: Significant efficacy in the treatment of moderate to severe atopic dermatitis in adults and children down to 2 years of age in the pivotal phase 3 ADORING trials. *J Am Acad Dermatol*. 2024[a];91(3):457-465. doi: 10.1016/j.jaad.2024.05.023.
- Silverberg JI, Wollenberg A, Reich A, et al. Nemolizumab with concomitant topical therapy in adolescents and adults with moderate-to-severe atopic dermatitis (ARCADIA 1 and ARCADIA 2): results from two replicate, double-blind, randomised controlled phase 3 trials. *Lancet*. 2024[b];404(10451):445-460. doi: 10.1016/S0140-6736(24)01203-0.
- Silverberg JI, Bunick CG, Hong HC, et al. Efficacy and safety of upadacitinib versus dupilumab in adults and adolescents with moderate-to-severe atopic dermatitis: week 16 results of an open-label randomized efficacy assessor-blinded head-to-head phase IIIb/IV study (Level Up). *Br J Dermatol*. 2024[c];192(1):36-45. doi: 10.1093/bjd/ljae404.
- Simpson EL, Bieber T, Guttman-Yassky E, et al, for the SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.
- Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol*. 2017;77(4):623-633.
- Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020[a];156(1):44-56.

- Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020[b];396(10246):255-266. doi: 10.1016/S0140-6736(20)30732-7.
- Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and safety of lebrikizumab in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: a randomized clinical trial (ADhere). *JAMA Dermatol*. 2023;159(2):182-191. doi: 10.1001/jamadermatol.2022.5534.
- Simpson EL, Eichenfield LF, Alonso-Llamazares J, et al. Roflumilast cream, 0.15%, for atopic dermatitis in adults and children: INTEGUMENT-1 and INTEGUMENT-2 randomized clinical trials. *JAMA Dermatol*. 2024;160(11):1161-1170. doi: 10.1001/jamadermatol.2024.3121.
- Simpson EL, Eichenfield LF, Papp KA, et al. Long-term safety and efficacy with roflumilast cream 0.15% in patients aged ≥6 years with atopic dermatitis: a phase 3 open-label extension trial. *Dermatitis*. 2025 Jan 10. doi: 10.1089/derm.2024.0418.
- Tacrolimus 0.1% ointment. Package insert. Encube Ethicals, Inc.; October 2023.
- Thyssen JP, de Bruin-Weller MS, Paller AS, et al. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy - international eczema council survey and opinion. *J Eur Acad Dermatol Venereol*. 2019;33(7):1224-1231.
- Tollefson MM, Bruckner AL; Section on Dermatology. Atopic dermatitis: skin-directed management. *Pediatrics*. 2014;134:e1735-e1744.
- Vtama. Package insert. Organon LLC; May 2025.
- Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol*. 2018;32(6):850-878.
- Wollenberg A, Blauvelt A, Guttman-Yassky E, et al; ECZTRA 1 and ECZTRA 2 study investigators. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol*. 2021;184(3):437-449. doi: 10.1111/bjd.19574.
- Worm M, Simpson EL, Thaçi D, et al. Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: A randomized clinical trial. *JAMA Dermatol*. 2020;156(2):131-143.
- Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8(8):853-866.
- Zoryve cream. Package insert. Arcutis Biotherapeutics, Inc.; July 2024.

Publication Date: 9/10/25