South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 26, 2026

South Dakota
Department of
Social Services

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South Dakota Department of Social Services

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

June 26, 2026
1:00 – 3:00 PM CT
12:00 – 2:00 PM MT

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_NmRhZGQ5MTktNDNmNS00OGQxLWFiOTQtN2I0M2ZiMzZhYmZh%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: 215 052 473 527 4
Passcode: HW27PB39

Join by Phone
+1 952-222-7450
Phone Conference ID: 514 944 78#

Call to Order

Approval of Previous Meeting Minutes

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

Old business
- **Opioid Update**
- **H. Pylori review**

New business
- **Prescription drug utilization report**
- **PA reviews**
- **Nurtec ODT**
- **Tonmya**
- **Icotyde**

Public input accepted after individual topic discussion
Next meeting date September 25, 2026 (tentative) & adjournment

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

Friday, March 13, 2026
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

New committee member Brian Wilson was introduced and welcomed.
Van Gilder called the meeting to order at 1:09 pm. The minutes of the December meeting were presented. Baack made a motion to approve. Nieuwenhuis 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 October 1, 2025, to December 31, 2025. A total of 8,540 PAs were reviewed of which 122 requests (1.43%) were received via telephone; 91 requests (1.07%) were received via fax; 5,448 requests (63.8%) were reviewed electronically; and 2,879 requests (33.7%) were reviewed via ePA.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from October 1, 2025, to December 31, 2025. The top five therapeutic classes based on paid amount were atypical antipsychotics, immunomodulator agents, incretin mimetics, tumor necrosis factor inhibitors, and interleukin-mediated agents. These top 15 therapeutic classes comprise 16.9% 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 7.85% of total claims. Vyvgart Hytrulo made its debut on the Top 50 drug list by paid amount. Tackett remarked more medical drugs shifting to pharmacy as these formulations with hyaluronidase allows quicker administration. Van Gilder asked if there were any public comments; none were offered.

Old Business

Non-Hormonal Drugs for Vasomotor Symptoms

Committee reviewed utilization of non-hormonal drugs for vasomotor symptoms. Baack commented on the challenge of adding PA for women who have contraindications and risks to hormonal therapy. Van Gilder asked if there were any public comments; none were offered. After discussion, Baack motioned to add prior authorization (PA). Nieuwenhuis seconded the motion. The motion was approved unanimously.

Opioid Update
The committee reviewed opioid outcomes compared to the previous quarter from the opioid initiatives. There was a slight increase in opioid utilization during 3Q2025 which corresponded to increases in utilization of all drugs in general. The average MME/day/utilizer stayed steady. Committee also reviewed breakdown of members using 3 or more pharmacies and prescribers. Van Gilder noted that the PDMP has significantly assisted in reducing poly prescriber and multi-pharmacy issues. Van Gilder asked if there were any public comments; none were offered.

New Business

Biosimilar PDL
The medical Preferred Drug List (PDL) process and initial PDL for PAD Biosimilar Agents on the medical side were presented to the committee. The preferred biosimilar drug on the PAD Biosimilar PDL would not require PA. Additionally, Koerner said providers will receive notification via the listserv. Van Gilder asked if there were any public comments; none were offered.

Brinsupri
Clinical information for Brinsupri was presented for review. After discussion, committee recommended monitoring utilization and review again in six months. Van Gilder asked if there were any public comments; none were offered.

Coxanto
Clinical information for Coxanto was presented for review. Van Gilder recommended PA on oxaprozin capsules. After discussion, Nieuwenhuis motioned to adopt PA. Van Gilder asked if there were any public comments; none were offered. Baack seconded the motion. The motion was approved unanimously.

MASH Treatments
Clinical information for Wegovy injection for MASH and review of Rezdiffra were presented for review. Baack said 20% of patients with MASH are non-obese. McGill raised concerns regarding GLP-1 agents in patients who are intolerant. Shawn Hansen, PharmD and Medical Account Director with Novo Nordisk, provided public comment. After discussion, Baack made motion to add criteria for trial and failure of Wegovy before Rezdiffra for patients with BMI 27 and over. Preuss seconded the motion. The motion was approved unanimously.

Zepbound OSA
Clinical information for Zepbound for OSA was presented for review. Beth Lubelczyk, PharmD and Health Outcome Liaison with Eli Lilly, provided public comment. Nieuwenhuis motioned to adopt PA criteria. Baack seconded the motion. The motion passed unanimously.

Adjournment
The next meeting is scheduled for March 27, 2026. The June meeting is tentatively scheduled for June 12, 2026. Sept meeting tentatively scheduled for Sept 25th. All motioned and were in favor of adjourning the meeting. The meeting adjourned at 2:47pm CT.

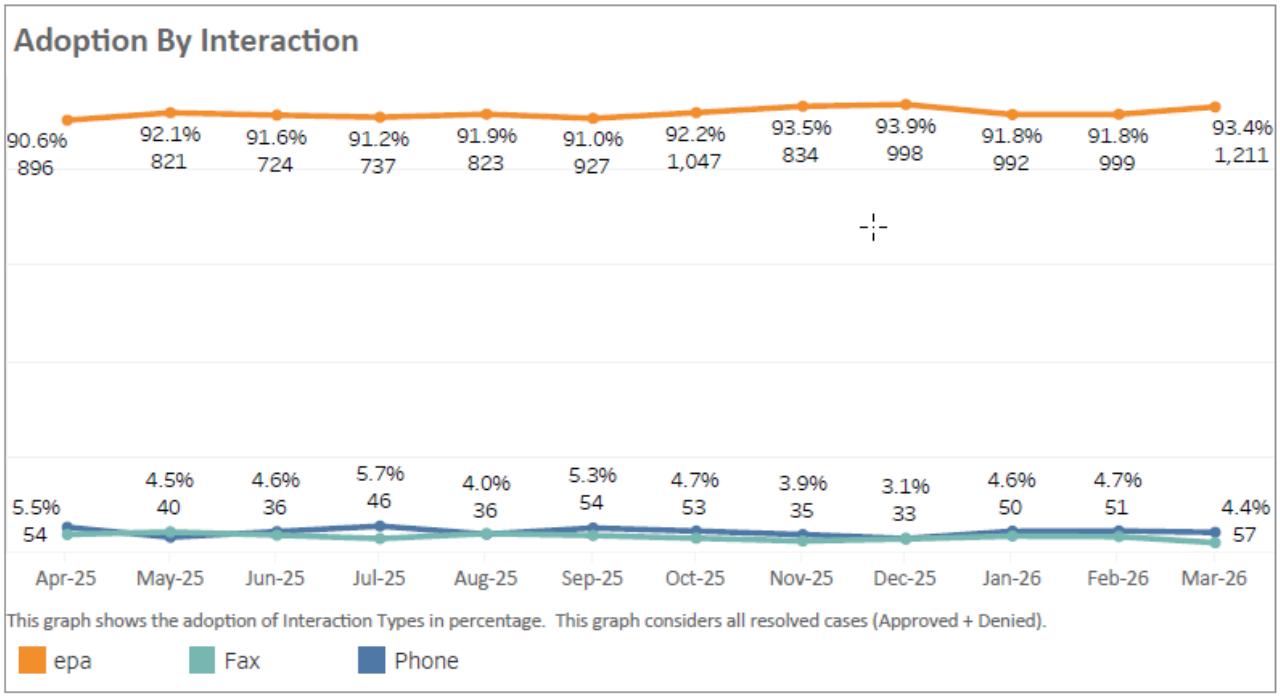
PA Report
1/1/2026 – 3/31/2026

Compliance Summary

Priority	Total PAs	PAs Compliant	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	5,836	5,836	1	99.98%	0.02%
Urgent	728	728	0	100.00%	0.00%
Grand Total	**6,564**	**6,564**	**0**		

Priority	Standard	Urgent
ePA	2,516	687
Fax	97	9
Phone	127	32
Real-Time	3,096	

Request Summary	Total # of Requests	Phone Requests		Fax Requests		Real-Time PA		ePA PA	
		#	%	#	%	#	%	#	%
Total	**6,564**	**159**	**2.46%**	**106**	**1.61%**	**3,096**	**47.2%**	**3,203**	**47.8%**



PA Initial Requests Summary

Month	Approved	Denied	Total
January-26	1,860	284	2,144
February-26	1,828	280	2,108
March-26	1,969	342	2,311
1Q26	**5,657**	**906**	6,563
Percent of Total	**86.2%**	**13.8%**	

Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
ANTIPSYCHOTICS/ANTIMANIC	2,059	42	2101	98.00%	32.01%	, ARIPIPRAZOLE
ANTIDIABETICS	711	92	803	88.54%	12.24%	, OZEMPIC
MEDICAL DEVICES & SUPPLIES	465	172	637	73.00%	9.71%	, FREESTYLE
ADHD/ANTI-NARCOLEPSY/ ANTI-OBESITY/ANOREX	409	170	579	70.64%	8.82%	, WEGOVY
ANALGESICS - OPIOID	361	48	409	88.26%	6.23%	HYDROCODONE /APAP
OTHERS -	1,652	382	2,034	81.22%	30.99%	
1Q26	**5,657**	**906**	**6,563**	**86.2%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
January-26	32	80.00%	8	20.00%	40
February-26	25	69.44%	11	30.56%	36
March-26	26	65.00%	14	35.00%	40
1Q26	**83**	**71.55%**	**33**	**28.45%**	**116**

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS	2059	42	2101	98.00%
27 - ANTIDIABETICS	711	92	803	88.54%
97 - MEDICAL DEVICES AND SUPPLIES	465	172	637	73.00%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	409	170	579	70.64%
65 - ANALGESICS - OPIOID	361	48	409	88.26%
90 - DERMATOLOGICALS	265	52	317	83.60%
58 - ANTIDEPRESSANTS	243	31	274	88.69%
67 - MIGRAINE PRODUCTS	222	34	256	86.72%
52 - GASTROINTESTINAL AGENTS - MISC.	215	34	249	86.35%
49 - ULCER/ANTISPASMODICS/ANTICHOLINERG	159	11	170	93.53%
66 - ANALGESICS - ANTI-INFLAMMATORY	116	27	143	81.12%
12 - ANTIVIRALS	51	13	64	79.69%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGT	55	6	61	90.16%
54 - URINARY ANTISPASMODICS	38	19	57	66.67%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGTS	40	10	50	80.00%
72 - ANTICONVULSANTS	36	10	46	78.26%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	21	19	40	52.50%
39 - ANTIHYPERLIPIDEMICS	30	3	33	90.91%
41 - ANTIHISTAMINES	25	7	32	78.13%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	18	9	27	66.67%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.	16	9	25	64.00%
28 - THYROID AGENTS	10	13	23	43.48%
75 - MUSCULOSKELETAL THERAPY AGENTS	14	8	22	63.64%
94 - DIAGNOSTIC PRODUCTS	2	17	19	10.53%
34 - CALCIUM CHANNEL BLOCKERS*	8	7	15	53.33%
33 - BETA BLOCKERS*	9	5	14	64.29%
99 - MISCELLANEOUS THERAPEUTIC CLASSES	8	2	10	80.00%
40 - CARDIOVASCULAR AGENTS - MISC.	6	3	9	66.67%
50 - ANTIEMETICS*	8	1	9	88.89%
42 - NASAL AGENTS - SYSTEMIC & TOPICAL	2	6	8	25.00%
83 - ANTICOAGULANTS	5	3	8	62.50%
36 - ANTIHYPERTENSIVES	4	3	7	57.14%
56 - GENITOURINARY AGENTS - MISC	5	1	6	83.33%
74 - NEUROMUSCULAR AGENTS	2	4	6	33.33%
38 - VASOPRESSORS	1	4	5	20.00%
64 - ANALGESICS - NONNARCOTIC*	1	3	4	25.00%
79 - MINERALS & ELECTROLYTES	2	2	4	50.00%
32 - ANTIANGINAL AGENTS	1	2	3	33.33%
82 - HEMATOPOIETIC AGENTS	3	0	3	100.00%
01 - PENICILLINS	2	0	2	100.00%
04 - TETRACYCLINES	1	1	2	50.00%
16 - ANTI-INFECTIVE AGENTS - MISC.	2	0	2	100.00%
19 - PASSIVE IMMUNIZING & TREATMENT AGENTS	2	0	2	100.00%
51 - DIGESTIVE AIDS	1	1	2	50.00%
22 - CORTICOSTEROIDS	1	0	1	100.00%
46 - LAXATIVES	0	1	1	0.00%
57 - ANTIANXIETY AGENTS	0	1	1	0.00%
85 - HEMATOLOGICAL AGENTS - MISC.	1	0	1	100.00%
86 - OPHTHALMIC AGENTS	1	0	1	100.00%
1Q26	**5,657**	**906**	**6,563**	
Percent of Total	**86.2%**	**13.8%**		

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LINZESS	6	3	9	66.67%
DEXCOM	3	5	8	37.50%
FREESTYLE LIBRE	4	4	8	50.00%
EMGALITY	3	1	4	75.00%
WEGOVY	1	3	4	25.00%
AJOVY	3	0	3	100.00%
ARIPIPRAZOLE	2	1	3	66.67%
BELSOMRA	2	1	3	66.67%
MALATHION	2	1	3	66.67%
OLANZAPINE	3	0	3	100.00%
TRAMADOL/ER	3	0	3	100.00%
AIMOVIG	1	1	2	50.00%
CABOMETYX	2	0	2	100.00%
CONTOUR	0	2	2	0.00%
GEMTESA	1	1	2	50.00%
HYDROCODONE BITARTRATE/APAP	2	0	2	100.00%
MAVYRET	2	0	2	100.00%
OMNITROPE	1	1	2	50.00%
QELBREE	2	0	2	100.00%
QUVIVIQ	0	2	2	0.00%
TREMFYA	2	0	2	100.00%
AUSTEDO	1	0	1	100.00%
BELBUCA	1	0	1	100.00%
CETIRIZINE	0	1	1	0.00%
DUPIXENT	1	0	1	100.00%
ENBREL MINI	1	0	1	100.00%
ENOXAPARIN	1	0	1	100.00%
EPCLUSA	0	1	1	0.00%
EUCRISA	1	0	1	100.00%
EVRYSDI	1	0	1	100.00%
FINTEPLA	1	0	1	100.00%
GLUCOCARD SHINE TEST STRIPS	0	1	1	0.00%
HUMIRA PEN-PS/UV STARTER	1	0	1	100.00%
IBSRELA	1	0	1	100.00%
INGREZZA	1	0	1	100.00%
JAKAFI	1	0	1	100.00%
JOURNAVX	0	1	1	0.00%
LEVOTHYROXINE	0	1	1	0.00%
LISDEXAMFETAMINE	1	0	1	100.00%
LUBIPROSTONE	1	0	1	100.00%
LYBALVI	0	1	1	0.00%
MOUNJARO	1	0	1	100.00%
MOVANTIK	1	0	1	100.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
NUCALA	1	0	1	100.00%
NURTEC	1	0	1	100.00%
OLUMIANT	0	1	1	0.00%
ONETOUCH ULTRA	1	0	1	100.00%
OPSUMIT	1	0	1	100.00%
OPZELURA	1	0	1	100.00%
ORENCIA CLICKJECT	1	0	1	100.00%
OTEZLA	1	0	1	100.00%
PREGABALIN	1	0	1	100.00%
PRUCALOPRIDE	1	0	1	100.00%
QUETIAPINE FUMARATE	1	0	1	100.00%

QUILLIVANT XR	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%
TIROSINT	1	0	1	100.00%
PRUCALOPRIDE	1	0	1	100.00%
QUETIAPINE FUMARATE	1	0	1	100.00%
QUILLIVANT XR	1	0	1	100.00%
UPTRAVI	1	0	1	100.00%
VIJOICE	1	0	1	100.00%
VRAYLAR	1	0	1	100.00%
VYVANSE	1	0	1	100.00%
WINLEVI	1	0	1	100.00%
XTANDI	1	0	1	100.00%
1Q26	**83**	**33**	**116**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2026 – 3/31/2026					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITOR	19,399	$258,553.65	$13.33	5.82%
2	ATYPICAL ANTIPSYCHOTICS	12,982	$5,359,632.12	$412.85	3.89%
3	RESPIRATORY AND CNS STIMULANT	11,078	$1,237,119.62	$111.67	3.32%
4	AMPHETAMINES	10,259	$732,760.18	$71.43	3.08%
5	PROTON-PUMP INHIBITORS	10,145	$255,988.05	$25.23	3.04%
6	SELECTIVE BETA-2-ADRENERGICS	10,046	$483,124.59	$48.09	3.01%
7	ADRENALS	9,273	$1,196,402.25	$129.02	2.78%
8	AMINOPENICILLIN ANTIBIOTICS	9,023	$137,173.20	$15.20	2.71%
9	GABA-MEDIATED ANTICONVULS	8,907	$216,766.45	$24.34	2.67%
10	OPIOID AGONISTS	8,473	$255,902.88	$30.20	2.54%
11	SECOND GENERATION ANTIHISTAMINES	8,278	$89,723.34	$10.84	2.48%
12	SEROTONIN MODULATORS	8,256	$230,564.90	$27.93	2.48%
13	ANTICONVULSANTS, MISC	7,718	$1,071,575.44	$138.84	2.31%
14	HMG-COA REDUCTASE INHIBITORS	7,290	$85,958.92	$11.79	2.19%
15	BETA-ADRENERGIC BLOCKING	6,640	$99,750.98	$15.02	1.99%
Total		**147,767**	**$11,710,996.57**	**$79.25**	**44.3%**

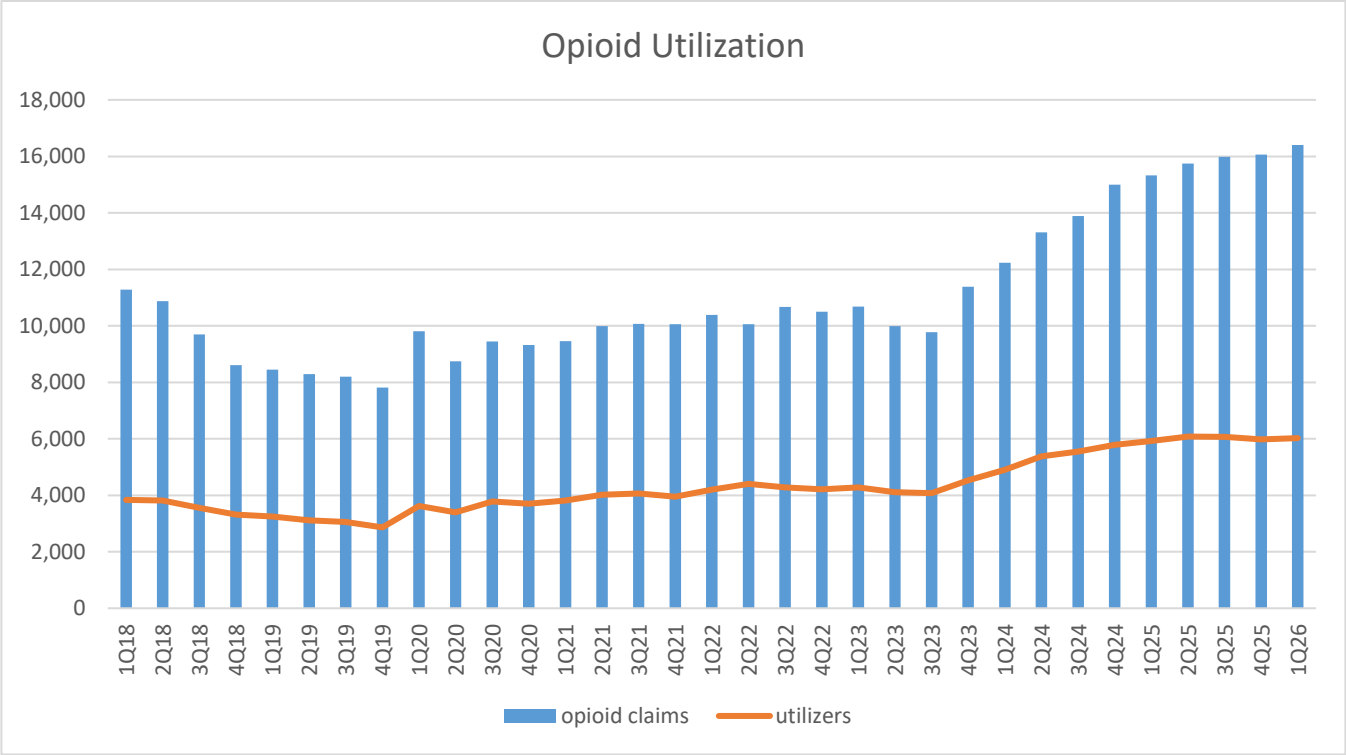
TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2026 – 3/31/2026					
	AHFS Description	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	IMMUNOMODULATORY AGENTS	1,139	$5,653,180.19	$4,963.28	0.34%
2	ATYPICAL ANTIPSYCHOTICS	12,982	$5,359,632.12	$412.85	3.89%
3	INCRETIN MIMETICS	4,222	$4,367,455.32	$1,034.45	1.27%
4	TUMOR NECROSIS FACTOR INHIBITOR	381	$3,161,295.47	$8,297.36	0.11%
5	INTERLEUKIN-MEDIATED AGENT	215	$2,716,874.81	$12,636.63	0.06%
6	ANTINEOPLASTIC AGENTS	452	$2,171,763.01	$4,804.79	0.14%
7	CYSTIC FIBROSIS (CFTR) CO	70	$1,686,759.90	$24,096.57	0.02%
8	HIV INTEGRASE INHIBITOR	333	$1,313,569.94	$3,944.65	0.10%
9	HEMOSTATICS	60	$1,238,988.86	$20,649.81	0.02%
10	RESPIRATORY AND CNS STIMULANTS	11,078	$1,237,119.62	$111.67	3.32%
11	ADRENALS	9,273	$1,196,402.25	$129.02	2.78%
12	CALCITONIN GENE-RELATED PEPTIDE	1,171	$1,138,945.09	$972.63	0.35%
13	ANTICONVULSANTS, MISC	7,718	$1,071,575.44	$138.84	2.31%
14	DEVICES	4,598	$832,364.19	$181.03	1.38%
15	SODIUM-GLUC COTRANSPORT 2	2,227	$808,873.64	$363.21	0.67%
Total		**55,919**	**$33,954,799.85**	**$607.21**	**16.77%**

Total Rx Claims from 1/1/2026 – 3/31/2026	**333,536**

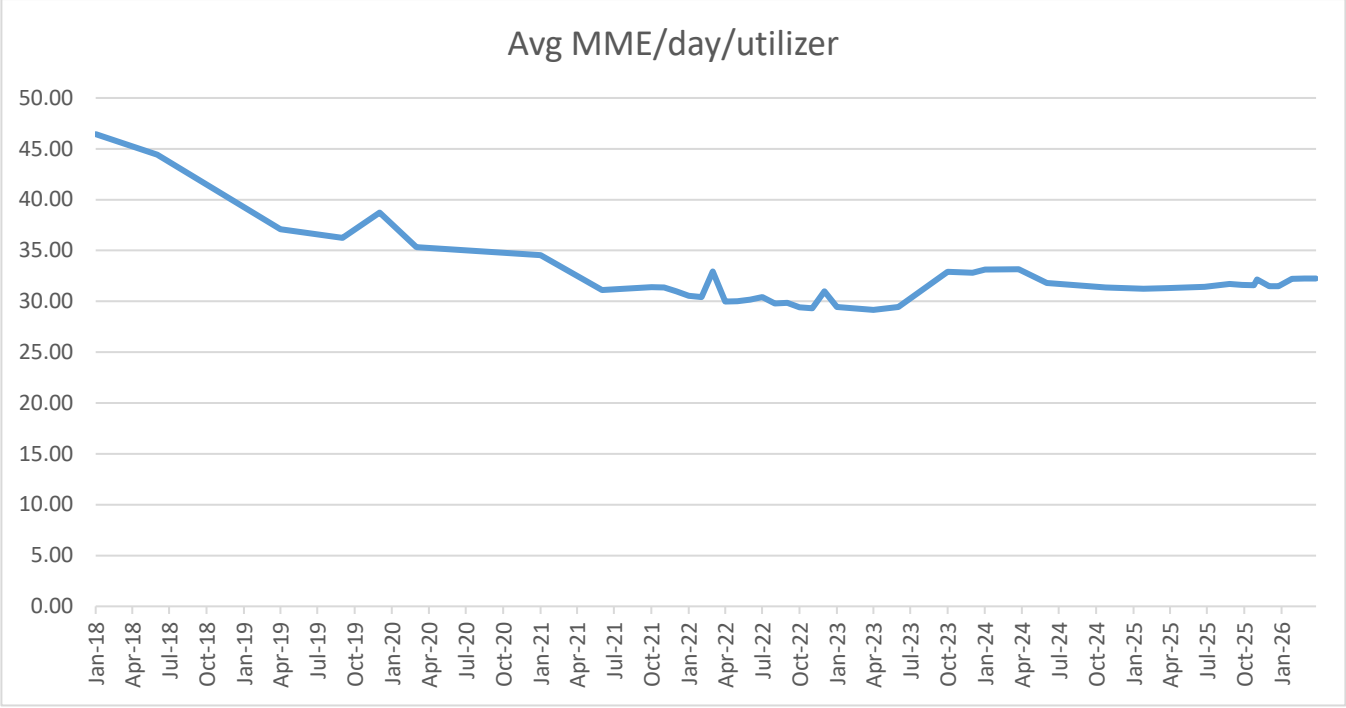
TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2026 – 3/31/2026						
	Therapeutic Class Name	**Drug Label Name**	**Total Rxs**	**Plan Paid Amount**	**Paid/Rx**	**% Total Claims**
1	Antidepressants	FLUOXETINE	6,652	$84,020.38	$12.63	1.99%
2	Penicillins	AMOXICILLIN	6,217	$85,867.34	$13.81	1.86%
3	Antidepressants	**SERTRALINE**	6,042	$78,672.50	$13.02	1.81%
4	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,981	$282,878.08	$47.30	1.79%
5	Anticonvulsants - 2nd Generation	GABAPENTIN	5,939	$87,146.99	$14.67	1.78%
6	Inhaled Bronchodilator	ALBUTEROL HFA	5,889	$174,066.59	$29.56	1.77%
7	Proton Pump Inhibitors	**OMEPRAZOLE**	5,703	$67,062.33	$11.76	1.71%
8	Antidepressants	TRAZODONE	5,660	$66,978.26	$11.83	1.70%
9	ADHD & Narcolepsy Medications	AMPHETAMINE/DEXTROAM	5,245	$157,452.86	$30.02	1.57%
10	Thyroid Hormones	LEVOTHYROXINE	5,015	$56,562.33	$11.28	1.50%
11	Antidepressants	ESCITALOPRAM OXALATE	4,988	$63,181.17	$12.67	1.50%
12	Antidepressants	**BUPROPION**	4,941	$75,605.91	$15.30	1.48%
13	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,555	$452,503.40	$99.34	1.37%
14	Antihistamines	**CETIRIZINE**	4,403	$44,642.98	$10.14	1.32%
15	Statins & Combos	ATORVASTATIN	4,113	$48,412.51	$11.77	1.23%
16	Antiadrenergic Antihypertensives	**CLONIDINE**	3,939	$60,070.71	$15.25	1.18%
17	Biguanides & Combos	**METFORMIN**	3,938	$48,397.55	$12.29	1.18%
18	ACE Inhibitors & Combos	LISINOPRIL	3,684	$37,696.84	$10.23	1.10%
19	Antiemetics	ONDANSETRON ODT	3,506	$48,336.54	$13.79	1.05%
20	Antianxiety Agents	**HYDROXYZINE**	3,465	$45,329.79	$13.08	1.04%
21	Antidepressants	DULOXETINE	3,447	$52,548.77	$15.24	1.03%
22	ADHD & Narcolepsy Medications	GUANFACINE	3,284	$53,231.72	$16.21	0.98%
23	Antianxiety Agents	**BUSPIRONE**	3,168	$42,315.67	$13.36	0.95%
24	Opioid Agonists & Combos	HYDROCODONE/AC	3,035	$50,880.54	$16.76	0.91%
25	Angiotensin II Receptor Antagonists & Combo	LOSARTAN POTASSIUM	2,944	$33,109.18	$11.25	0.88%
26	Leukotriene Modulators	MONTELUKAST SODIUM	2,868	$35,998.78	$12.55	0.86%
27	Penicillins	AMOXICILLIN/CLAVULANAT	2,800	$49,515.83	$17.68	0.84%
28	Glucocorticosteroids	PREDNISONE	2,780	$27,590.73	$9.92	0.83%
29	Calcium Channel Blockers	AMLODIPINE BESYLATE	2,678	$28,195.87	$10.53	0.80%
30↑	Influenza Agents	OSELTAMIVIR PHOSPHATE	2,666	$59,979.25	$22.50	0.80%
31	Atypical Antipsychotics	ARIPIPRAZOLE	2,608	$36,458.19	$13.98	0.78%
32	Muscle Relaxants & Combos	CYCLOBENZAPRINE	2,604	$27,098.30	$10.41	0.78%
33	Anticonvulsants - 2nd Generation	LAMOTRIGINE	2,542	$34,033.94	$13.39	0.76%
34	Statins & Combos	ROSUVASTATIN	2,509	$29,178.97	$11.63	0.75%
35	Proton Pump Inhibitors	PANTOPRAZOLE	2,454	$29,552.66	$12.04	0.74%
36↓	Macrolides	AZITHROMYCIN	2,450	$34,742.42	$14.18	0.73%
37	GLP-1 Receptor Agonists	MOUNJARO	2,422	$2,581,446.38	$1,065.83	0.73%
38	Atypical Antipsychotics	QUETIAPINE	2,354	$31,827.78	$13.52	0.71%
39	Beta Blockers & Combos	METOPROLOL ER	2,310	$28,917.25	$12.52	0.69%
40	Anticonvulsants - 2nd Generation	TOPIRAMATE	2,118	$29,394.46	$13.88	0.64%
41	Anticonvulsants - 2nd Generation	CLONAZEPAM	2,049	$23,323.03	$11.38	0.61%
42	Opioid Agonists & Combos	**OXYCODONE**	2,047	$30,273.00	$14.79	0.61%
43	Nonsteroidal Anti-Inflammatory Agents	MELOXICAM	2,007	$20,821.35	$10.37	0.60%
44	Inhaled Bronchodilator	ALBUTEROL ORAL	1,991	$40,967.72	$20.58	0.60%
45	Antidepressants	MIRTAZAPINE	1,991	$27,235.05	$13.68	0.60%
46	Nasal Steroids	FLUTICASONE	1,964	$33,987.99	$17.31	0.59%
47	Antidepressants	**VENLAFAXINE**	1,961	$29,480.19	$15.03	0.59%
48	Cephalosporins	CEPHALEXIN	1,954	$28,986.56	$14.83	0.59%
49	Atypical Antipsychotics	RISPERIDONE	1,855	$25,039.20	$13.50	0.56%
50	Diuretics & Combos	SPIRONOLACTONE	1,832	$26,514.91	$14.47	0.55%
	Total Top 50 Drugs		**166,178**	**$5,107,666.09**	**$30.74**	**51.73%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2026 – 3/31/2026						
	Therapeutic Class Name	Drug Label Name	Total Rxs	Plan Paid Amount	Paid/Rx	% Total Claims
1	Chronic Inflammatory Disease	DUPIXENT	752	$3,202,403.62	$4,258.52	0.23%
2	GLP-1 Receptor Agonists	MOUNJARO	2,422	$2,581,446.38	$1,065.83	0.73%
3	Chronic Inflammatory Disease	**HUMIRA/PEN**	227	$2,042,211.84	$8,996.53	0.07%
4	Chronic Inflammatory Disease	**SKYRIZI/PEN**	80	$1,796,741.69	$22,459.27	0.02%
5	GLP-1 Receptor Agonists	OZEMPIC	1,454	$1,452,592.53	$999.03	0.44%
6	Cystic Fibrosis	TRIKAFTA	61	$1,436,192.21	$23,544.13	0.02%
7	Atypical Antipsychotics	**INVEGA/HAFYERA/SUSTENNA**	426	$1,417,496.42	$3,327.46	0.13%
8	Atypical Antipsychotics	VRAYLAR	901	$1,270,522.90	$1,410.13	0.27%
9	HIV-Multiclass Combo	BIKTARVY	242	$991,821.34	$4,098.44	0.07%
10	Chronic Inflammatory Disease	STELARA	34	$959,587.86	$28,223.17	0.01%
11	Chronic Inflammatory Disease	**COSENTYX/SENSOREADY/UNOREADY**	74	$946,214.98	$12,786.69	0.02%
12	Chronic Inflammatory Disease	**ENBREL/MINI/SURECLICK**	98	$813,037.28	$8,296.30	0.03%
13	Diabetes Monitoring and Testing	**DEXCOM**	1,776	$649,084.75	$365.48	0.53%
14↑	Chronic Inflammatory Disease	TALTZ	63	$624,926.66	$9,919.47	0.02%
15	Anticonvulsants - 2nd Generation	EPIDIOLEX	183	$571,413.56	$3,122.48	0.05%
16↑	Movement Disorder Drug Therapy	INGREZZA	70	$559,422.87	$7,991.76	0.02%
17	Metabolic Modifiers	VYKAT XR	18	$548,973.90	$30,498.55	0.01%
18	Atypical Antipsychotics	**ARISTADA/INITIO**	186	$546,495.85	$2,938.15	0.06%
19	Atypical Antipsychotics	**ABILIFY MAINTENA/ ASIMTUFII**	161	$535,070.94	$3,323.42	0.05%
20	SGLT-2 Inhibitors & Combos	JARDIANCE	1,483	$518,861.59	$349.87	0.44%
21	Oncology	KISQALI	33	$462,421.57	$14,012.77	0.01%
22	ADHD & Narcolepsy Medications	LISDEXAMFETAMINE	4,555	$452,503.40	$99.34	1.37%
23	Atypical Antipsychotics	CAPLYTA	282	$451,659.86	$1,601.63	0.08%
24	Atypical Antipsychotics	REXULTI	297	$422,671.02	$1,423.13	0.09%
25	Inhaled Asthma/COPD Combo	TRELEGY ELLIPTA	615	$414,407.70	$673.83	0.18%
26	Chronic Inflammatory Disease	RINVOQ	60	$409,237.85	$6,820.63	0.02%
27↑	Antihemophilic Products	HEMLIBRA	7	$394,270.49	$56,324.36	0.00%
28	Chronic Inflammatory Disease	BIMZELX	25	$385,866.69	$15,434.67	0.01%
29↑	Metabolic Modifiers	SEPHIENCE	6	$360,063.30	$60,010.55	0.00%
30↓	Oral Anticoagulants	**ELIQUIS/STARTER PACK**	1,016	$357,969.31	$352.33	0.30%
31	Growth Hormones	NORDITROPIN FLEXPRO	81	$346,470.72	$4,277.42	0.02%
32	Migraine Products	NURTEC	246	$295,192.28	$1,199.97	0.07%
33	Chronic Inflammatory Disease	TREMFYA	20	$288,244.42	$14,412.22	0.01%
34	ADHD & Narcolepsy Medications	**METHYLPHENIDATE**	5,981	$282,878.08	$47.30	1.79%
35	Cystic Fibrosis	PULMOZYME	58	$276,880.61	$4,773.80	0.02%
36	Psychotherapeutic-Neurological	LYBALVI	168	$270,917.65	$1,612.61	0.05%
37	Antihemophilic Products	NOVOSEVEN RT	3	$265,531.65	$88,510.55	0.00%
38	ADHD & Narcolepsy Medications	JORNAY PM	584	$261,365.70	$447.54	0.18%
39↑	Asthma	TEZSPIRE	53	$259,329.88	$4,893.02	0.02%
40↓	Hepatitis C	MAVYRET	19	$244,348.40	$12,860.44	0.01%
41↑	Oncology	JAKAFI	10	$243,851.51	$24,385.15	0.00%
42	Migraine Products	UBRELVY	227	$242,163.55	$1,066.80	0.07%
43↓	Antihemophilic Products	NUWIQ	3	$238,641.45	$79,547.15	0.00%
44↑	Asthma	XOLAIR	80	$235,972.86	$2,949.66	0.02%
45↑	Cystic Fibrosis	ALYFTREK	8	$227,318.16	$28,414.77	0.00%
46	ADHD & Narcolepsy Medications	AZSTARYS	529	$226,587.89	$428.33	0.16%
47↑	Movement Disorder Drug Therapy	**AUSTEDO/XR**	31	$225,700.01	$7,280.65	0.01%
48↑	Multiple Sclerosis	KESIMPTA	22	$224,616.99	$10,209.86	0.01%
49	Atypical Antipsychotics	UZEDY	75	$221,210.25	$2,949.47	0.02%
50↓	Irritable Bowel Syndrome (IBS) Agt	LINZESS	726	$215,862.89	$297.33	0.22%
	Total Top 50 Drugs		**26,531**	**$32,668,675.31**	**$1,231.34**	**7.95%**

Opioid Summary



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



Opioid Initiatives:

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

Other Initiatives:

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

Total Eligibles and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,090	21.9%
2Q2020	126,777	20,746	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,489	17.2%
1Q2021	139,748	24,407	17.5%
2Q2021	142,872	26,206	18.3%
3Q2021	146,023	27,933	19.1%
4Q2021	149,034	29,317	19.7%
1Q2022	151,735	29,092	19.2%
2Q2022	154,608	28,370	18.3%
3Q2022	157,627	29,167	18.5%
4Q2022	160,060	32,124	20.1%
1Q2023	162,684	31,612	19.4%
2Q2023	142,001	27,296	19.2%
3Q2023	131,292	26,218	19.9%
4Q2023	134,270	29,320	21.8%
1Q2024	141,162	32,891	23.3%
2Q2024	149,613	32,686	21.8%
3Q2024	159,160	35,263	22.2%
4Q2024	162,163	36,468	22.5%
1Q2025	164,446	38,367	23.3%
2Q2025	161,372	34,446	21.3%
3Q2025	158,250	34,997	22.1%
4Q2025	157,279	37,099	23.6%
1Q2026	157,180	37,968	24.2%

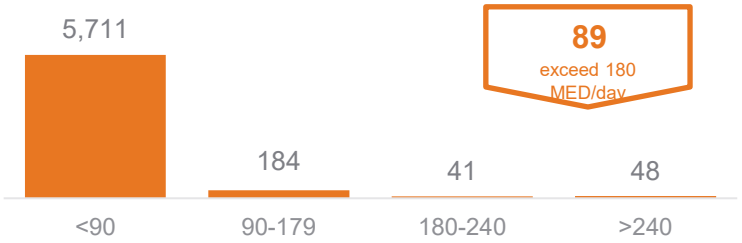
Opioid Utilization Snapshot

SDM 4Q2025
Sep 25 to Dec 25

Opioid Claims **16,058**
3.1% prescription claims filled for an opioid
1.4% higher than Medicaid FFS benchmark

Utilizers **5,984**
33.3% are high utilizers [1]
7.8% higher than high utilizers Medicaid FFS

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



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

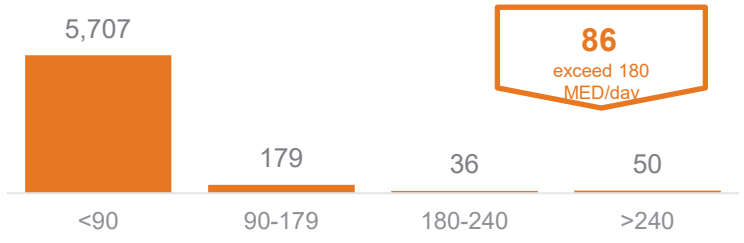
608 Shoppers: Poly Prescriber
opioid utilizing members with 3+ prescribers

1Q2026
Dec 26 to Mar 26

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

Utilizers **6,024**
34.6% are high utilizers [1]
8.2% higher than high utilizers Medicaid FFS

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



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

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

OPTUMRx®

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

Opioid Utilization

SDM
Opportunities date range: Dec 2025 - Mar 2026
Benchmark: MEDICAID FEE FOR SERVICE

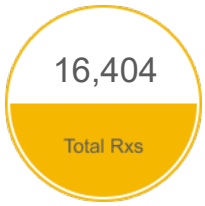
Utilizers: 6,024

3.1% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.1% of all prescriptions this period, which is 1.5% higher than the benchmark
- 2,084 high opioid utilizers were identified this period, which is 8.2% higher than the benchmark

Opioid claims



PERCENT NON-COMPLIANT
11.6%

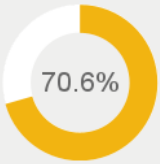
Opioid utilizers

HIGH UTILIZERS
34.6%
2,084 high utilizers

8.2% over benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

70.6% of all opioid Rxs were filled for short acting opioids. **3,808** Rxs were for medication assisted therapy (MAT) and **154** 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

86 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	5,707	179	36	50

MED – view definition

Opioid Opportunity Assessment

SDM

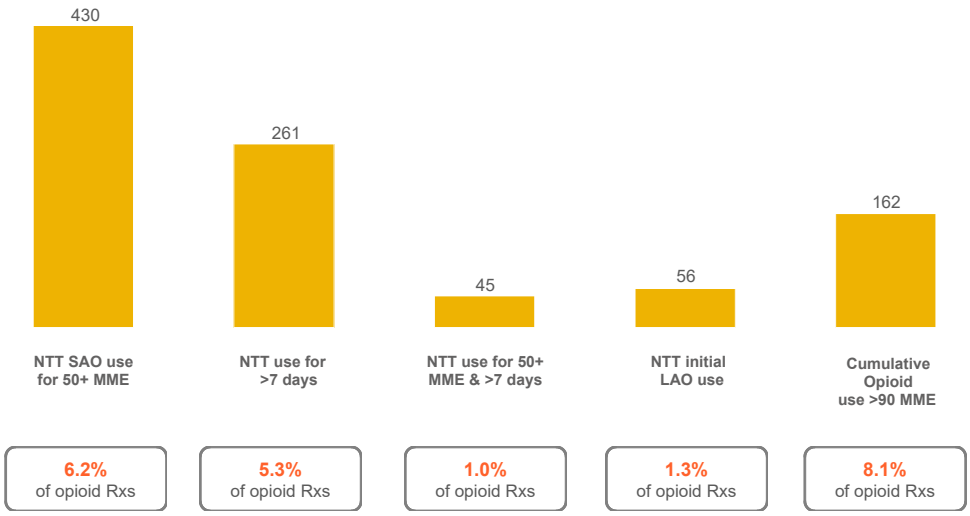
Opportunities date range: Dec 2025 - Mar 2026

Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 11.6%

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?

74 opioid utilizing members use 3 or more pharmacies and 631 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
1,366	853	1,199	768	168

Anticonvulsants –view definition

Old Business

H. Pylori Review

Regimen	Drugs (doses)	Dosing frequency	Duration (days)
Optimized bismuth quadruple (component therapy)	PPI standard dose	Twice daily	14
	bismuth subsalicylate 300 or 525mg	4 times daily	
	tetracycline 500mg		
	metronidazole 500mg	3 or 4 (preferred) daily	
Bismuth quadruple (as Pylera combination capsules plus PPI)	PPI standard dose	Twice daily	10 to 14 days
	bismuth subcitrate 420mg	4 times daily	
	metronidazole 375mg		
	tetracycline 375mg		
Rifabutin-amoxicillin-PPI triple (Talicia)	omeprazole 40mg,	3 times daily	14
	rifabutin 50mg		
	amoxicillin 1g		
Lansoprazole-amoxicillin-clarithromycin (Prevpac)	lansoprazole 30mg	Twice daily	10
	amoxicillin 1g		
	clarithromycin 500mg		
Vonoprazan-amoxicillin dual (Voquezna Dual Pak)	Vonoprazan 20mg	Twice daily	14
	amoxicillin 1g	3 times daily	
Vonoprazan-amoxicillin-clarithromycin triple (Voquezna Triple Pak)	Vonoprazan 20mg	Twice daily	14
	amoxicillin 1g		
	clarithromycin 500mg		

Time frame: 2025 to 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizer	Age Range
metronidazole/tetracycline/bismuth subsalicylate (Helidac)						
lansoprazole/amoxicillin/ clarithromycin (Prevpac)	3	$,2694.12	$898.04	112/19 days	3	43 – 48
bismuth subsalicylate/metronidazole/ tetracycline (Pylera)	27	$11,952.92	$442.70	123/14 days	25	17 – 63
Pylera (bismuth subsalicylate/ metronidazole/ tetracycline	1	$372.42	$372.42	120/10 days	1	61
Talicia (amoxicillin/rifabutin/omeprazole)	3	$2,430.76	$810.25	168/14 days	3	22 – 44
Voquezna Triple Pak (amoxicillin/ clarithromycin/vonoprazan)	7	$5,825.81	$832.81	112/18 days	2	14 – 45
Voquezna Dual Pak (amoxicillin/vonoprazan)	6	$4,993.86	$832.31	112/14 days	7	30 – 53
amoxicillin cap 500mg			*$16*	56		
clarithromycin tab 500mg			*$25 – $50*	28-56		
metronidazole tab 250mg			*$14*	56		
rifabutin tab 150mg			*$270*	28		
tetracycline 500mg			*$40*	56		
omeprazole 40mg			*$13*	42		
lansoprazole cap 30mg			*$14*	28		
Voquezna 40mg/day			*$638*	28		
bismuth subsalicylate (OTC only)						

*Red font denotes drug on PA/ST

Potential PA Criteria

State A

Approval Criteria – Brand Pylera and Brand Talicia
1. Documentation of recent positive H. Pylori test**

Approval Criteria – generic bismuth subcitrate/metronidazole/tetracycline, generic lansoprazole/amoxicillin/ clarithromycin, Voquezna Dual Pak, and Voquenza Triple Pak
1. Documentation of recent positive H. Pylori test*
2. Trial and failure, contraindication, or intolerance to one preferred combination agent

Commercial

Approval Criteria – Voquezna 20mg
1. Diagnosis of Helicobacter pylori infection
2. Provider attests to both of the following:
   - Patient is experiencing a new occurrence of Helicobacter pylori (H. pylori) infection
   - Medication will not be used for longer than 14 days for any one occurrence for the treatment of Helicobacter pylori (H. pylori) infection
3. One of the following:
   - Used in combination with amoxicillin and clarithromycin for the treatment of H. pylori infection
   - Used in combination with amoxicillin for the treatment of H. pylori infection
4. Trial and failure, contraindication, or intolerance to bismuth quadruple therapy (e.g., bismuth and metronidazole and tetracycline and proton pump inhibitor [PPI])

New Business

PA Reviews

Rosacea and Acne PA Review

Time Frame: 1Q2026

Indication	Drug Name	Approvals	Denials	Total	Utilizer
Rosacea	azelaic acid gel 15%	0	1	1	1
	azelaic acid cream 20%	2	0	2	2
	ivermectin cream 1%	2	3	5	5
	ivermectin lotion 0.5%	1	0	1	1
	NORITAKE (metronidazole cream 1%)	0	1	1	1
Topical Acne	benzoyl peroxide 7% wash (Brand)	0	1	1	1
	clindamycin-tretinoin gel 1.2-0.025%	0	1	1	1
	dapsone gel	3	1	4	4
	erythromycin gel 2%	2	4	6	4
	sulfacetamide sulfur cleanser	2	3	5	5
	TWYNEO (tretinoin/benzoyl peroxide cream)	0	2	2	2
	WINLEVI (clascoterone cream 1%)	1	2	3	3

Appeals

Indication	Drug Name	Approvals	Denials	Total
Topical Acne	WINLEVI (clascoterone) cream 1%	1	0	1

Rosacea Utilization

Time Frame: 1Q2026

PA	Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range
Rosacea	azelaic gel 15%	14	$574.25	$41.02	12	50	14 – 49
	FINACEA AER 15% (azelaic)	1	$426.67	$426.67	1	50	58
	ivermectin cream 1%	7	$1,010.59	$144.37	6	45	20 – 63
	metronidazole cream 0.75%	57	$1,356.87	$23.80	48	45	0 – 64
	metronidazole gel 0.75%	29	$729.16	$25.14	23	45	2 – 63
	metronidazole gel 1%	20	$1,244.03	$62.20	19	60	2 – 63
	metronidazole lotion 0.75%	1	$127.82	$127.82	1	59	47
	WINLEVI 1% cream	12	$7,273.60	$606.13	11	60	13 – 48

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

Rosacea ST Criteria

Trial of a generic topical acne agent (benzoyl peroxide, tretinoin, clindamycin phosphate, erythromycin, sulfacetamide sodium/sulfur, sulfacetamide sodium, metronidazole cream/gel/lotion, adapalene cream, adapalene gel, adapalene/benzoyl peroxide 0.1-2.5%, or clindamycin/benzoyl peroxide) in the last 120 days.

Topical Acne Utilization

Time Frame: 1Q2026

PA	Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizer	Avg Qty	Age Range
Topical Acne	adapalene gel 0.1%	18	$2,209.84	**$122.77**	16	45	10 – 44
	adapalene gel 0.3%	21	$823.83	$39.23	18	45	0 – 54
	adapalene gel 0.3% PMP	1	$53.56	$53.56	1	45	18
	adapalene-benzoyl gel 0.1-2.5%	25	$623.36	$24.93	17	45	10 – 64
	adapalene-benzoyl gel 0.3-2.5%	4	$152.33	$38.08	3	45	13 – 30
	clindamycin-benzoyl gel 1.2-2.5%	8	$403.17	$50.40	4	50	11 – 31
	clindamycin-benzoyl gel 1.2-3.75%	4	$845.30	**$211.33**	2	50	12, 20
	clindamycin-benzoyl gel 1.2-5%	29	$902.66	$31.13	21	45	12 – 42
	clindamycin-benzoyl gel 1-5%	93	$3,842.69	$41.32	72	46.7	10 – 42
	clindamycin AER 1%	2	$272.70	**$136.35**	1	50	11
	clindamycin gel 1%	189	$7,274.35	$38.49	162	53.3	10 – 63
	clindamycin gel 1% 1XDLY	3	$982.71	**$327.57**	3	75	11 – 16
	clindamycin gel 1% 2XDLY	104	$1,753.06	$16.86	95	51.6	11 – 60
	clindamycin lotion 1%	332	$9,428.61	$28.40	248	61.8	0 – 64
	clindamycin MIS 1%	59	$1,600.43	$27.13	34	62	13 – 49
	clindamycin solution 1%	76	$1,427.80	$18.79	63	57.2	2 – 64
	clindamycin-tretinoin gel	2	$291.69	$145.85	1	30	23
	dapsone gel 5%	18	$1,154.65	$64.15	12	63.3	14 – 32
	dapsone gel 7.5%	8	$485.58	$60.70	7	67.5	17 – 31
	erythromycin/benzoyl gel 3-5%	9	$460.17	$51.13	8	31	11 – 54
	erythromycin gel 2%	3	$202.04	$67.35	3	30	1 – 55
	erythromycin solution 2%	6	$196.79	$32.80	5	60	15 – 63
	sulfacetamide lotion 10%	1	$93.25	$93.25	1	118	18
	sulfacetamide w/ sulfur liquid 10-5%	11	$810.66	$73.70	10	180.5	11 – 42
	tretinoin cream 0.025%	248	$10,752.00	$43.35	207	37.5	7 – 64
	tretinoin cream 0.05%	163	$8,321.24	$51.05	135	39.5	10 – 64
	tretinoin cream 0.1%	89	$4,028.31	$45.26	64	42.1	3 – 64
	tretinoin gel 0.025%	30	$2,869.31	$95.64	21	31.5	11 – 61
	tretinoin gel 0.01%	16	$1,669.81	**$104.36**	13	21	4 – 41
	tretinoin gel 0.05%	6	$1,033.30	**$172.22**	6	45	14 – 38
	WINLEVI cream 1% (clascoterone)	12	$7,273.60	**$606.13**	11	60	17 – 48
	tazarotene gel 0.05%	2	$465.95	**$232.98**	1	30	37
	tazarotene cream 0.1%	6	$667.01	**$111.17**	4	50	14 – 39

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

Topical Acne ST Criteria

Trial of a generic topical acne agent (benzoyl peroxide, tretinoin, clindamycin phosphate, erythromycin, sulfacetamide sodium/sulfur, sulfacetamide sodium, adapalene cream, adapalene gel, adapalene/benzoyl peroxide 0.1-2.5%, clindamycin-benzoyl peroxide) in the past 120 days

Tazorac (tazarotene) Criteria

1. Diagnosis of acne vulgaris – Topical Acne Criteria
2. Diagnosis of plaque psoriasis

Oral Allergen Extracts PA Review

Time Frame: 2025 – 5/31/2026

Drug Name	Allergen	Approvals	Denials	Total	Utilizers
Odactra	Dust mite mixed allergen extract	1	1	2	2
Oralair	Grass mixed pollens allergen extract				
Ragwitek	Short ragweed pollen allergen extract	1	1	2	1
Grastek	Timothy grass pollen allergen extract				
Palforzia	Peanut (Arachis hypogaea) allergen powder-dnfp				

Oral Allergen Extract Utilization

Time Frame: 2019 to 5/2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range	Year
Odactra SL tab	8	$1,484.30	$184.54	1	30/30 days	22 M	11/25-current
Oralair SL tab	15	$6,722.10	$448.14	1	30/30 days	15 F	5/19-8/21
Ragwitek SL tab	2	$373.20	$373.20	1	30/30 days	22 M	4/26-current
Grastek SL tab	0						
Palforzia cap	17	$10,758.67	$632.86	1	depends on level	15 F	7/22-4/23

*Red font denotes drug is on PA; Excludes IHS

PA Criteria

1. Patient must have a U.S. Food and Drug Administration (FDA)-approved indication for the drug requested:
   - For Grastek: Allergic rhinitis (with or without allergic conjunctivitis) induced by Timothy grass or cross-reactive grass pollens
   - For Oralair: Allergic rhinitis (with or without allergic conjunctivitis) induced by grass pollen, specifically sweet vernal, orchard, perennial rye, timothy, or Kentucky bluegrass
   - For Ragwitek: Allergic rhinitis (with or without allergic conjunctivitis) induced by short ragweed pollen
   - For Odactra: Allergic rhinitis (with or without allergic conjunctivitis) induced by house mites (HDM) allergen
2. Diagnosis must be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies
3. History of failure or intolerance to subcutaneous allergen immunotherapy (allergy shots)
4. Does not have severe, unstable or uncontrolled asthma
5. Has tried and failed two of the following (each from different categories):
   - Oral antihistamines (cetirizine, desloratadine, fexofenadine, levocetirizine, or loratadine)
   - Intranasal antihistamines (azelastine, olopatadine, azelastine/fluticasone)
   - Intranasal corticosteroids (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone)
   - Leukotriene inhibitors (e.g., montelukast, zafirlukast, zileuton)

PA Criteria Consideration for Palforzia

State A

Initial Authorization – 6 months

1. Diagnosis of peanut allergy confirmed by one of the following:
   1.1. Serum peanut-specific immunoglobulin E (IgE) of greater than or equal to 0.35 kUA/L **OR**
   1.2. Mean wheal diameter greater than or equal to 3 mm compared to control on skin prick testing for peanut
2. Prescriber attests initial doses for each up-dose will be administered at the prescriber's office and distributed by a specialty pharmacy
3. Prescribed by or in consultation with an allergist or immunologist
4. Prescriber is certified/enrolled in the Palforzia REMS (Risk Evaluation and Mitigation Strategy) Program
5. Must be used in conjunction with a peanut-avoidant diet
6. Patient must not have ANY of the following:
   - Uncontrolled Asthma
   - History of eosinophilic esophagitis or other eosinophilic gastrointestinal disease
   - History of severe or life-threatening episode(s) of anaphylaxis or anaphylactic shock within the past 2 months

Reauthorization – 12 months

1. Documentation (medical records, chart notes, etc..) of tolerance to therapy during the initial dose escalation and up-dosing phases
2. Prescribed by or in consultation with an allergist or immunologist
3. Must be used in conjunction with a peanut-avoidant diet
4. Prescriber is certified/enrolled in the Palforzia REMS (Risk Evaluation and Mitigation Strategy) Program
5. Documentation of positive clinical response to Palforzia therapy

State B

Initial Authorization – 12 months

1. Diagnosis of peanut allergy
2. Member is between 1 and 17 years of age*
3. Prescribed by, or in consultation with, one of the following:
   - Allergist
   - Immunologist
4. Member does not have any of the following contraindications:
   - Severe, unstable or uncontrolled asthma
   - Severe or life-threatening anaphylaxis reaction in the past 60 days
   - History of eosinophilic esophagitis or other eosinophilic GI disease

Reauthorization – 12 months

1. Must meet both of the following:
   1.1. History of the requested agent within the past 90 days, as confirmed by claims history, chart documentation, or provider attestation including dates of use (excluding claims with emergency supply indicator)*
   1.2. Requested maintenance dose does not exceed 300mg daily**

Commercial

Initial Authorization – 12 months

1. Diagnosis of peanut allergy, as confirmed by both of the following:
   1.1. Positive clinical history of peanut allergy (e.g., immediate reaction of typical systemic allergy symptoms such as hives, swelling, or wheezing, following isolated ingestion of peanut) [A, 4]
   1.2. One of the following: [A-C, 3]
      - A serum peanut-specific IgE level of greater than or equal to 0.35 kUA/L
      - A mean wheal diameter that is at least 3mm larger than the negative control on skin-prick testing for peanut
      - An Ara h 2 sIgE level greater than or equal to 0.35 kUA/L
2. One of the following:
   2.1. Both of the following:
      - Patient is 1 to 17 years of age
      - Patient is in the initial dose escalation phase of therapy
   2.2. Both of the following:
      - Patient is 1 year of age and older
      - Patient is in the up-dosing or maintenance phase of therapy
3. Patient does not have any of the following:
      - History of eosinophilic esophagitis (EoE) or eosinophilic gastrointestinal disease
      - History of severe or life-threatening episode(s) of anaphylaxis or anaphylactic shock within the past 2 months
      - Severe or poorly controlled asthma
4. Prescribed by or in consultation with one of the following:
      - Allergist
      - Immunologist

Reauthorization – 12 months

1. Prescribed by or in consultation with one of the following:
      - Allergist
      - Immunologist

Altabax and Xepi PA Review

- for treatment of impetigo

Time Frame: 4Q2020

Drug Name	Approvals	Denials	Total	Utilizers
Altabax (retapamulin) 1% topical ointment	1	0	1	1

Altabax Utilization

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range	Year
Altabax oint 1%	6	$1,830.39	$305.07	6	17.5/18 days	1 – 52	2017-2019
mupirocin cream 2%	22	$822.66	$37.39	18	30/17 days	0 – 61	1Q2026
mupirocin oint 2%	1,133	$15,566.08	$15.74	1,036	23/12 days	0 – 64	1Q2026
Xepi (ozenoxacin) cream	*0*		*$375*		*30 gm*		

*Red font denotes drug is on PA; Excludes IHS

PA Criteria – Altabax and Xepi (effective 4/1/2022)

1. Patient must have a tried and failed generic mupirocin ointment or cream for a minimum of 5 days within the last 90 days OR
2. Patient must be diagnosed with methicillin resistant Staphylococcus aureus (MRSA)

Angiotensin Receptor Blocker (ARB) PA Review

Edarbi and Edarbyclor PA Review

Time Frame: June 2025

Drug Name	Approvals	Denials	Total	Utilizers	Limits
Edarbyclor	1	0	1 (PA)	1	

Frame: 1Q2026

Drug Name	Approvals	Denials	Total	Utilizers	Limits
irbesartan 150mg	1	1	2 (QL)	2	1/day
losartan 25mg	1	1	2 (QL)	2	1.5/day
losartan 50mg	1	0	1 (QL)	1	1.5/day
Entresto (sacubitril-valsartan)	0	1	1 (DAW)	1	

Edarbi and Edarbyclor Utilization

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Edarbyclor (azilsartan-chlorthalidone)	2	$531.38	$265.69	1	64
Edarbi (azilsartan)	0				
amlodipine-olmesartan	10	$187.86	$18.79	6	18 – 66
amlodipine-valsartan	13	$452.58	$34.81	7	26 – 55
amlodipine-valsartan-HCTZ	3	$1,012.15	$337.38	2	29, 62
candesartan	32	$845.30	$26.42	15	20 – 64
candesartan- HCTZ	3	$132.96	$44.32	1	54
irbesartan	36	$481.09	$13.36	17	41 – 64
irbesartan- HCTZ	5	$82.96	$16.59	3	34 – 61
losartan	2,942	$34,869.70	$11.85	1,397	5 – 81
losartan-HCTZ	355	$4,624.80	$13.03	180	17 – 85
olmesartan	199	$2,688.02	$13.51	92	21 – 64
olmesartan-HCTZ	43	$713.42	$16.59	18	33 – 63
olmesartan-amlodipine-HCTZ	6	$264.08	$44.01	2	47, 56
sacubitril-valsartan	379	$20,251.84	$53.43	165	4 – 78
telmisartan	45	$626.51	$13.92	21	30 – 61
telmisartan-amlodipine	6	$1,121.68	$186.95	2	42, 63
telmisartan-HCTZ	2	$42.49	$21.25	2	60, 61
valsartan	149	$2,284.36	$15.33	68	23 – 64
valsartan-HCTZ	28	$495.75	$17.71	13	36 – 64

*Red font denotes drug is on PA; Excludes IHS

Angiotensin Receptor Blocker PA Criteria

1. Patient has been stable on the requested ARB for more than 60 days OR
2. Patient has tried an angiotensin-converting enzyme (ACE) inhibitor or a generic ARB within the last 120 days OR
3. Patient has an additional diagnosis of chronic obstructive pulmonary disease (COPD) or acute/chronic renal failure

Antidepressants PA Review

Time Frame: 1Q2026

	Drug Name	Approvals	Denials	Total	Utilizers
SSRI	citalopram 10mg	1	0	1 (QL)	1
	escitalopram tab	5	3	8 (QL)	8
	escitalopram solution	10	0	10 (PA)	8
	LEXAPRO	1	0	1 (PA)	1
	fluoxetine solution	55	0	55 (QL)	52
	fluoxetine DR 90mg	0	1	1 (QL)	1
	paroxetine 30mg tab	2	2	5 (QL)	4
	paroxetine ER	2	0	2 (PA)	2
	paroxetine suspension	1	0	1 (PA)	1
	sertraline solution	11	0	11 (QL)	11
	ZOLOFT	1	0	1 (DAW)	1
SNRI	desvenlafaxine ER (Khedezla/Desvenlafax)	9	0	9 (PA)	9
	duloxetine	0	2	2 (QL)	2
	DRIZALMA sprinkle (duloxetine)	3	0	3 (PA)	3
	venlafaxine	1	3	4 (QL)	4
	venlafaxine ER	5	4	9 (QL)	9
Misc	bupropion ER/XL	3	7	10 (QL)	10
	mirtazapine	5	4	9 (QL)	8
	mirtazapine ODT	13	0	13 (PA)	13
	vilazodone	16	1	17 (PA)	15
	AUVELITY (dextromethorphan-bupropion)	17	0	17 (PA)	17
	TRINTELLIX (vortioxetine)	13	0	13 (PA)	13
	ZURZUVAE (zuranolone)	8	4	12 (PA)	10

Antidepressant Utilization

Time Frame: 1Q2026

	Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizer	Age Range
SSRI	citalopram tab	996	$10,883.08	$10.93	452	7-70
	citalopram cap 30mg	3	$517.86	$172.62	1	36
	citalopram solution	20	$649.02	$32.45	9	4-26
	escitalopram tab	4,939	$59,452.10	$12.04	2,250	6-73
	escitalopram cap 15mg	8	$1,416.96	$177.12	4	13-55
	escitalopram solution	36	$2,248.86	$62.47	17	7-61
	LEXAPRO (escitalopram)	5	$2,385.55	$477.11	2	55, 64
	fluoxetine tab	674	$9,885.42	$14.67	337	4-64
	fluoxetine cap	5,748	$66,399.93	$11.55	2,397	4-65
	fluoxetine DR 90mg	16	$2,234.13	$139.63	8	13-45
	fluoxetine solution	230	$7,735.03	$33.63	106	4-64
	fluvoxamine	81	$1,625.20	$20.06	32	11-61
	fluvoxamine ER	19	$3,847.15	$202.48	7	21-53
	paroxetine tab	537	$6,210.86	$11.57	208	11-77
	paroxetine tab ER	23	$642.86	$27.95	9	22-59
	paroxetine suspension	4	$1,976.92	$494.23	2	36, 54
	sertraline tab	5,938	$69,490.17	$11.70	2,730	5-95
	sertraline cap	45	$6,715.46	$149.23	23	16-50
	sertraline solution	60	$2,480.53	$41.34	24	6-48
	ZOLOFT tab 50mg (sertraline)	1	$458.32	$458.32	1	56
SNRI	Desvenlafax ER	14	$2,076.17	$148.29	9	20-60
	desvenlafaxine ER (Pristiq)	1,022	$24,050.32	$23.53	385	9-64
	duloxetine cap DR	3,447	$52,548.77	$15.24	1,381	8-83
	DRIZALMA sprinkle (duloxetine)	9	$1,997.91	$221.99	4	12-64
	FETZIMA cap (levomilnacipram)	15	$8,951.59	$596.77	4	42-64
	venlafaxine tab	115	$1,752.83	$15.24	52	7-64
	venlafaxine tab ER	121	$3,208.26	$26.51	62	15-64
	venlafaxine cap ER	1,725	$24,519.10	$14.21	629	7-65
	EFFEXOR XR cap 75mg (venlafaxine)	3	$5,305.58	$1,768.53	1	56
Misc	bupropion	126	$2,140.42	$16.99	63	11-64
	bupropion ER/XL	4,897	$74,683.12	$15.25	2,091	9-69
	mirtazapine tab	1,991	$27,388.73	$13.76	868	5-78
	mirtazapine ODT	24	$528.82	$22.03	14	8-60
	REMERON tab 15mg (mirtazapine)	3	$606.65	$202.22	1	61
	vilazodone tab	345	$14,570.14	$42.23	129	16-64
	VIIBRYD (vilazodone)	3	$1,130.49	$376.83	1	62
	TRINTELLIX (vortioxetine)	224	$116,816.58	$521.50	90	16-63

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

PA Criteria

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

Auvelity and Exxua PA Review

Time Frame: 1Q2026

Drug Name	Approvals	Denials	Total	Utilizers
AUVELITY (dextromethorphan-bupropion)	17	0	17 (PA)	17
EXXUA (gepirone)			0	

Auvelity and Exxua Utilization

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
AUVELITY	128	$130,000.75	$1,015.63	56	18-64
EXXUA	0				

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

PA Criteria

1. Diagnosis for treatment of major depressive disorder (MDD) in adults.
2. The patient is unresponsive to other treatment modalities, unless contraindicated (i.e. other medications or behavioral modification attempted)
3. The physician attests that the requested medication is medically necessary.
4. Patient has a history of failure, contraindication or intolerance to at least 3 preferred alternatives* in the last 3 years:
   - bupropion/SR/XL
   - citalopram
   - desvenlafaxine succinate extended-release (ER)
   - duloxetine
   - escitalopram
   - fluoxetine
   - fluvoxamine
   - mirtazapine
   - paroxetine
   - sertraline
   - trazodone
   - venlafaxine/ER
5. For continuation of prior therapy

Antiemetics PA Review

Time Frame: June 2025 – May 2026

Drug Name	Approvals	Denials	Total	Utilizers	Time Frame
Bonjesta 20-20mg	9	0	9	7	10/2025 – 5/2026
Diclegis 10-10mg	0	1	1	1	10/2025
doxylamine-pyridoxine tab 10-10mg	41	5	46	45	6/2025 – 5/2026
Sancuso patch	1	0	1	1	12/2025

Antiemetics Utilization

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range
Akynzeo (netupitant-palonosetron)	0					
Bonjesta tab 20-20mg (doxylamine-pyridoxine)	4	$2,710.23	$677.56	2	60/30 days	25, 33
Diclegis tab 10-10mg (doxylamine- pyridoxine)	0					
doxylamine-pyridoxine tab 10-10mg	7	$471.96	$67.42	7	47/18 days	16 – 37
dronabinol cap 2.5mg (Marinol)	13	$1,351.47	$103.96	6	51/51 days	38 – 59
dronabinol cap 5mg	3	$952.10	$317.37	2	89/25 days	19, 38
aprepitant cap (Emend)	49	$9,945.58	$202.97	9	4/5 days	5 – 48
Emend susp	1	$336.56	$336.56	1	1/3 days	3
granisetron tab (Sancuso)	9	$519.92	$57.77	4	41/27 days	5 – 42
Sancuso patch			*~$827.00*		*Qty 1*	
meclizine tab	172	$2,240.82	$13.03	113	42/14 days	11 – 69
ondansetron tab (Zofran)	944	$10,994.74	$11.65	756	23/8 days	1 – 74
ondansetron ODT	3,485	$48,089.12	$13.80	2,717	22/7 days	0 – 64
ondansetron solution	362	$7,747.13	$21.40	340	40/5 days	0 – 20
scopolamine DIS	126	$4,752.33	$37.72	66	5.6/17 days	1 – 99
NEREUS cap 85mg (tradipitant) ***-new*** *for prevention of motion sickness*	0		*~$300.00*		*Qty 1*	
VARUBI tab (rolapitant)	0		*~$390.00*		*Qty 1*	

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

PA Criteria

Akynzeo and Varubi

1. Diagnosis of chemotherapy-induced nausea/vomiting prophylaxis
2. Patient must be receiving highly emetogenic chemotherapy regimens or regimens including anthracyclines and cyclophosphamide in the past 90 days.

Bonjesta 20-20mg and Diclegis/doxylamine-pyridoxine 10-10mg

1. Diagnosis of hyperemesis gravidarum

Sancuso Tab and Patch

1. Trial of a generic 5-Hydroxytryptamine type 3 (5-HT3) receptor antagonist for 14 days in the past 90 days and Patient is receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days
2. Patient is unable to tolerate oral medications for chemotherapy-induced nausea and vomiting due to a diagnosis of difficulty swallowing

Non-Sedating Antihistamines (NSA)

Time Frame: 1Q2026

Drug Name	Approvals	Denials	Total	Utilizers
cetirizine tab and Zyrtec tab	4	3	7 (QL)	7
cetirizine CHEW	20	1	21 (PA)	21
desloratadine tab	2	0	2 (PA)	2
Fexofenadine 180mg tab	0	2	2 (QL)	2
levocetirizine solution	0	3	3 (QL)	3
loratadine CHEW	12	0	12 (PA)	12
Claritin CHEW	1	0	1 (PA)	1
loratadine tab	1	1	2 (QL)	2

NSA Utilization

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Allegra ODT	0				
Clarinex ODT	0				
desloratadine ODT	0				
Zyrtec ODT	0				
Clarinex Syrup	0				
Claritin Reditab / loratadine RDT	0				
cetirizine tab	4,306	$39,615.54	$9.20	1,906	2 – 104
cetirizine solution/syrup	1,210	$16,846.92	$13.92	734	0 – 59
cetirizine CHEW	7	$494.96	$70.71	5	3 – 57
Zyrtec CHEW	3	$95.43	$31.81	1	6
desloratadine tab	3	$56.63	$18.88	1	57
fexofenadine tab	475	$6,316.85	$13.30	193	9 – 95
fexofenadine solution	2	$38.61	$19.31	1	6
levocetirizine tab	221	$2,712.53	$12.27	108	5 – 64
levocetirizine solution	29	$861.50	$29.71	16	1 – 11
loratadine tab	1792	$18,177.27	$10.14	725	6 – 103
loratadine solution	145	$2,173.32	$14.99	75	0 – 75
loratadine CHEW	2	$51.41	$25.71	1	6

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

NSA PA Criteria – ODT, Chewable Formulations, Clarinex Syrup, Claritin RDT/loratadine RDT

1. Patient is younger than 13 years of age OR (electronic PA review)
2. Has documented difficulty in swallowing diagnosis (electronic PA review)

NSA PA Criteria – Allegra tab, Clarinex/desloratadine tab, Claritin cap/tab, Xyzal/levocetirizine tab, Zyrtec cap/tab, Allegra-D tab, Claritin-D tab, Clarinex-D tab, Zyrtec-D tab

1. Patient must have first tried and failed a 14-day trial of one of the following: cetirizine, fexofenadine, loratadine, cetirizine & pseudoephedrine, loratadine & pseudoephedrine, or fexofenadine & pseudoephedrine. Patient preference does not constitute treatment failure.

Nurtec ODT

PA Criteria

1. Diagnosis of migraine with or without aura requiring acute treatment – quantity 8 tablets per 30 days
    a. Patient has had a trial and failure of a triptan in the last 120 days OR
    b. Patient has had an inadequate response to, intolerance to, or contraindication to triptans

2. Diagnosis of episodic migraine requiring prophylaxis – quantity 16 tablets/30 days
    a. Patient has had a trial and failure of CGRP injectable (i.e., Aimovig, Ajovy, Emgality) for 90 days OR
    b. Patient has had an inadequate response to, intolerance to, or contraindication to CGRP injectable (i.e., Aimovig, Ajovy, Emgality)

Tonmya (cyclobenzaprine 2.8mg ODT) – for treatment of fibromyalgia for ages 15 years and older

Time Frame: 1Q2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizer	Age Range
cyclobenzaprine tab 5mg	654	$6,330.51	$9.68	34.5/17.5 days	435	13 – 78
cyclobenzaprine tab 10mg	1,940	$20,349.99	$10.49	41/19 days	1,187	13 – 78
cyclobenzaprine cap 15 ER	9	$407.07	$45.23	30/30 days	2	43, 47
Amrix 15mg and 30mg ER cap	0					
Fexmid 7.5mg	0					
Tonmya ODT 2.8mg	5	$5,743.45	$1,148.69	37.2/26 days	2	47, 55

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

Alternative Dosage Form PA Criteria

1. Patient is less than 8 years of age
2. Patient has a diagnosis which confirms a difficulty in swallowing
3. Patient is on a g-tube for feeding

Amrix and Fexmid PA Criteria

Patient has had at least a 60-day trial and failure of cyclobenzaprine 5 mg tablets OR cyclobenzaprine 10 mg tablets within the past 120 days

State A PA Criteria

1. Requested drug is FDA-approved for the condition being treated
2. Submission of medical records (e.g., chart notes) or verification of paid claims confirming one of the following:
   a. Trial and failure, or intolerance to a generic equivalent of the requested drug in a solid dosage form
   b. Patient is unable to swallow a solid dosage form (e.g., oral tablet, capsule) due to one of the following:
      - Age
      - Physical impairment (e.g., difficulties with motor or oral coordination)
      - Dysphagia
      - Patient is using a feeding tube or nasal gastric tube

Commercial PA Criteria

1. Requested drug is being used for a Food and Drug Administration (FDA)-approved indication
2. Trial and failure, or intolerance to generic cyclobenzaprine*
3. Trial and failure, contraindication, or intolerance to one of the following:
   - amitriptyline*
   - duloxetine
   - gabapentin (generic Neurontin)
   - pregabalin immediate-release

*Amitriptyline and cyclobenzaprine are considered to be potentially inappropriate medications for use in patients 65 years of age and older.

Icotyde (icotrokinra) – for treatment of moderate to severe plaque psoriasis in individuals who are candidate for systemic therapy or phototherapy

Oral and Topical Agents

Drug Name	Target	RA	SJIA	PJIA	PsO	PsA	AS	HS	UV
Icotyde (icotrokinra)	**IL-23 inhibitor**				✔ ≥ 12 ≥40kg				
Olumiant (baricitinib)	Small molecule JAK inhibitor	✔							
Otezla/Otezla XR (apremilast)	Small-molecule phosphodiesterase 4 inhibitor				✔ ≥ 6	✔ ≥ 6			
Rinvoq ER (upadacitinib)	Small molecule JAK inhibitor	✔		✔ ≥ 2		✔ ≥ 2	✔		
Rinvoq LQ solution	Small molecule JAK inhibitor			✔ ≥ 2		✔ ≥ 2			
Sotyktu (deucravacitinib)	Tyrosine kinase 2 (TYK2) inhibitor				✔	✔			
Xeljanz/Xeljanz oral solution (tofacitinib)	Small molecule JAK inhibitor	✔		✔ ≥ 2		✔ ≥ 2	✔		
Xeljanz XR (tofacitinib)	Small molecule JAK inhibitor	✔		✔		✔	✔		
Vtama (tapinarof) cream	aryl hydrocarbon receptor (AhR) agonist				✔				
Zoryve (roflumilast) Cream & foam	phosphodiesterase-4 (PDE4) inhibitor				✔ ≥ 6				

Abbreviations: RA = rheumatoid arthritis; PJIA = polyarticular juvenile idiopathic arthritis; PsO = plaque psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; HS = hidradenitis suppurativa; UV = uveitis. Preferred drugs in bold font.

Injectables

Drug Name	Target	RA	SJIA	PJIA	PsO	PsA	AS	HS	UV
Bimzelx (bimekizumab-bkzx)	Anti-IL17A/F/AF mAb				✔	✔	✔	✔	
Cimzia (certolizumab)	TNFα inhibitor	✔		✔ ≥ 2	✔	✔	✔		
Cosentyx (secukinumab)	Human mAb to IL-17A				✔ ≥ 6	✔ ≥ 2	✔	✔	
Enbrel (etanercept)	sTNFR fusion protein, TNFα inhibitor	✔		✔ ≥ 2	✔ ≥ 4	✔ ≥ 2	✔		
Humira (adalimumab) & biosimilars **(Yuflyma**)	TNFα inhibitor	✔		✔ ≥ 2	✔	✔	✔	✔	✔
Ilumya (tildrakizumab-asmn)	Human mAb to **IL-23**				✔				
Skyrizi (risankizumab-rzaa)	Human mAb to **IL-23**				✔	✔			
Siliq (brodalumab)	Human mAb directed against the IL-17 receptor A (IL-17RA)				✔				
Stelara (ustekinumab) & biosimilars (**Pyzchiva, Selarsdi, Steqeyma**)	Human mAb targeting the IL-12 and **IL-23** cytokines				✔ ≥ 6	✔ ≥ 6			
Taltz (ixekizumab)	Human mAb to IL-17A				✔ ≥ 6	✔	✔		
Tremfya (guselkumab)	Human mAb to **IL-23** cytokine				✔ ≥ 6	✔			

Utilization of drugs with indication for plaque psoriasis

Time frame: January to May 2026

Drug Name	Total Rx	Paid Amount	Paid/Rx	*Net Price*	Avg Qty/DS	Utilizer	Age Range
Icotyde 200mg tab	0		*~$9,000*		*30/30 days*		
Otezla/Otezla XR tab	50	$265,481.39	$5,309.63	$	59/29.9 days	15	15 – 59
Sotyktu 6mg tab	1	$7,146.10	$7,146.10	$$	30/30 days	1	47
Vtama 1% cream	5	$9,084.64	$1,816.93	$	72/27 days	4	2 – 61
Zoryve 3% cream	6	$5,602.23	$933.71	$	60/30days	4	25 – 46
Zoryve 3% foam	8	$5,720.14	$715.02	$	60/31 days	6	6 – 63
Bimzelx 160mg/ml Bimzelx 320mg/2ml	19 25	$218,100.29 $466,262.46	$11,478.96 $18,650.50	$$$$$	1.4/28 days 2.3/31 days	10	23 – 54
Cimzia prefill kit Cimzia starter kit	46 4	$277,470.66 $72,912.36	$6,031.97 $18,228.09	$$$	1.3/30 days	13	24 – 62
Cosentyx	135	$1,738,160.27	$12,875.26	$$$$	3/28 days	37	13 – 64
Enbrel	187	$1,526,500.80	$8,163.11	$	3.9/28 days	53	6 – 64
Humira (adalimumab) & biosimilars **(Yuflyma)**	409	$3,700,280.98	$9,047.14	$	2.4/28 days	103	9 – 64
Ilumya	1	$18,331.22	$18,331.22	$$$$$	1/28 days	1	58
Skyrizi	134	$3,036,728.11	$22,662.15	$$$	1.9/71 days	70	19 – 64
Stelara (ustekinumab) & biosimilars (**Pyzchiva, Selarsdi, Steqeyma**)	42	$1,198,028.58	$28,524.49	$$$$$	0.9/52 days	21	7 – 47
Selarsdi	34	$125,168.00	$3,681.41	$	0.96/49 days	15	9 – 50
Steqeyma	18	$73,277.42	$4,070.97	$	0.97/51 days	11	14 – 53
Taltz	120	$1,143,892.73	$9,532.44	$$	1.3/27 days	30	8 – 64
Tremfya	51	$824,237.90	$16,161.53	$$	1.4/45 days	20	15 – 61

*Red font denotes drug is on PA; Excludes IHS
Preferred drugs in bold font.

South Dakota Medicaid Preferred Drugs

- Ebglyss
- Enbrel
- Humira, Yuflyma
- Omvoh
- Pyzchiva, Selardsi, Steqeyma
- Rinvoq/LQ
- Skyrizi
- Taltz
- Tremfya
- Tyenne

PA Criteria for consideration

State A

1. Submission of medical records (e.g., chart notes) confirming a diagnosis of moderate to severe plaque psoriasis (PsO)
2. Both of the following:
    - Patient is 12 years of age or older
    - Patient weighs at least 40 kg
3. One of the following:
    - Greater than or equal to 3% body surface area involvement
    - Severe scalp psoriasis
    - Palmoplantar (i.e., palms, soles), facial, or genital involvement
4. Paid claims or submission of medical records (e.g., chart notes) confirming a trial and failure of a minimum 30-day supply (14-day supply for topical corticosteroids), contraindication, or intolerance to one of the following topical therapies:
    - Corticosteroids (e.g., betamethasone, clobetasol)
    - Vitamin D analogs (e.g., calcitriol, calcipotriene)
    - Tazarotene
    - Calcineurin inhibitors (e.g., tacrolimus, pimecrolimus)
5. Submission of medical records (e.g., chart notes) or verification of paid claims documenting ALL of the following:
    5.1. History of failure to a 3-month trial of methotrexate at the maximally indicated dose within the last 6 months, unless contraindicated or clinically significant adverse effects are experienced
    5.2. History of failure, contraindication, or intolerance to one of the following topical therapies:
        - Vtama
        - Zoryve 0.3% cream
    5.3. History of failure, contraindication, or intolerance to ALL of the following:
        - A preferred adalimumab biosimilar or Enbrel (etanercept)
        - infliximab
        - Otezla (apremilast)
        - A preferred ustekinumab biosimilar
6. Prescribed by or in consultation with a dermatologist

Reauthorization

1. Patient demonstrates positive clinical response to therapy as evidenced by ONE of the following:
    - Reduction in the body surface area (BSA) involvement from baseline
    - Improvement in symptoms (e.g., pruritus, inflammation) from baseline
2. Prescribed by or in consultation with a dermatologist

Optum Rx®

Therapeutic Class Overview

Antiemetics

Introduction

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

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

Table 1. Medications Included Within Class Review

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

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

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

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

Indications

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

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

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

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

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

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

Abbreviations: PONV = postoperative nausea and vomiting.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinical Efficacy Summary

Anorexia in patients with acquired immunodeficiency syndrome (AIDS)

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

CINV

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

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

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

NVP

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

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

PONV

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

RINV

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

Motion sickness

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

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

Clinical Guidelines

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

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

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

Safety Summary

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

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

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

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

Dosing and Administration

Table 8. Dosing and Administration

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

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

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

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

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

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

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

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

(Micromedex 2026)

Conclusion

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

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

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

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

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Optum Rx®

Therapeutic Class Overview

Neuropathic pain and fibromyalgia

Introduction

- Neuropathic pain is commonly described by patients as burning or electrical in nature resulting from injury or damage to the nervous system (*Kominek and Mullins 2025*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue and sleep disturbances, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2025*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg and Kaplan 2025*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or postherpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine delayed-release [DR]), Gralise (gabapentin extended-release [ER]), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), Tonmya (cyclobenzaprine), and ZTlido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, skeletal muscle relaxants, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2025, Gralise 2025, Horizant 2025, Lidoderm 2022, Lyrica 2025, Lyrica CR 2026, Neurontin 2025, Nucynta ER 2025, Qutenza 2026, Savella 2025, Tonmya 2025, ZTLido 2024*).

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2025*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman 2025*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman 2025*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in patients with type 2 diabetes is less certain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman 2026*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman 2026*).
  - Often, diabetic neuropathy can be severe enough to impact quality of life and require pharmaceutical treatment. The American Academy of Neurology (AAN) and American Diabetes Association (ADA) guidelines suggest that gabapentinoids, SNRIs, sodium channel blockers, and tricyclic antidepressants can be used as initial treatment options; combinations of these agents may provide additional relief. The ADA notes that opioids, including tramadol, should not generally be used due to the potential for adverse events (*ADA 2026, Price et al 2022*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw 2009*).
  - Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity *(Crofford 2025*).

- The prevalence of fibromyalgia in the general U.S. population is estimated to be 2% to 5% and increases with age *(Goldenberg and Kaplan 2025)*. It is more common in women than in men, with a ratio of approximately 6:1 for patients seen in specialty clinics and a ratio of 2:1 for the general population (*Crofford 2025)*.
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw 2009, Crofford 2025*).

PHN

- PHN refers to the occurrence or persistence of the pain of herpes zoster 90 days or more from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PHN are older age, race, immunocompromised state, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or lifelong (*Kissoon 2026*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Kissoon 2026*). Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN *(Albrecht and Levin 2025).*
- Several treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, SNRIs, opioids (for short term-relief while other agents are being titrated), capsaicin, topical lidocaine, behavioral therapy, acupuncture, epidural injections or nerve blocks, , botulinum toxin and neuromodulation (*Kissoon 2026*).
- The scope of this review includes the treatment of neuropathic pain and fibromyalgia. Indications outside of this (eg, acute/chronic pain) will not be reviewed.
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs).

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)[a]
Cymbalta (duloxetine DR)	✔
Gralise (gabapentin ER)[b]	✔
Horizant (gabapentin enacarbil ER) [b]	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	✔
Lyrica CR (pregabalin ER)	✔
Neurontin (gabapentin)	✔
Nucynta ER (tapentadol ER)	✔
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	✔
Tonmya (cyclobenzaprine)	-
ZTlido (lidocaine topical system)	-

[a] For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.
[b] Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

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

Indications

Table 2. Food and Drug Administration Approved Indications

Indication	Cymbalta (duloxetine DR)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)	Tonmya (cyclobenzaprine)
Management of chronic musculoskeletal pain	✔ a										
Management of fibromyalgia in adults	✔				✔					✔	✔
Management of fibromyalgia in adults and pediatric patients 13 years of age and older	✔										
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ c	✔		
Management of neuropathic pain associated with spinal cord injury					✔						
Management of PHN		✔	✔		✔	✔	✔				
Relief of pain associated with PHN				✔					✔		
Other indications											
Adjunctive therapy for adult patients with partial onset seizures					✔						
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔				
Adjunctive therapy for patients 1 month of age and older with partial onset seizures					✔						
Moderate-to-severe primary restless legs syndrome			✔ b								
Treatment of generalized anxiety disorder	✔										
Treatment of major depressive disorder	✔										
Management of severe and persistent pain in adults								✔ c			

Abbreviations: DR = delayed-release; ER = extended-release; PHN = postherpetic neuralgia.
[a] This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
[b] Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
[c] Medication is not for use as an as-needed analgesic. Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve use for patients in whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

(*Prescribing information: Cymbalta 2025, Gralise 2025, Horizant 2025, Lidoderm 2022, Lyrica 2025, Lyrica CR 2026, Neurontin 2025, Nucynta ER 2025, Qutenza 2026, Savella 2025, Tonmya 2025, ZTlido 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

Neuropathic Pain

- Pregabalin has demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- A Phase 3, randomized-withdrawal, placebo-controlled study demonstrated the superiority of tapentadol ER over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores ($p = 0.017$ for ≥ 30% improvement; $p = 0.028$ for ≥ 50% improvement), responder rates, and Patient Global Impression of Change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- A second, 12-week, randomized withdrawal trial of tapentadol ER in adults with painful diabetic peripheral neuropathy evaluated the mean change in average pain intensity from the start of the double-blind treatment period to week 12. Overall, the change was 1.3 in the placebo group, indicating a worsening in pain intensity, and 0.28 in the tapentadol ER group (least squares mean difference, -0.95; 95% confidence interval [CI], -1.42 to -0.49; $p < 0.001$). From pre-titration to week 12 of double-blind treatment, a ≥ 30% improvement in pain intensity was observed in 55.4% of tapentadol ER-treated patients and 45.4% of placebo-treated patients ($p = 0.032$). A ≥ 50% improvement in pain intensity was observed in 40.4% of tapentadol ER-treated patients and 28.9% of placebo-treated patients ($p = 0.015$) (*Vinik et al 2014*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory (BPI), Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by BPI Modified Short Form (BPI-MSF) average pain (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Quilici et al 2009, Soliman et al 2025, Wernicke et al 2007[a], Wiffen et al 2017, Liampas et al 2021*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, one of 12 weeks' duration and the other of 16 weeks' duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if

doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores compared to placebo, and increased the proportion of patients with at least a 30% or 50% reduction from baseline in pain score (*Lyrica prescribing information 2025*, *Siddall et al 2006, Vranken et al 2008*).

- An 8-week, international, non-inferiority randomized controlled trial (RCT) compared continuing twice-daily pregabalin (75 mg) with switching to once-daily pregabalin (150 mg) in 130 patients with diabetic peripheral neuropathy. The change in visual analog scale pain score showed least square means of -17.95 with once-daily pregabalin and -18.74 with twice-daily pregabalin (difference, 0.79; 95% CI, -5.99 to 7.58). Non-inferiority was met based on the prespecified margin of 9.2 (*Joung et al 2024*).
- The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blind studies of oral and topical therapy for neuropathic pain and required a NNT for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase (*Finnerup et al 2015*). In a 2025 meta-analysis of 313 trials (N = 48, 789) evaluated the proportion of patients with a 50% or 30% reduction in baseline pain intensity or moderate pain relief (primary endpoint) with various pharmacotherapies or neuromodulation. Overall, the estimated number needed to treat (NNT) to achieve the primary endpoint was: 4.6 for TCAs, 7.4 for SNRIs, 8.9 for gabapentinoids, 13.2 for capsaicin 8% patches, and 14.5 for lidocaine 5% plasters (*Soliman et al 2025).*
- A 2022 network meta-analysis of 20 RCTs (N = 1198) evaluated the efficacy of drug therapies in treatment of neuropathic pain after spinal cord injury *(Ling et al 2022).* Among agents included in this review, no significant differences were found among amitriptyline, duloxetine, gabapentin, and pregabalin in outcomes of pain relief, mental or sleep-related symptom relief, and adverse events.
- The efficacy of capsaicin 8% in diabetic peripheral neuropathy was assessed in a placebo-controlled trial *(Simpson et al 2017)*. The primary endpoint, percentage reduction in average daily pain score from baseline through 8 weeks, was significantly improved with capsaicin 8%. Patients treated with capsaicin also had significant improvements in median time to treatment response and in sleep interference scores through week 8.
- The OPTION-DM trial was a double-blind, multicenter, head-to-head study that evaluated the comparative efficacy of combinations of guideline recommended treatments including amitriptyline, duloxetine and pregabalin in 130 patients with diabetic neuropathy. All patients were started on monotherapy for 6 weeks, and then supplemented with a second drug if pain relief was suboptimal. The primary outcome was the difference in 7-day average daily pain during the final week of the 16-week pathway. Overall, the 7-day average numerical rating scores (10-point scale) at week 16 decreased from a mean 6.6 points at baseline to 3.3 at week 16 for all three pathways (amitriptyline with pregabalin add-on; pregabalin with amitriptyline add-on; duloxetine with pregabalin add-on) (*Tesfaye et al 2022*).

Fibromyalgia

- Several RCTs and meta-analyses have demonstrated the efficacy of duloxetine, pregabalin, milnacipran, and sublingual cyclobenzaprine for the treatment of fibromyalgia (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lederman et al 2023, Lederman et al 2026, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Pathak et al 2025, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with the tricyclic antidepressant amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine, and the SNRIs duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).
  - In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled NNT to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
  - Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each drug (*Hauser et al 2010*).

- A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
- A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee et al 2016*).
- A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).
- A systematic review and meta-analysis of 40 randomized trials (N = 10,608) evaluating pharmacological treatments for sleep disturbance in fibromyalgia found that pregabalin (8 studies, doses 300 to 600 mg) demonstrated a statistically significant improvement in sleep quality (pooled standardized mean difference [SMD], -0.35; 95% CI, -0.54 to -0.16; p < 0.01), with a dose–response trend favoring 450 mg (SMD, -0.43; 95% CI, -0.71 to -0.16) over 300 mg (SMD, -0.26; 95% CI, -0.46 to -0.07), but no additional benefit at 600 mg (SMD, -0.29; 95% CI, -0.72 to 0.14). In contrast, pooled data for amitriptyline (8 studies, 25 to 50 mg daily) showed no significant benefit (SMD, -0.71; 95% CI, -2.05 to 0.63), and milnacipran (6 studies, up to 200 mg daily) showed no effect (SMD, -0.01; 95% CI, -0.07 to 0.05) (*Pathak et al 2025).*
- Duloxetine is approved for treatment of fibromyalgia in patients aged 13 years and older. Pediatric approval was supported by findings of a 13-week, placebo-controlled RCT (N = 184) of patients aged 13 to 17 years with juvenile fibromyalgia (*Upadhyaya et al 2019*). The primary outcome, mean change in BPI average pain severity, was not statistically different between groups; however, significantly more duloxetine- vs placebo-treated patients had a treatment response of ≥ 30% reduction (52% vs 36%, respectively) and ≥ 50% reduction (40% vs 24%) on BPI average pain severity.
- A 2026 systematic review and meta-analysis of 4 trials (N = 1,684) compared sublingual cyclobenzaprine to placebo in adult patients with fibromyalgia to determine effects on pain reduction, changes in the Patient Global Impression of Change, changes in the Fibromyalgia Impact Questionnaire-Revised (FIQ-R), and safety (*Al-Qudah et al 2026*). Sublingual cyclobenzaprine increased the likelihood of achieving a ≥ 30% and ≥ 50% reduction in pain compared to placebo (relative risk [RR], 1.44; 95% CI, 1.15 to 1.81 and RR, 1.43; 95% CI, 1.12 to 1.82, respectively). Although FIQ-R scores did not differ between groups, response on the PGIC demonstrated greater improvements with sublingual cyclobenzaprine compared to placebo (RR, 1.52; 95% CI, 1.29 to 1.79). Treatment-emergent adverse events that were more frequent with sublingual cyclobenzaprine included oral hypoesthesia, oral paresthesia, and abnormal taste.
- A 2025 systematic review and meta-analysis of 4 trials (N = 1,993) evaluated the effects of sublingual cyclobenzaprine on daily diary pain scores. Secondary outcomes included changes in FIQ-R function, FIQ-R symptoms, daily diary sleep scores, and adverse events (*Maggi et al 2025*). Compared to controls, sublingual cyclobenzaprine reduced daily diary pain intensity (SMD, -0.25; 95% CI -0.34 to -0.16; p < 0.001). Cyclobenzaprine was also associated with greater reductions in FIQ-R function (SMD, -0.18; 95% CI, -0.35 to -0.02; p = 0.028), FIQ-R symptoms (SMD, -0.23; 95% CI, -0.33 to -0.13; p < 0.001), and sleep daily diary score (SMD, -0.21; 95% CI, -0.32 to -0.11; p < 0.001. The most common adverse events included oral hypoesthesia and paresthesia.

- A 2022 network meta-analysis of 36 trials (N = 11,930) compared the efficacy and acceptability of off-label use of amitriptyline with FDA-approved treatments for fibromyalgia *(Farag et al 2022)*. Compared with placebo, duloxetine 120 mg was associated with the greatest improvement in pain (SMD, -0.33; 95% credible interval [CrI], -0.36 to -0.30) and depression (SMD, -0.25; 95% CrI, -0.32 to -0.17). Based on relative rankings of treatments, the agents most likely to be most effective were duloxetine 120 mg for treating pain and depression; amitriptyline for improving sleep, fatigue, and overall quality of life; and amitriptyline for acceptability.

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to

placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).

- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (area under the curve [AUC]) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2024)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin were also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).
- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, short-form McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).
- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (n = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirmed these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN support the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*).

Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).

- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2026*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

Clinical Guidelines

- The 2022 Centers for Disease Control (CDC) clinical practice guideline for prescribing opioids for pain recommend the use of non-opioid therapies for subacute and chronic pain. Tricyclic antidepressants, SNRI antidepressants, selected anticonvulsants, or transdermal lidocaine are recommended for neuropathic pain syndromes (eg, diabetic neuropathy or PHN). In patients with fibromyalgia, tricyclic antidepressants (eg, amitriptyline), SNRI antidepressants (eg, duloxetine, milnacipran), NSAIDs (eg, topical diclofenac), and specific anticonvulsants (eg, pregabalin and gabapentin) are used to improve pain, function, and quality of life (*Dowell et al 2022*).
- Updated recommendations from the Special Interest Group on Neuropathic Pain (NeuPSIG) suggest the use of gabapentinoids (eg, gabapentin, pregabalin mirogabalin [not available in the United States]), SNRIs (ie, duloxetine, venlafaxine), and TCAs as first line options for the treatment of neuropathic pain. Second line recommendations include the use of topical treatments (ie lidocaine 5% patches, capsaicin 8% patches, capsaicin cream, or botulinum toxin type A) for localized peripheral neuropathic pain; however topical treatments may be appropriate as first line in vulnerable patients (eg, older adults or people with multiple diseases, or cases of polypharmacy). Opioids and tramadol are considered third line recommendations (*Soliman et al 2025*).

Diabetic Neuropathy

- The AAN guidelines recommend the following (*Price et al 2022 [Reaffirmed February 2025]*):
  - In patients with painful diabetic neuropathy, clinicians should offer tricyclic antidepressants, SNRIs, gabapentinoids, and/or sodium channel blockers to reduce pain.
  - In patients preferring topical, nontraditional, or nonpharmacological interventions, providers may offer topicals (capsaicin, glyceryl trinitrate spray, Citrullus colocynthis), nontraditional (ginkgo biloba), and/or nonpharmacologic interventions (cognitive behavioral therapy [CBT], exercise, Tai Chi, mindfulness).
  - Given similar efficacy, clinicians should consider factors other than efficacy, including potential adverse effects, patient comorbidities, cost, and patient preference when recommending treatment.
  - In patients of child-bearing potential with diabetic neuropathy, clinicians should not offer valproic acid.
  - Clinicians should not prescribe valproic acid in all patients with diabetic neuropathy, given the potential for adverse effects unless other effective medications have failed.
  - Clinicians should counsel patients that a series of medications may need to be tried to identify the treatment of most benefit for patients with painful diabetic neuropathy.
  - Clinicians should determine that an individual intervention to reduce neuropathic pain is a failure either when the medication has been titrated to a demonstrated efficacious dose for approximately 12 weeks without clinically significant pain reduction or when side effects from the medication outweigh any benefit in reduced neuropathic pain.
  - Clinicians should offer patients a trial of a medication from a different effective class when they do not achieve meaningful improvement or if they experience significant adverse effects with the initial therapeutic class.
  - For patients who achieve partial improvement with an initial therapeutic class, clinicians should offer a trial of a medication from a different effective class or combination therapy by adding a medication from a different effective class.
  - If patients are currently on opioids for the treatment of painful diabetic neuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative non-opioid treatment strategies.
  - Opioids or opioids/SNRI dual mechanism agents should not be used for the treatment of painful neuropathy.
  - If patients are currently on tramadol and tapentadol (opioids/SNRI dual mechanism agents) for the treatment of painful diabetic neuropathy, clinicians may offer the option of a safe taper off these medications and discuss alternative nonopioid treatment strategies.

- The 2026 ADA guideline acknowledges the following regarding pharmacologic treatment of diabetic neuropathic pain, which may reduce pain and improve quality of life (*ADA 2026*):
  - Gabapentinoids, SNRIs, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes; combinations of these agents may offer additional relief.
  - Topical capsaicin (8%) can be considered when there are contraindications to oral therapy or in those who prefer topical treatments.
  - Lidocaine patches have limited data supporting use for diabetic peripheral neuropathy and are not effective for pain that is widely distributed. However, they may be of use in individuals with nocturnal neuropathic foot pain.
  - The ADA recommends against the use of opioids, including tramadol and tapentadol for the management of neuropathic pain due to the potential for adverse events.

PHN

- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first-line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear *(Attal et al 2010)*.

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane et al 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

Safety Summary

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with sublingual cyclobenzaprine, duloxetine, milnacipran, and tapentadol ER.
  - Duloxetine is contraindicated for use by patients treated with linezolid or intravenous methylene blue.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
  - Sublingual cyclobenzaprine is contraindicated in patients with hyperthyroidism, arrhythmias, heart block or conduction disturbances, congestive heart failure, or during the acute recovery phase of myocardial infarction.
- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Duloxetine and milnacipran may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- Tapentadol ER has a boxed warning for serious, life-threatening risks including the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system (CNS) depressants that can cause profound sedation, respiratory depression, coma, and death. The FDA strongly encourages a Risk Evaluation and Mitigation Strategy (REMS) program and counseling of opioid analgesics (including tapentadol ER) to assure safe use of these medications.
- Key warnings and precautions with the use of tapentadol ER include opioid induced hyperalgesia and allodynia, serotonin syndrome, life threatening respiratory depression in patients with chronic pulmonary disease, elderly,

cachectic or debilitated patients, adrenal insufficiency, severe hypotension, risks of use in patients with increased intracranial pressure, brain tumors, head injury or impaired consciousness, gastrointestinal complications, increased risk of seizures in patients with a history of seizures, withdrawal, risks with driving or operating heavy machinery, and the risk of toxicity in patients with renal or hepatic impairment.

- Key warnings for sublingual cyclobenzaprine include embryofetal toxicity, serotonin syndrome, tricyclic-depressant and atropine-like adverse reactions, CNS depression and risk with driving or operating heavy machinery, and oral mucosal reactions.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Gabapentin, gabapentin enacarbil, pregabalin, and pregabalin ER carry warnings regarding the risk of respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment.
- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. Methemoglobinemia has been reported in association with local anesthetic use.
- Topical capsaicin carries warnings for severe irritation with unintended exposure or exposure to eyes or mucous membranes, pain associated with application, potential respiratory exposure from inhalation of airborne capsaicin upon rapid removal of the patch, and temporary reductions in sensory function. It is recommended that healthcare workers wear nitrile gloves, a face mask, and protective glasses and administer capsaicin in a well-ventilated treatment area. Pain associated with application may be reduced with optional pretreatment with a topical anesthetic.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin. Suicidal behavior and ideation have also been reported in patients after discontinuation of gabapentin, pregabalin, and pregabalin ER.
  - Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, MAOIs, linezolid, and methylene blue).
  - Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored after initiating tapentadol ER treatment, when making dose adjustments, and throughout treatment due to an increased risk of respiratory depression.
  - Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
  - Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
  - Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
  - Patients receiving tapentadol ER should be considered for prescribing of naloxone for emergency treatment of opioid overdose based on the patient's risk factors for overdose.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with CNS-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.
  - Caution is advised when prescribing pregabalin, gabapentin, or gabapentin enacarbil concomitantly with opioids due to risk of CNS depression.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine DR)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Should be administered with evening meal Dose should be reduced in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Once or twice daily	Should be administered with food Dose should be reduced in CrCl < 60 mL/min or hemodialysis; not recommended for RLS if CrCl < 15 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Should be applied for up to 12 hours within a 24-hour period Caution advised in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Dose should be reduced in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Dose should be reduced in CrCl < 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis Should be administered after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Dose should be reduced in CrCl < 60 mL/min or hemodialysis
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance Max 500 mg daily Should not be used in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment. Dose should be reduced in moderate hepatic impairment Do not abruptly discontinue
Qutenza (capsaicin)	Patch	Transdermal	30-minute (DPN) or 60-minute (PHN) application of up to 4 patches every 3 months	Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	Dose should be reduced in CrCl < 30 mL/min Caution advised in patients with moderate renal impairment or severe hepatic impairment
Tonmya (cyclobenzaprine)	Tablet	Sublingual	Once daily at bedtime	Dose reduce in mild hepatic impairment; not recommended in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				moderate or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; DPN = diabetic peripheral neuropathy; DR = delayed-release; ER = extended-release; ESRD = end stage renal disease; PHN = postherpetic neuralgia; RLS = restless leg syndrome.
See the current prescribing information for full details.

Conclusion

- Clinical trials support the use of these neuropathic pain and fibromyalgia agents for their FDA-approved indications; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are less available, and consistent benefit of one agent over another has not been demonstrated.
  - The agents approved for diabetic neuropathy include capsaicin, duloxetine, pregabalin, pregabalin ER, and tapentadol ER.
  - Agents approved for the management or relief of pain associated with PHN include gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin.
- A head-to-head study has supported the use of dual combination therapy with amitriptyline, SNRIs, and gabapentinoids, which demonstrated similar rates of reduced pain rating scores for the treatment of diabetic neuropathy. There is limited data supporting the use of lidocaine patches for widespread diabetic neuropathy; however, it may be useful in patients with nocturnal neuropathic foot pain. Topical capsaicin 8% can be considered when oral therapy is contraindicated or in patients who prefer oral therapy. Strong opioids have demonstrated efficacy compared to placebo; however, there are concerns regarding long-term safety, including addiction potential and misuse.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, sublingual cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg and Kaplan 2025*).

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Optum Rx®

Therapeutic Class Overview

Immunomodulators

Introduction

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), hidradenitis suppurativa (HS), alopecia areata, and uveitis (UV), which will be the focus of this review.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*); which are the targets of various biologic agents approved by the Food and Drug Administration (FDA). Currently, there are 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab; 10 biosimilars available), Remicade (infliximab; 4 biosimilars available), and Simponi/Simponi Aria (golimumab).
- Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved. These include:
  - Orencia (abatacept), which inhibits CD28-B7 mediated co-stimulation of the T-cell.
  - Rituxan (rituximab; 3 biosimilars available), which targets CD20, a molecule that is found on the surface of B-cells.
  - Actemra (tocilizumab; 3 biosimilars available) and Kevzara (sarilumab) have activity against the IL-6 receptor.
  - Kineret (anakinra), which targets the IL-1 receptor.
  - Ilaris (canakinumab), which binds to the IL-1ß receptor.
  - Stelara (Ustekinumab; 8 biosimilars available), which targets the IL-12 and IL-23 cytokines.
  - Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A; Bimzelx (bimekizumab-bkzx), is a monoclonal antibody against IL-17A, IL-17F, and IL-17AF.
  - Siliq (brodalumab) is an IL-17 receptor antagonist.
  - Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn) are IL-23 antagonists.
- Oral immunomodulator agents on the market include:
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Rinvoq/Rinvoq LQ (upadacitinib), Olumiant (baricitinib), and Leqselvi (deuruxolitinib) which target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
  - Otezla (apremilast), a small-molecule phosphodiesterase 4 (PDE-4) inhibitor.
  - Sotyktu (deucravacitinib), a tyrosine kinase (TYK2) inhibitor.
  - Litfulo (ritlecitinib), a JAK3 and tyrosine kinase inhibitor.
  - Icotyde (icotrokinra), an IL-23 inhibitor.
- Several immunomodulators carry additional FDA-approved indications for rare conditions mentioned below. These indications may be briefly discussed, but will not be reviewed in detail within this overview:
  - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), familial cold autoinflammatory syndrome, and Muckle-Wells syndrome; 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); 4) familial Mediterranean fever (FMF); 5) adult-onset Still's disease; and 6) symptomatic treatment of gout flares when other therapies are inadequate or inappropriate.
  - Kineret for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID), and deficiency of interleukin-1 receptor antagonist (DIRA).
  - Actemra and its biosimilars Avtozma, Tyenne and Tofidence for giant cell arteritis (GCA); Actemra, Avtozma, and Tyenne for cytokine release syndrome (CRS); Actemra for systemic sclerosis-associated interstitial lung disease (SSc-ILD).
  - Rinvoq for GCA.
  - Cimzia, Cosentyx, Bimzelx, Rinvoq, and Taltz for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
  - Orencia for prophylaxis of acute graft-versus-host disease (GVHD).
  - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
  - Cosentyx (secukinumab) for enthesitis-related arthritis (ERA) in patients 4 years and older.
  - Rituxan and biosimilars (Truxima, Riabni, Ruxience) for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). Rituxan is additionally indicated for pemphigus vulgaris.

- Olumiant, Actemra, Avtozma, Tyenne, Tofidence for the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19) requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.
- Kevzara for polymyalgia rheumatica (PMR).

- The indications of Crohn's disease (CD), ulcerative colitis (UC), and atopic dermatitis will not be discussed in this review.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Alternative Available (same molecular entity)*	Type of Agent/Target
Injectables – Reference products		
Actemra (tocilizumab)	✔	Human mAb targeting the IL-6 receptor
Bimzelx (bimekizumab-bkzx)	-	Anti-IL17A/F/AF mAb
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human mAb to IL-17A
Enbrel (etanercept)	-	sTNFR fusion protein, TNFα inhibitor
Humira (adalimumab)	✔	TNFα inhibitor
Ilaris (canakinumab)	-	Human mAb that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human mAb to IL-23
Kevzara (sarilumab)	-	Human mAb targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Remicade (infliximab)	✔ a	TNFα inhibitor
Rituxan (rituximab)	✔	Anti-CD20 mAb
Skyrizi (risankizumab-rzaa)	-	Human mAb to IL-23
Siliq (brodalumab)	-	Human mAb directed against the IL-17 receptor A (IL-17RA)
Simponi/Simponi Aria (golimumab)	-	TNFα inhibitor
Stelara (ustekinumab)	✔ a	Human mAb targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human mAb to IL-17A
Tremfya (guselkumab)	-	Human mAb to IL-23 cytokine
Actemra biosimilars		
Avtomza (tocilizumab-anoh)	✔ c	Human mAb to IL-6 receptor
Tofidence (tocilizumab-bavi)	N/A	Human mAb to IL-6 receptor
Tyenne (tocilizumab-aazg)	N/A	Human mAb to IL-6 receptor
Humira biosimilars		
Abrilada (adalimumab-afzb)	✔ c	TNFα inhibitor
adalimumab-aacf	N/A d	TNFα inhibitor
Amjevita (adalimumab-atto)	✔ b, c	TNFα inhibitor
Cyltezo (adalimumab-adbm)	✔ b, c	TNFα inhibitor
Hadlima (adalimumab-bwwd)	✔ c	TNFα inhibitor
Hulio (adalimumab-fkjp)	✔ b, c	TNFα inhibitor
Hyrimoz (adalimumab-adaz)	✔ b, c	TNFα inhibitor
Simlandi (adalimumab-ryvk)	✔ c	TNFα inhibitor
Yuflyma (adalimumab-aaty)	✔ b, c	TNFα inhibitor
Yusimry (adalimumab-aqvh)	N/A	TNFα inhibitor

Drug	Alternative Available (same molecular entity)*	Type of Agent/Target
Remicade biosimilars		
Avsola (infliximab-axxq)	N/A	TNFα inhibitor
Inflectra (infliximab-dyyb)	N/A	TNFα inhibitor
Renflexis (infliximab-abda)	N/A	TNFα inhibitor
Rituxan biosimilars		
Riabni (rituximab-arrx)	N/A	Anti-CD20 mAb
Ruxience (rituximab-pvvr)	N/A	Anti-CD20 mAb
Truxima (rituximab-abbs)	N/A	Anti-CD20 mAb
Stelara biosimilars		
Imuldosa (ustekinumab-srlf)	N/A	Human mAb targeting the IL-12 and IL-23 cytokines
Otulfi (ustekinumab-aauz)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Pyzchiva (ustekinumab-ttwe)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Selarsdi (ustekinumab-aekn)	✔ [b, c]	Human mAb targeting the IL-12 and IL-23 cytokines
Starjemza (ustekinumab-hmny)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Steqeyma (ustekinumab-stba)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Wezlana (ustekinumab-auub)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Yesintek (ustekinumab-kfce)	✔ [c]	Human mAb targeting the IL-12 and IL-23 cytokines
Oral agents		
Icotyde (icotrokinra)	-	IL-23 inhibitor
Litfulo (ritlecitinib)	-	JAK3 and tyrosine kinase inhibitor
Leqselvi (deuruxolitinib)	-	JAK inhibitor
Olumiant (baricitinib)	-	Small molecule JAK inhibitor
Otezla/Otezla XR (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Rinvoq/Rinvoq LQ (upadacitinib)	-	Small molecule JAK inhibitor
Sotyktu (deucravacitinib)	-	Tyrosine kinase 2 (TYK2) inhibitor
Xeljanz/Xeljanz XR (tofacitinib)	-	Small molecule JAK inhibitor

Abbreviations: N/A = approved biosimilar, not interchangeable; mAb = monoclonal antibody; JAK = janus kinase
*For example, authorized generic, branded generic (unless not considered therapeutically equivalent by the Orange Book), generic, unbranded biologic, or interchangeable biologic.

[a] Unbranded reference product is available.

[b] Unbranded biosimilar product is available.

[c] Designated interchangeable with reference product.

[d] Branded Idacio has been discontinued, but unbranded adalimumab-aacf remains available.

(Drugs@FDA 2026, Purple Book: Database of Licensed Biological Products 2026)

Indications

- Additional rare indications are noted in the introduction. See package insert for full indication details.

Table 2. FDA approved indications – Injectable agents

Indication	RA	SJIA	PJIA	PsO	PsA (incl. juvenile)	AS	HS	UV
Injectable agents – no biosimilars								
Bimzelx (bimekizumab-bkzx)				✔	✔	✔	✔	
Cimzia (certolizumab)	✔		✔ (≥ 2)	✔ [a]	✔	✔		
Cosentyx (secukinumab)				✔ [a] (≥ 6)	✔ (≥ 2)	✔	✔	
Enbrel (etanercept)	✔ [b]		✔ (≥ 2)	✔ (≥ 4)	✔ [b] (≥ 2)	✔		

Indication	RA	SJIA	PJIA	PsO	PsA (incl. juvenile)	AS	HS	UV
Ilaris (canakinumab)		✔ (≥ 2)						
Ilumya (tildrakizumab-asmn)				✔ a				
Kevzara (sarilumab)	✔ c		✔ (≥ 63kg)					
Kineret (anakinra)	✔ d							
Orencia (abatacept)[e]	✔		✔ (≥ 2)		✔ (≥ 2)			
Skyrizi (risankizumab-rzaa)				✔	✔			
Siliq (brodalumab)				✔ f				
Simponi (golimumab)	✔ g				✔ b	✔		
Simponi Aria (golimumab)	✔ g		✔ (≥ 2)		✔ (≥ 2)	✔		
Taltz (ixekizumab)				✔ a (≥ 6)	✔	✔		
Tremfya (guselkumab)				✔ a (≥ 6 and ≥ 40kg)	✔ (≥ 6 and ≥ 40kg)			
Injectable agents with FDA-approved biosimilars (bolded agent is reference product)								
Actemra (tocilizumab) Avtozma (tocilizumab-anoh); Tofidence (tocilizumab-bavi), Tyenne (tocilizumab-aazg)	✔ c	✔ (≥ 2) c	✔ (≥ 2) c					
Humira (adalimumab); Abrilada* (adalimumab-afzb), Amjevita* (adalimumab-atto), Cyltezo* (adalimumab-adbm), Hadlima* (adalimumab-bwwd), Hulio* (adalimumab-fkjp), Hyrimoz* (adalimumab-adaz), Simlandi* (adalimumab-ryvk), Yuflyma* (adalimumab-aaty); Yusimry (adalimumab-aqvh), adalimumab-aacf.	✔ h		✔ b (≥ 2)	✔	✔ h	✔	✔ k	✔ k
Remicade (infliximab); Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda),	✔ g			✔ i	✔	✔		
Rituxan (rituximab); Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), Truxima (rituximab-abbs)	✔ j							
Stelara (ustekinumab); Otulfi* (ustekinumab-aauz), Pyzchiva* (ustekinumab-ttwe), Selarsdi* (ustekinumab-aekn), Starjemza (ustekinumab-hmny)				✔ (≥ 6)	✔ (≥ 6)			

Indication	RA	SJIA	PJIA	PsO	PsA (incl. juvenile)	AS	HS	UV
Steqeyma* (ustekinumab-stba), Wezlana* (ustekinumab-auub), Yesintek* (ustekinumab-kfce); Imuldosa (ustekinumab-srlf).								

Abbreviations: RA = rheumatoid arthritis; SJIA = systemic juvenile idiopathic arthritis; PJIA = polyarticular juvenile idiopathic arthritis; PsO = plaque psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; HS = hidradenitis suppurativa; UV = uveitis.
*Designated as an interchangeable with the reference product.

[a] In patients who are candidates for systemic therapy or phototherapy

[b] With or without methotrexate (MTX) in adults.

[c] Patients with moderately to severely active disease who have had an inadequate response or intolerance to ≥ 1 disease-modifying anti-rheumatic drugs (DMARDs) (Actemra, Avtozma, Kevzara, Tofidence, Tyenne).

[d] Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients who have failed one or more DMARDs.

[e] Limitation of use: Concomitant use with other potent immunosuppressives (eg, DMARDS, JAK inhibitors) is not recommended.

[f] In patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

[g] In combination with MTX

[h] Can be used alone or in combination with MTX or other DMARDs.

[i] Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

[j] In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1 TNF antagonist therapies.

[k] Amjevita, Cyltezo, Hyrimoz, Simlandi , Yuflyma, approved for adolescent (12+) HS; Amjevita, Cyltezo, Hyrimoz, Simlandi, Yuflyma, approved for pediatric (2+) UV

(Prescribing information: Abrilada 2025, Actemra 2025, adalimumab-aacf 2024, Amjevita 2025, Avsola 2025, Avtozma 2026, Bimzelx 2025, Cimzia 2026, Cosentyx 2026, Cyltezo 2025, Enbrel 2025, Hadlima 2025, Hulio 2025, Humira 2025, Hyrimoz 2025, Ilaris 2025, Ilumya 2025, Imuldosa 2025, Inflectra 2025, Kevzara 2025, Kineret 2025, Orencia 2024, Otulfi 2025, Pyzchiva 2025, Remicade 2025, Renflexis 2025, Riabni 2025, Rituxan 2025, Ruxience 2025, Selarsdi 2025, Siliq 2024, Simlandi 2025, Simponi 2025, Simponi Aria 2025, Skyrizi 2025, Stelara 2026, Steqeyma 2025, Taltz 2024, Tofidence 2025, Tremfya 2025, Truxima 2025, Tyenne 2025, Wezlana 2026, Yesintek 2026, Yuflyma 2025, Yusimry 2025)

Table 3. FDA approved indications – Oral agents

Drug	RA	PJIA	PsO	PsA	AS	Alopecia Areata
Icotyde (icotrokinra)			✔ [c] (≥ 12 and ≥ 40 kg)			
Leqselvi (deuruxolitinib)[a]						✔
Litfulo (ritlecitinib)[a]						✔ (≥ 12)
Olumiant (baricitinib)[a]	✔ [b]					✔
Otezla/Otezla XR (apremilast)			✔ [c] (≥ 6)	✔ (≥ 6)		
Rinvoq (upadacitinib)[a]	✔ [b]	✔ [b] (≥ 2)		✔ [b] (≥ 2)	✔ [b]	
Rinvoq LQ (upadacitinib)[a]		✔ [b] (≥ 2)		✔ [b] (≥ 2)		
Sotyktu (deucravacitinib)			✔	✔		
Xeljanz/Xeljanz oral solution (tofacitinib)[a]	✔ [b]	✔ [b] (≥ 2)		✔ [b] (≥ 2)	✔ [b]	

Drug	RA	PJIA	PsO	PsA	AS	Alopecia Areata
Xeljanz XR (tofacitinib)[a]	✔ b	✔ b		✔ b	✔ b	

Abbreviations: RA = rheumatoid arthritis; PJIA = polyarticular juvenile idiopathic arthritis; PsO = plaque psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis.

[a] Not recommended for use in combination with other JAK inhibitors (Leqselvi, Litfulo, Olumiant, Rinvoq, Xeljanz), biologic immunomodulators or with potent immunosuppressants (eg, azathioprine, cyclosporine).

[b] Patients with moderately to severely active disease who have had an inadequate response or intolerance to ≥ 1 TNF blocker (Olumiant, Rinvoq, Xeljanz).

[c] In patients who are candidates for systemic therapy or phototherapy.

(*Prescribing information: Icotyde 2026, Leqselvi 2025, Litfulo 2025, Olumiant 2026, Otezla/Otezla XR 2025, Rinvoq/Rinvoq LQ 2025, Sotyktu 2026, Xeljanz/Xeljanz XR/Xeljanz oral solution 2026.*

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

Clinical Efficacy Summary

Rheumatoid arthritis (RA)

Abatacept

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20; defined as a 20% improvement over baseline in tender and swollen joint counts (#1 and #2), and a 20% improvement in 3 of the 5 remaining core data set measures of participant global assessment of pain, participant global assessment of disease activity, physician global assessment of disease activity, participant assessment of physical function, and acute phase reactant value) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (N = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (RCT; N = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).

Adalimumab

- Amjevita (adalimumab-atto) was compared with US-licensed Humira in patients with moderate to severe RA despite treatment with MTX in a randomized, double-blind, equivalence study *(Cohen et al 2017)*. Patients were randomized to Amjevita or adalimumab (40 mg) every 2 weeks. At week 24, the primary endpoint of ACR20 occurred in 74.6% and

72.4% of patients treated with Amjevita or Humira, respectively; because the 90% CI for risk ratio of ACR lay between 0.738 and 1.355, biosimilarity of Amjevita to Humira was established.

- Cyltezo (adalimumab-adbm) was compared to US-licensed Humira in patients with moderate to severe RA on stable MTX therapy (*Cohen et al 2018*). Patients (N = 645) were randomized to either 40 mg of Cyltezo or Humira every 2 weeks. The percentage of patients achieving ACR20 at Week 12 for the Cyltezo group was 67.0% vs 61.1% for the Humira reference product; the difference was 5.9 (90% CI, -0.9 to 12.7). At Week 24 the percentage of patients achieving ACR20 for Cyltezo was 69.0% vs 64.5% for the Humira reference product; the difference was 4.5 (95% CI, -3.4 to 12.5). Biosimilarity of Cyltezo to Humira was established.
- Hyrimoz was compared to US-licensed Humira in the ADMYRA trial in patients with moderate to severe RA who had an inadequate response to DMARDs (*Wiland et al 2020*). Patients (N = 353) were randomized to receive either 40 mg of Hyrimoz or Humira every other week. The primary outcome of change in Disease Activity Score-28 including high-sensitivity C-reactive protein (DAS28-CRP) score from baseline to Week 12 was -2.16 for Hyrimoz and -2.18 for the reference product; the least square means difference was 0.02 (95% CI, -0.24 to 0.27). Hyrimoz also demonstrated a comparable safety and immunogenicity profile to Humira.
- Hadlima was compared to US-licensed Humira in patients with moderate to severe RA despite treatment with MTX (*Weinblatt et a 2018a*). Patients (N = 544) were randomized to receive either 40 mg Hadlima or Humira once every other week for 24 weeks. The primary outcome of ACR20 response rate at Week 24 was found to be equivalent between patients treated with Hadlima and those treated with Humira (Hadlima, 72.4% vs Humira, 72.2%; difference, 0.1%, [95% CI, -7.83% to 8.13%]). Both agents were also well tolerated and had comparable safety, pharmacokinetic, and immunogenicity profiles.
  - Hadlima was also evaluated in a 24-week transition study in patients who switched from Humira to Hadlima (*Weinblatt et al 2018b*). Patients (N = 542) were initially randomized to receive Hadlima or Humira (40 mg SQ every other week); patients in the Humira group were then re-randomized at 24 weeks to continue with Humira or to switch to Hadlima up to week 52. The proportion of patients who achieved ACR20, ACR50, or ACR70 response at week 24 was maintained after the transition from Humira to Hadlima, and response rates were comparable across treatment groups.
- Hulio was compared to US-licensed Humira in patients with moderate to severe RA (*Genovese et al 2019*). Patients (N = 730) were randomized to receive 40 mg Hulio or Humira once every other week for 24 weeks. The primary outcome of patients achieving ACR20 at Week 24 was 74.1% for Hulio vs 75.7% for Humira; the 95% CI for the treatment difference was -7.9% to 4.7% and the 90% CI for the treatment difference was -7.3% to 3.6%. All CI values fell within their predefined equivalence margins. Hulio also demonstrated comparable safety and immunogenicity to Humira.
  - Hulio was also evaluated in a long-term safety extension trial (*Genovese et al 2020*). Patients (N = 645) were re-randomized 2:1, either remaining on the same study drug or switching to the other. Patients treated with Hulio or Humira for up to 2 years experienced equivalent levels of effectiveness, safety, and immunogenicity; single- or double-switching therapy had no impact on these outcomes.
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).

Certolizumab

- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab)

monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; p < 0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).

- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, p ≤ 0.05) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (N = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; p < 0.001). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; p < 0.001) (*Atsumi et al 2017*).

Golimumab

- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).
- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg IV every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; p < 0.001) (*Kremer et al 2010*). In the GO-FURTHER trial (N = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [p < 0.001]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).

Tocilizumab

- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).

- AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (Jones et al 2010).
- LITHE evaluated 1196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
- OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (*Smolen et al 2008*).
- TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008*).
- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1 TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (Emery et al 2008). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).

- Tyenne (tocilizumab-aazg) was compared to European Union-approved tocilizumab in patients with moderate to severe active RA who had an inadequate prior response to ≥ 1 DMARD (*Zubrzycka-Sienkiewicz et al 2024*). Patients (N = 604) were randomized to receive weekly SQ injections of either 162 mg of Tyenne or European Union-approved tocilizumab for 24 weeks. The least squares mean difference between groups in the change from baseline in the DAS28-ESR score at Week 24 was 0.01 (95% CI, -0.19 to 0.22). Biosimilarity of Tyenne to reference tocilizumab was established.
- Tofidence (tocilizumab-bavi) was compared to reference tocilizumab in a Phase 3, multicenter, double-blind, active-control, randomized trial in 621 patients with moderate to severe RA with inadequate response to MTX. For the primary endpoint at week 12, estimated ACR 20 response was 64.8% in the reference tocilizumab group vs 69% in the Tofidence treated group (difference, 4.1%; 95% CI, -3.6 to 11.9). In addition to efficacy, comparable pharmacokinetic and immunogenicity profiles were observed for the reference tocilizumab and Tofidence (*Leng et al 2024*).
- Avtozma (tocilizumab-anoh) was compared to European Union-approved tocilizumab in adult patients with moderate to severe active RA treated with MTX for ≥ 12 weeks. Patients received IV injections of 8mg/kg of Avtozma or European

Union-approved tocilizumab for 48 weeks. At week 24, patients on reference tocilizumab were re-randomized to continue the reference treatment or switched to Avtozma. The number of patients maintained on Avtozma, switched to Avtozma, and maintained on reference tocilizumab were 225, 110, and 109, respectively. At week 52, the mean change form baseline in DAS28-ESR score was -4.279, -4.376, and -4.231 in the Avtozma maintenance, Avtozma switched, and reference tocilizumab groups, respectively. Comparable and maintained efficacy, safety, and immunogenicity was established for Avtozma (*Burmester et al 2025*).

- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (N = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤ 4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (N = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be noninferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).

Sarilumab

- A Phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 RCTs has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (odds ratio [OR], 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2018).*

Tofacitinib

- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab.

Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019[a]*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.

Baricitinib

- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, Phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). Disease control with baricitinib was maintained at 3 years follow up with no new safety signals (*Smolen et al 2021*).

Upadacitinib

- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (N = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. Differences in clinical responses between upadacitinib and MTX were maintained for up to 5 years of treatment (*van Vollenhoven et al 2024*). In SELECT-MONOTHERAPY (N = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. A long-term extension of SELECT-MONOTHERAPY found that upadacitinib monotherapy maintained efficacy for up to 260 weeks (*Smolen et al* 2025). In SELECT-COMPARE, which evaluated MTX-IR patients (N = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p < 0.001$ and $p < 0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. Differences in clinical responses between upadacitinib and adalimumab were maintained for up to 5 years of treatment (*Fleischmann et al 2024*). In SELECT-BEYOND (N = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p < 0.0001$) *(Genovese et al 2018)*.
  - A network meta-analysis of the SELECT trials found that upadacitinib plus MTX was more effective than MTX alone, and upadacitinib 15 mg plus MTX was most likely to achieve the best ACR 20 response rate (followed by upadacitinib 30 mg plus MTX, adalimumab 40 mg plus MTX, upadacitinib 30 mg, upadacitinib 15 mg, and MTX, in order) (*Song and Lee 2020*).
- A 24-week, Phase 3, double-blind trial explored the efficacy of upadacitinib compared with abatacept in 612 patients with RA. The mean change in the DAS28-CRP was -2.52 in the upadacitinib group and -2.00 in the abatacept group

from baseline to week 12 (difference, -0.52 points; 95% CI, -0.69 to -0.35; p < 0.001 for noninferiority; p < 0.001 for superiority). Additionally, 30% of patients in the upadacitinib group and 13.3% of patients in the abatacept group achieved remission (difference, 16.8%; 95% CI, 10.4 to 23.2; p < 0.001 for superiority) (*Rubbert-Roth et al 2020*).

Infliximab

- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N = 606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
  - In the extension study (N = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized Phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints were also very similar between the 2 groups.
  - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Avsola (infliximab-axxq) was evaluated and compared to Remicade (infliximab) in 558 patients in a double-blind, multicenter, randomized equivalence trial (*Genovese et al 2020*). The primary endpoint, ACR 20 at week 22, was achieved by 68.1% and 59.1% of patients in the Avsola and Remicade groups, respectively (TD, 9.37%; 90% CI, 2.67% to 15.96%). The upper bound exceeded the pre-specified equivalence criteria by 0.96% such that superiority could not be ruled out statistically. In a post hoc analysis with adjustment for imbalances in baseline factors, the CI was narrowed (90% CI, 0.75% to 13.62%). Secondary endpoints were also very similar between the 2 groups.

Rituximab

- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life (QoL).
- In the open-label ORBIT study (N = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
  - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified noninferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was noninferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high

percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).

- Truxima (rituximab-abbs) was compared to Rituxan (rituximab) in 372 patients in a double-blind, multicenter, randomized Phase 3 trial (*Park et al 2018*). The primary efficacy endpoint, change from baseline in DAS28-CRP at week 24, was -2.13 and -2.09 for Truxima and Rituxan, respectively (TD, -0.04; 95% CI, -0.29 to 0.21). Equivalence was demonstrated between the 2 products. Secondary endpoints were also very similar between the 2 groups.
  - In an extension of this study, 330 patients received a second 24-week course of their assigned study drug (Truxima or Rituxan) (Suh et al 2019). Mean change in DAS28-CRP from baseline to week 48 was similar between groups (-2.7 and -2.6 for Truxima and Rituxan, respectively). ACR 20/50/70 responses were also similar between groups at week 48.
  - After week 48, 295 patients entered a second extension phase that continued until week 72; during this extension phase, patients who were previously receiving Truxima or Rituxan (European Union formulation) received Truxima, while patients who were previously receiving Rituxan (United States formulation) were randomized 1:1 to continue receiving Rituxan (United States formulation) or switch to Truxima (Shim et al 2019). All patients experienced similar improvements in disease activity parameters, including DAS28 and ACR response rates. Switching from Rituxan to Truxima did not result in any clinically meaningful efficacy differences.
- Riabni (rituximab-arrx) was compared to Rituxan (rituximab) in a double-blind, multicenter, RCT (*Burmester et al 2020*). The primary efficacy endpoint, change from baseline in DAS28-CRP at week 24, was -2.197 and -2.125 for Riabni and Rituxan, respectively (difference between means, -0.02%; 90% CI, -0.225 to 0.264). Equivalence was demonstrated between the 2 products.

Comparative Studies of Multiple Agents/Meta-analyses

- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (N = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
  - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months

when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).

- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine, and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
  - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
  - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016[b]*). A total of 41 randomized trials (N = 14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (N = 3364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.

  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- A Bayesian network meta-analysis of 5 randomized trials (N = 1547) examined the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib (not approved in the U.S.) and peficitinib (not approved in the U.S.) in patients with RA. The ranking probability based on SUCRA revealed the following agents with the highest probability to achieve the ACR 20 response rate: peficitinib 150 mg (highest probability) followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo *(Ho Lee at al 2020)*.
- A meta-analysis of 20 randomized trials (N = 8982) assessed the efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib 10 mg (RR, 2.48; 95% CI, 1.97 to 3.14; $p < 0.001$) had to the highest ACR20 response rates followed by tofacitinib 5 mg (RR, 2.16; 95% CI, 1.81 to 2.58; $p < 0.001$). Tofacitinib displayed higher ACR 20 response rates compared with baricitinib and upadacitinib (*Wang et al 2020*).
- Another recent Cochrane review (*Hazelwood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- A network meta-analysis of individual patient data from 38 RCTs compared various MTX-biologic combinations for RA in patients with an inadequate response to MTX alone (*Janke et al 2020*). Anakinra plus MTX showed relatively less benefit than other combinations in terms of clinical remission or low disease activity, and certolizumab plus MTX showed relatively higher rates of serious AEs or infections; however, differences between combinations were generally minor.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of RCTs included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The OR for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept, and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept, and 4.14 (95% CI, 2.42 to 7.46) with infliximab compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class

showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; p < 0.05) (*Nixon et al 2007*).

- The Agency for Healthcare Research and Quality published a review (now archived) of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (N = 1927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.
- A meta-analysis investigated the relative efficacy and safety profiles of tofacitinib, baricitinib, upadacitinib, and filgotinib (not approved in the US) in patients with active RA refractory to biologics (*Lee et al 2021*). The ranking probability based on the SUCRA suggested that upadacitinib had the highest probability of being the best treatment for achieving ACR 20, followed by filgotinib (200 mg), baricitinib, filgotinib (100 mg), and tofacitinib. For achievement of ACR 50, the SUCRA suggested that baricitinib was the best treatment, followed by filgotinib (200 mg), tofacitinib, upadacitinib, and filgotinib (100 mg). Tofacitinib was superior to filgotinib (100 mg) and upadacitinib for achievement of ACR 70. Tofacitinib and filgotinib (200 mg) showed a significantly lower serious adverse event rate than upadacitinib.
- A network meta-analysis of 42 studies was conducted to find the optimal treatment (based on the efficacy and safety rankings of each drug) in patients with RA whose disease activity remained uncontrolled despite the use of ≥ 2 conventional synthetic, biologic, or targeted synthetic DMARDs. Tocilizumab 8 mg every 4 weeks demonstrated the best efficacy, followed by sarilumab 200 mg every 2 weeks and baricitinib 4 mg daily, compared with placebo. Based on AEs, rituximab was generally determined to be the safest drug (*Su et al 2024*).
- Persistence of efficacy at 5 years in patients with RA was evaluated in an exploratory meta-analysis of 29 studies of second-line treatment with biological DMARDs including adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, tocilizumab, abatacept, rituximab, sarilumab, and infliximab-dyyb. Tocilizumab had the highest persistence (66%, 95% CI 60 to 72), followed by golimumab (62%, 95% CI 47 to 75) and abatacept (59%, 95% CI 38 to 77) (*Schneeberger et al 2026*)

Ankylosing spondylitis (AS)

Adalimumab

- The FDA approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (N = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; p < 0.001). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness that is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients (p < 0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (p < 0.001) (*van der Heijde et al 2006*).

Etanercept

- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo (p < 0.001) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo (p < 0.001) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response, and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache, and diarrhea. A total of 71% of patients

were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).

Golimumab

- The FDA approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (N = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.

Infliximab

- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$) (*Braun et al 2002*). At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$) (*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (N = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
  - In the extension study (N = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.

Certolizumab

- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (N = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis, which includes AS (*Sieper et al 2015b*).

Secukinumab

- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with SQ secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150

mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).

- The efficacy and safety of IV secukinumab in adults with active AS, including both radiographic and nonradiographic forms, was evaluated in the randomized, double-blind INVIGORATE-1 trial. A total of 526 patients were randomized in a 1:1 ratio to receive either IV secukinumab at 6 mg/kg at baseline, followed by 3 mg/kg every 4 weeks, or IV placebo, for an initial 16-week period. At week 16, placebo recipients were switched to secukinumab, and secukinumab recipients continued their regimen through week 52. At week 16, 40.9% of the secukinumab group achieved ASAS 40 (primary outcome) compared to 22.9% in the placebo group ($p < 0.0001$). Patients who transitioned from placebo to secukinumab at week 16 attained ASAS 40 responses by week 24 that were comparable to those initially assigned to secukinumab. Clinical responses were maintained through week 52. The safety profile of IV secukinumab was consistent with existing data on its SQ formulation (*Deodhar et al 2025*).

Ixekizumab

- The efficacy and safety of Taltz (ixekizumab) were evaluated in the Phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, including biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common AEs included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The ASAS 40 response seen at week 16 was sustained through week 52 in both trials and through 3 years in 1 trial (*Dougados et al 2020, van der Heijde et al 2022[a]*).

Tofacitinib

- Efficacy and safety of Xeljanz (tofacitinib) in AS were assessed in a placebo-controlled, randomized, double-blind trial in 269 patients with active disease *(Deodhar et al 2021)*. Patients were randomized to double-blind tofacitinib 5 mg twice daily or placebo for 16 weeks, followed by an additional 32 weeks of treatment with tofacitinib 5 mg twice daily in all patients. The primary endpoint of ASAS 20 response at week 16 was significantly improved in patients treated with tofacitinib compared with placebo (56% vs 29%, respectively; $p < 0.0001$).

Upadacitinib

- Efficacy and safety of Rinvoq (upadacitinib) in AS were assessed in 2 RCTs, SELECT-AXIS 1 and SELECT-AXIS 2 (*van der Heijde et al 2019[b]; van der Heijde et al 2022[b]*). SELECT-AXIS 1 randomized 187 biologic-naïve patients with active AS to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (52% vs 26%; $p = 0.0003$) (*van der Heijde et al 2019[b]*). Clinical response was maintained for up to 2 years in the open label extension phase of SELECT-AXIS 1 (*van der Heijde et al 2022[c]*). SELECT-AXIS 2 randomized 420 patients with active AS and inadequate response to biologic DMARDs to receive upadacitinib 15 mg daily or placebo and found that more patients in the upadacitinib group achieved an ASAS 40 response at week 14 (45% vs 18%; $p < 0.0001$) (*van der Heijde et al 2022[b]*). An open-label extension of the SELECT-AXIS 2 trial (N = 366) indicated ASAS 40 response rates continued to improve through week 52 follow-up with upadacitinib (66%) (*Baraliakos et al 2023*). Likewise, upadacitinib continued to show sustained improvement in ASAS 40 response rates in an open-label extension through week 104 (n = 331) (*Baraliakos et al 2024[b]).*

Bimekizumab

- The efficacy and safety of Bimzelx (bimekizumab) in AS were assessed in a randomized, double-blind, placebo-controlled trial in 332 patients with active disease. Patients were randomized 2:1 to receive bimekizumab 160 mg or placebo every 4 weeks for 16 weeks; from week 16, all patients received bimekizumab 160 mg every 4 weeks up to week 52. The primary endpoint of ASAS 40 response at week 16 was significantly improved in patients treated with bimekizumab compared with placebo (44.8% vs 22.5%, respectively; $p < 0.001$). Improvements were sustained to week

52 in patients treated with bimekizumab (*Baraliakos et al 2024[a]*). An open-label extension of this trial found sustained improvements through week 104, with no new safety concerns (Baraliakos et al 2025).

Comparative Trials/Meta-analyses

- Secukinumab and adalimumab were compared for their effects on spinal radiographic progression in biologic-naive patients with active radiographic AS in the SURPASS study. Eligible patients were at high risk for radiographic progression, defined by high-sensitivity C-reactive protein (hsCRP) levels ≥ 5 mg/L and/or the presence of ≥ 1 syndesmophyte(s) on baseline spinal radiographs. A total of 859 patients were randomized in a 1:1:1 ratio to receive secukinumab 150 mg, secukinumab 300 mg, or an adalimumab biosimilar 40 mg. The primary endpoint was the proportion of patients with no radiographic progression at week 104, defined as a change from baseline in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) ≤ 0.5. At week 104, 66.1% of patients in the secukinumab 150 mg group, 66.9% in the secukinumab 300 mg group, and 65.6% in the adalimumab group met the primary endpoint (p=not significant). Mean change in mSASSS from baseline was 0.54, 0.55, and 0.72, respectively. Among patients with ≥ 1 syndesmophyte at baseline, 56.9% in the secukinumab 150 mg group, 53.8% in the secukinumab 300 mg group, and 53.3% in the adalimumab group had no new syndesmophyte formation at week 104 (*Baraliakos et al 2024[c]*).
- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.
- A Bayesian network meta-analysis of 6 RCTs compared upadacitinib, secukinumab, tofacitinib, and filgotinib (not approved in the US) for the treatment of AS and found no statistically significant difference in ASAS response rates between these agents (*Lee 2022*).

Hidradenitis suppurativa (HS)

Adalimumab

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Secukinumab

- Two identical Phase 3, double-blind, double-dummy, multicenter, placebo-controlled randomized trials, SUNSHINE and SUNRISE, evaluated secukinumab for the treatment of HS. Adults with a ≥ 1-year history of moderate-to-severe HS were randomized 1:1:1 to receive secukinumab 300 mg every 2 or 4 weeks (following initiation with 5 weekly doses in both groups) or placebo; after the first 16 weeks of treatment, patients initially randomized to placebo were re-randomized to 1 of the secukinumab groups. Treatment continued through week 52. The primary endpoint was clinical response, defined as a ≥50% decrease in abscess and inflammatory nodule count without an increase in the number of abscesses or draining fistulae relative to baseline, at week 16. Approximately 24% of patients had previously received biologic therapy. In the SUNRISE trial, more patients had severe disease in the secukinumab 2 weeks group compared to the other 2 treatment groups. Overall, the primary endpoint was met in the secukinumab 2 weeks group for both trials; the primary endpoint was not met for the secukinumab 4 weeks group in the SUNSHINE trial. However, in both trials, the clinical efficacy observed at 16 weeks was sustained through week 52 (*Kimball et al 2023*).
  - In the SUNSHINE trial, among 541 patients included, secukinumab every 2 weeks led to clinical response in 45% compared with 34% of placebo recipients (OR, 1.8; 95% CI, 1.1 to 2.7; p = 0.007) at 16 weeks, whereas no significant difference was noted in the secukinumab every 4 weeks group (42%; OR, 1.5; 95% CI, 1.0 to 2.3; p = 0.042) relative to placebo.
  - In the SUNRISE trial, among 543 patients included, secukinumab every 2 weeks and every 4 weeks led to clinical response in 42% (OR 1.6 vs placebo; 95% CI, 1.1 to 2.6; p = 0.015) and 46% (OR 1.9 vs placebo; 95% CI, 1.2 to 3.0; p = 0.0022), respectively, at 16 weeks.
  - Improvements in health-related quality of life (as assessed by DLQI) was also demonstrated in both studies for both secukinumab groups compared with placebo at 16 weeks and sustained up to week 52.
  - At week 52, patients who completed SUNSHINE or SUNRISE were eligible to enroll in a long-term extension study. Patients who were responders at week 52 were randomized to continue their secukinumab regimen (every 2 weeks or every 4 weeks) or switch to placebo from week 52 to week 104. The primary endpoint was time to loss of response through week 104; loss of response was defined as a ≥ 50% increase in abscess and inflammatory nodule count at any visit and an increase ≥ 3 in abscess and inflammatory nodule count vs the average of the previous 3 visits or vs the week 52 visit (whichever was lower). The primary endpoint was not met for either secukinumab dosing regimen. The estimated risk reduction for loss of response was 13% for patients treated with secukinumab every 2 weeks (hazard ratio, 0.87; 95% CI, 0.59 to 1.29; p = 0.25) and 30% for patients treated with secukinumab every 4 weeks (hazard ratio, 0.70; 95% CI, 0.47 to 1.05; p = 0.04) (*Kimball et al 2025*).

Bimekizumab

- The FDA approval of Bimzelx (bimekizumab-bkzx) for the treatment of HS was based on data from 2 identical Phase 3, double-blind studies, BE HEARD I (N = 505) and BE HEARD II (N = 509). Patients were randomized 2:2:2:1 to bimekizumab 320 mg every 2 weeks; bimekizumab 320 mg every 2 weeks to week 16 followed by every 4 weeks to week 28; bimekizumab 320 every 4 weeks to week 48; or the placebo to week 16 followed by bimekizumab 320 every 2 weeks. The primary outcome was an HS clinical response of at least 50% at week 16, which was met in the patients who received bimekizumab every 2 weeks (*Kimball et al 2024*).
  - In BE HEARD I, 138/289 (48%) in the bimekizumab every 2 weeks group versus 21/72 (29%) in the placebo group (OR, 2.23; 97.5% CI, 1.16 to 4.31; p = 0·0060).
  - In BE HEARD II, 151/291 (52%) in the bimekizumab every 2 weeks group vs 24/74 (32%) in the placebo group met HiSCR50 (OR, 2.29; 97.5% CI, 1.22 to 4.29; p=0·0032). The primary endpoint was also met in the bimekizumab every 4 weeks group vs placebo in BE HEARD II only (54% vs 32%; OR, 2.42; 97.5% CI, 1.22 to 4.80; p = 0.0038).

Meta-analyses

- The relative efficacy and safety of FDA-approved regimens for HS was evaluated in a network meta-analysis of 16 randomized trials reporting 16-week efficacy outcomes. Efficacy outcomes included HiSCR-50, Dermatology Life Quality Index (DLQI), and Numeric Rating Scale 30 (NRS30). The efficacy of FDA-approved regimens for bimekizumab, adalimumab and secukinumab (every 4 week and every 2-week regimen) were not significantly different in terms of HiSCR-50 and NRS30. Vimekizumab demonstrated significant improvement compared to adalimumab in DLQI (mean difference – 0.85, 95% CI -1.22 to -0.47, p<0.05) (*Gupta et al 2025*).

Juvenile idiopathic arthritis (JIA)

Abatacept

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).

Adalimumab

- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).
- A double-blind, multicenter, RCT compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with ERA (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo, -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.

Etanercept

- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; CRP levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).

Tocilizumab

- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (N = 112). Children aged 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001) (*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024). Disease control with tocilizumab was maintained at 2 years follow up with no new safety signals (*Brunner et al 2021*).

Golimumab

- The approval of Simponi Aria (IV golimumab) for polyarticular JIA was based on an open-label Phase 3 study (N = 127). Children 2 to < 18 years of age with active polyarticular course JIA and inadequate response to MTX were enrolled. The primary endpoints were pharmacokinetic exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52. Other endpoints included ACR response rates. The ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70%, and 47%, respectively, at week 28. Golimumab serum concentrations and AUC_{ss} were 0.40 mcg/mL and 399 mcg•day/mL at week 28. ACR response rates, serum concentrations, and AUC_{ss} were maintained at week 52 (*Ruperto et al 2021[a]*).
  - Long-term extension study results with continued golimumab treatment demonstrated the following response rates at week 116 (*Brunner et al 2024*):
    - JIA-ACR30: 72.4%

- JIA-ACR50: 71.7%
- JIA-ACR70: 63.8%
- JIA-ACR90: 50.4%
- No more than minimal pain (VAS <35 mm): 33.9%
- Normal physical function (CHAQ-DI score of 0): 29.1%

Upadacitinib

- The approval of Rinvoq/Rinvoq LQ (upadacitinib) for polyarticular JIA in patients aged 2 years or older is based on exposure-matched extrapolation from efficacy trials of upadacitinib in RA, and a multicenter, open-label, single arm safety and efficacy analysis conducted in 83 children with JIA with active polyarthritis. Efficacy in these analyses was generally consistent with responses in patients with RA (*Rinvoq/Rinvoq LQ prescribing information 2025*).

Tofacitinib

- The approval of Xeljanz/Xeljanz oral solution (tofacitinib) for polyarticular JIA was based on a 44-week study (N = 225) that enrolled patients 2 to 17 years old with polyarticular course JIA and inadequate responses to at least 2 DMARDs. The primary endpoint was the occurrence of disease flare at week 44. Compared with patients receiving placebo, patients receiving tofacitinib experienced significantly fewer disease flares (31% with tofacitinib vs 55% with placebo; difference in proportions -25% [95% CI, -39% to -10%]; p = 0.0007) (*Xeljanz prescribing information 2025, Ruperto et al 2021[b]*).

Certolizumab

- The approval of Cimzia (certolizumab) for polyarticular JIA was based on pharmacokinetic exposure and extrapolation of established efficacy in patients with RA. The efficacy of certolizumab was also assessed in an open-label study in patients 2 to 17 years of age (N = 193) with JIA with active polyarthritis with an inadequate response or intolerance to ≥ 1 DMARD (nonbiologic or biologic). Of the 193 patients, 105 received the recommended dose. Patients had the following subtypes of JIA: polyarthritis rheumatoid factor-positive (20%), polyarthritis rheumatoid factor-negative (44.8%), extended oligoarthritis (13.3%), juvenile PsA (4.8%), and ERA (19%). Patients could be on stable MTX, glucocorticoids, and/or NSAIDs. Efficacy was assessed as secondary endpoints through 24 weeks of treatment, and was generally consistent with responses in patients with RA (*Cimzia prescribing information 2024*).

Canakinumab

- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).

Meta-analyses

- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.
- A Cochrane review of 9 studies (N = 678) examined the efficacy of TNF inhibitors in patients with JIA and found that TNF inhibitors may result in a higher proportion of patients achieving clinical improvement compared to placebo; however, the effects of TNF inhibitors on pain, function, and quality of life compared to placebo were uncertain. The effects of TNF inhibitor plus MTX on clinical improvement and remission versus MTX alone were also uncertain (*Cagnotto et al 2025a*).

Plaque psoriasis (PsO)

Adalimumab

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX ($p < 0.001$) and placebo ($p < 0.001$) groups, respectively (*Saurat et al 2008*).
- Amjevita (adalimumab-atto) was compared with US-licensed Humira in a randomized, double-blind, multicenter study in patients with moderate to severe psoriasis and intolerance or non-response to ≥ 1 conventional systemic therapy *(Papp et al 2017[a])*. At week 16, the primary endpoint of PASI change from baseline was within the predefined equivalence margin of ± 15 (least-squares mean difference, -2.18; 95% CI, -7.39 to 3.02), demonstrating similarity of Amjevita to Humira.
  - At week 16, patients treated with Amjevita who had ≥ 50% improvement in the PASI score continued Amjevita, whereas Humira-treated patients were rerandomized to either Amjevita or Humira *(Papp et al 2017[b])*. At up to 52 weeks of treatment, patients who were rerandomized to transition from Humira to Amjevita achieved similar improvement in PASI scores as those who continued treatment with Humira.
- Cyltezo (adalimumab-adbm) demonstrated interchangeability to Humira (adalimumab) in the VOLTAIRE-X trial (*Menter et al 2022*). The double-blind, active comparator RCT incorporated a 14-week run-in period with Humira that was followed by a period of 34 weeks where adult patients with moderate to severe chronic PsO randomly received either continuous Humira (n = 120) or switched back and forth from Humira to Cyltezo (n = 118). The trial demonstrated that primary and secondary pharmacokinetic outcomes were equivalent between agents, there was no difference in safety or immunogenicity between agents, and clinical outcomes (eg, PASI scores) were highly similar between the continuous Humira group and the switching group.
- Hyrimoz (adalimumab-adaz) was compared to US-licensed Humira in patients with moderate to severe PsO in the ADACCESS trial (*Blauvelt et al 2018*). Patients (N = 465) were randomized to receive either 80 mg Hyrimoz or the Humira reference product followed by 40 mg every other week. Patients who had achieved at least 50% improvement in PASI at Week 16 were randomized at Week 17 to continue initial treatment or undergo alternating treatment switches until Week 35; the study also included an extension period from Weeks 35 to 51. Biosimilarity was established between Hyrimoz and Humira for the primary outcome of PASI 75 response at Week 16 (Hyrimoz, 66.8% vs reference product, 65.0%; difference, 1.8% ± 4.75 [95% CI, -7.46 to 11.15]) along with key secondary endpoints, safety, pharmacokinetic, and immunogenicity parameters.
- Adalimumab-aacf was compared to US-licensed Humira in patients with chronic moderate to severe PsO in the AURIEL-PsO trial (*Hercogova et al 2020*). Patients (N = 443) were randomized to receive an initial dose of 80 mg of adalimumab-aacf or the Humira reference product followed by 40 mg every other week. The primary outcome of PASI 75 response at Week 16 was 89.7% for adalimumab-aacf vs 91.6% for Humira; the difference was -1.9% (95% CI, -7.82 to 4.07). There were no clinically meaningful differences in safety or immunogenicity seen between treatment groups. Biosimilarity was established between adalimumab-aacf and Humira.
- Yusimry (adalimumab-aqvh) was compared to US-licensed Humira in patients with chronic moderate to severe PsO in the PsOsim trial (*Yusimry FDA Multi-Discipline Review 2021*). Patients (N = 545) were randomized to an initial dose of 80 mg of Yusimry or the Humira reference product followed by 40 mg every other week. The primary efficacy outcome of percentage change in PASI from baseline to Week 16 was -83.1% for Yusimry vs -82.3% for the reference product; the estimated difference was -0.9% (90% CI, -4.78% to 3.01%) which was contained within the FDA recommended margins. No meaningful clinical differences between treatment groups were found.
- Simlandi (adalimumab-ryvk) was compared to US-licensed Humira in a Phase 3, multicenter, double-blind, parallel-group, randomized, trial in 413 patients with moderate to severe chronic PsO. The primary efficacy outcome of percentage improvement in PASI score from baseline to Week 16 was 91.6% for Simlandi vs 89.6% for Humira (95% CI, which was contained within the FDA recommended margins (± 10%). Efficacy continued through week 50 of the in all treatment groups, including those who switched from originator Humira to Simlandi (*Feldman et al 2021*). No new clinical or safety information was included in the interchangeability application in 2023 (*Simlandi FDA Multi-Discipline Review 2024*).

Ustekinumab

- More than 2200 patients were enrolled in 2 published, pivotal, Phase 3 trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg, or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi*

et al 2008, Papp et al 2008, Langley et al 2015). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 ($p < 0.0001$ for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 ($p < 0.0001$) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo ($p < 0.0001$). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).

- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Imuldosa (ustekinumab-srlf) was compared to EU-licensed ustekinumab in adult patients with moderate-to-severe PsO (*Imuldosa FDA Multi-Discipline Review 2024*). Patients (N = 598) were randomized in a 1:1 ratio to receive either ustekinumab or Imuldosa at weeks 0, 4, and 16. Prior to week 28, patients initially assigned to reference ustekinumab were re-randomized in a 1:1 ratio to continue reference ustekinumab or switch to Imuldosa; patients receiving Imuldosa continued Imuldosa. Additional doses of the assigned treatment were given at weeks 28 and 40. The primary endpoint was the percent change in PASI score from baseline to week 12. Mean percent improvement in PASI score at week 12 was equivalent between Imuldosa and ustekinumab (mean difference, -0.17%; 90% CI, -2.05% to 1.7%).
- Otulfi (ustekinumab-aauz) was compared to EU-licensed ustekinumab in adult patients with moderate-to-severe PsO and inadequate response or intolerance to ≥ 1 previous systemic treatment for PsO (*Papp et al 2025*). Patients (N = 392) were randomized to receive either ustekinumab or Otulfi 45 mg at weeks 0, 4, and 16; the primary outcome was the percent improvement in PASI score from baseline to week 12. Mean percent improvement in PASI score at week 12 was equivalent between Otulfi and ustekinumab (least squares mean difference, 3.27%; 95% CI, -0.9% to 7.44%).
- Pyzchiva (ustekinumab-ttwe) was compared to reference product ustekinumab in adult patients with moderate-to-severed PsO (*Feldman et al 2024a, Feldman et al 2024b*). Patients (N = 503) were randomized to receive a weight-based dose of either ustekinumab or Pyzchiva at weeks 0, 4, and every 12 weeks thereafter until week 40. The main study period lasted through week 28; the primary endpoint was the percent change in PASI score from baseline to week 12. Mean percent change in PASI score at week 12 was equivalent between Pyzchiva and ustekinumab (mean difference, -0.6%; 95% CI, -3.78% to 2.579%). At week 28, patients initially randomized to Pyzchiva continued treatment, while patients initially randomized to reference ustekinumab were re-randomized in a 1:1 ratio to continue reference ustekinumab or switch to Pyzchiva. The percent change in PASI score from baseline through week 52 was comparable across groups (95.8% for patients on Pyzchiva, 95.6% for patients who switched between treatments, and 94.5% for patients on reference ustekinumab).
- Selarsdi (ustekinumab-aekn) was compared to EU-licensed ustekinumab in adult patients with moderate to severe PsO and inadequate response or intolerance to ≥ 1 previous systemic treatment for PsO (*Feldman et al 2023*). Patients (N = 581) were randomized in a 1:2 ratio to receive a weight-based dose of either Selarsdi or reference ustekinumab at weeks 0 and 4. Prior to week 16, patients initially assigned to reference ustekinumab were re-randomized in a 1:1 ratio to continue reference ustekinumab or switch to Selarsdi; patients receiving Selarsdi continued Selarsdi. Additional doses of the assigned treatment were given at weeks 16, 28, and 40. The primary endpoint was the percent improvement in PASI score from baseline to week 12. Mean percent improvement in PASI score at week 12 was equivalent between Selarsdi and ustekinumab (mean difference, 0.4%; 90% CI, -2.14% to 3.01%). Efficacy measures remained comparable between patients who received reference ustekinumab, patients who switched treatments, and patients who received Selarsdi through the end of the study at week 52.

- Steqeyma (ustekinumab-stba) was compared to EU-licensed ustekinumab in adult patients with moderate-to-severe PsO (*Papp et al 2024*). Patients (N = 509) were randomized to receive a weight-based dose of either ustekinumab or Steqeyma at weeks 0 and 4. Prior to week 16, patients initially assigned to reference ustekinumab were re-randomized in a 1:1 ratio to continue reference ustekinumab or switch to Steqeyma; patients receiving Steqeyma continued Steqeyma. Additional doses of the assigned treatment were given at weeks 16, 28, and 40. The primary endpoint was the percent improvement in PASI score from baseline to week 12. Mean percent improvement in PASI score at week 12 was equivalent between Steqeyma and ustekinumab (mean difference, 2.05%; 90% CI, -0.23% to 4.32%). At week 28, efficacy measures remained comparable between patients who received reference ustekinumab, patients who switched treatments, and patients who received Steqeyma.
- Wezlana (ustekinumab-auub) was compared to reference ustekinumab in adult patients with moderate-to-severe PsO and inadequate response or intolerance to ≥ 1 previous systemic treatment for PsO (*Blauvelt et al 2025*). Patients (N = 563) were randomized to receive a weight-based dose of either ustekinumab or Wezlana at weeks 0, 4, and 16; the primary outcome was the percent improvement in PASI score from baseline to week 12. Mean percent improvement in PASI score at week 12 was equivalent between Wezlana and ustekinumab (mean difference, 0.14%; 90% CI, -2.6% to 2.9%).

Apremilast (oral)

- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a PASI 75 response. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; p < 0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; p < 0.0001) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
  - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on HRQoL, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (Rich et al 2016), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Otezla (apremilast) received approval for treatment of moderate-to-severe PsO in pediatric patients aged 6 years and older weighing 20 kg or more based on the results from the Phase 3, multicenter, randomized, double-blind, placebo-controlled SPROUT trial. In this trial, 235 patients aged 6 to 17 years with moderate to severe PsO were randomized to receive apremilast (after a 7-day titration period), dosed at 20 mg twice daily for patients weighing 20 to < 50 kg or 30 mg twice daily for patients weighing ≥ 50 kg, or placebo. The primary endpoint was the proportion of patients achieving static Physician's Global Assessment (sPGA) response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. More patients receiving apremilast achieved a sPGA response at week 16 compared to placebo (33.1% vs 11.5%; p < 0.0001) (*Fiorillo et al 2024*).
  - 52-week results: 186 patients completed treatment with apremilast. The primary outcome of sPGA response was observed in 47.7% in those who maintained apremilast treatment and reached 44.4% in patients switched from placebo to apremilast. Approximately 60% of patients achieved PASI 75 in both groups (*Paller et al 2025*).
- Otezla (apremilast) has additionally been studied in patients with moderate to severe PsO of the scalp in the Phase IIIb, double-blind, randomized, placebo-controlled STYLE trial. In this trial, 303 patients with moderate to severe scalp PsO who had an inadequate response to 1 or more topical scalp therapies were randomized 2:1 to receive apremilast 30 mg twice daily (with a titration period) or placebo for 16 weeks. The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. Patients receiving apremilast were more likely to achieve ScPGA response at week 16 (43.3% vs 13.7%; p < 0.0001) (*Van Voorhees et al 2020*).

- Otezla (apremilast) has also been studied in patients with mild to moderate PsO in a double-blind, placebo-controlled study *(Stein Gold et al 2022)*. Patients with inadequate response or intolerance to ≥ 1 topical therapy (N = 595) were randomized to apremilast 30 mg twice daily or placebo. At week 16, the primary endpoint of static Physician Global Assessment response was significantly greater with apremilast compared with placebo (21.6% vs 4.1%; p < 0.0001).

Secukinumab

- Cosentyx (secukinumab) was evaluated in 2 large, Phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
  - In ERASURE (N = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
  - In FIXTURE (N = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, Phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
  - In FEATURE (N = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
  - In JUNCTURE (N = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, RCT in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; p < 0.0001) and modified IGA score of 0/1 (72.3% vs 55.3%; p < 0.0001) (*Bagel et al 2018*). The significant trend of benefit for secukinumab over ustekinumab was maintained at 52 weeks with no new safety signals (*Bagel et al 2021*).
- The efficacy of Cosentyx (secukinumab) in children 6 years of age and older with moderate to severe PsO was established in a multicenter, randomized, double-blind, active-controlled trial that enrolled 162 patients (*Bodemer et al 2021*). Patients were randomized to secukinumab low- or high-dose groups, etanercept, or placebo. In the secukinumab groups, patients with body weight < 25 kg received 75 mg (categorized as both low-dose [LD] and high-dose [HD] for this weight range), those with body weight 25 to < 50 kg received either 75 mg (LD) or 150 mg (HD), and those with body weight ≥ 50 kg received either 150 mg (LD) or 300 mg (HD). There was a significant trend of benefit in favor of LD and HD secukinumab over placebo for PASI 75 at week 12 (80.0% and 77.5%, respectively vs 14.6%; p < 0.0001 for both comparisons to placebo) and IGA score improvement to 0 or 1 (70% and 60%, respectively, vs 4.9%; p < 0.0001 for both comparisons to placebo). Statistical significance in favor of LD and HD secukinumab was also reached for comparisons to etanercept with regard to IGA score improvement to 0 or 1 (70% and 60%, respectively vs 34.1%; p < 0.05) and PASI 90 (72.5% and 67.5% vs 29.3%; p < 0.05).

- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.

Ixekizumab

- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
  - UNCOVER-1 (N = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
  - UNCOVER-2 (N = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - UNCOVER-3 (N = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-Q study (N = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, $p < 0.001$) (*Ryan et al 2018*).
- The IXORA-S study (N = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted $p < 0.05$).

- The IXORA-R study (N = 1027) compared Taltz (ixekizumab) to Tremfya (guselkumab) in adults with moderate-to-severe PsO (*Blauvelt et al 2021*). At week 24, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 (50% vs 52%, respectively; difference, -2.3%; 95% CI, -8.4 to 3.8 [within the 11.4% noninferiority margin]); statistical significance was not reached for this comparison (p = 0.41).

Brodalumab

- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
  - AMAGINE-1 (N = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).
  - AMAGINE-2 (N = 1831) and AMAGINE-3 (N = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
    - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab). After week 52, patients receiving ustekinumab or placebo were switched to brodalumab and treatment was continued to week 120 (*Puig et al 2020*). At 120 weeks, 84.4%, 75.6%, and 61.1% of patients achieved PASI 75, PASI 90, and PASI 100, respectively, with brodalumab treatment.
    - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.007 for brodalumab 140 mg vs ustekinumab).
    - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA

success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

Guselkumab

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, NAVIGATE, and ECLIPSE trials. All were Phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (N = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p < 0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$). In a long-term extension of this study, PASI and IGA response rates were maintained to week 204 with continuous guselkumab treatment (*Griffiths et al 2022*).
    - In VOYAGE 2 (N = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
  - In NAVIGATE (N = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2018*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to blinded guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; $p < 0.001$). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; $p = 0.001$). At week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group ($p \leq 0.001$).
  - In ECLIPSE (N = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$). The proportion of patients with adverse events, infections, and serious AEs were similar between the treatments.

Tildrakizumab

- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, Phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1090 patients). Enrolled adult patients with moderate-to-severe chronic PsO received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017[a]*).

  - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons).
  - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons). A higher proportion of patients in the tildrakizumab 100 mg group achieved PASI 75 vs etanercept (61% vs 48%, respectively; p = 0.001), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; p = 0.0663).
- Ilumya (tildrakizumab-asmn) was studied in patients with moderate to severe PsO of the scalp in a Phase 3b, double-blind, randomized, placebo-controlled trial. Patients received treatment with tildrakizumab-asmn 100 mg or placebo. At week 16, the proportion of patients achieving an IGA scalp response (primary endpoint) was 49.4% vs 7.3% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.00001) (*Gebauer et al 2024*). Clinical efficacy was maintained for up to 52 weeks of treatment (*Sofen et al 2025*).

Risankizumab

- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (N = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; p < 0.0001 for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (N = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) (p < 0.0001) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (N = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients (p < 0.001) at week 16 (*Langley et al 2019*).
- The Phase 3 IMMerge randomized noninferiority trial compared Skyrizi (risankizumab) 150 mg (n = 164) and Cosentyx (secukinumab) 300 mg (n = 163) in patients with moderate to severe PsO (*Warren et al 2021[b]*). Risankizumab demonstrated noninferiority to secukinumab in the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively; difference, 8.2%; 96.25% CI, -2.2 to 18.6 [within the 12% noninferiority margin] and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; difference, 29.8%; 95% CI, 20.8 to 38.8; p < 0.001).
- The LIMMitless open-label extension trial is enrolling participants of earlier phase 3 trials of Skyrizi (risankizumab) for PsO. In an interim analysis of 897 patients with median risankizumab exposure of 5.3 years, 5-year rates of PASI 90 and PASI 100 response were > 85% and > 52%, respectively, and mean change from baseline PASI was ≥ 95% from weeks 28 to 256 (*Papp et al 2023*).
  - Week 304 response rates (n=661 patients) (*Papp et al 2025*):
    - PASI 90: 86%
    - PASI 100: 54.2%
    - sPGA 0/1: 84.7%
    - DLQI 0/1: 76.3%
- In a Phase 4, randomized, open-label, assessor-blinded trial (IMMpulse), Skyrizi (risankizumab) was compared to apremilast for the treatment of PsO. Adults with a ≥ 6-month history of moderate PsO were randomized 1:2 to receive risankizumab 150 mg SQ at weeks 1 and 4 followed by every-12-week dosing or apremilast 30 mg orally twice daily. At week 16, patients initially assigned to apremilast were re-randomized 1:1 to receive risankizumab (following the dosing schedule above) or to continue apremilast (*Stein Gold et al 2023).*
  - In the initial treatment period (through week 16), of 352 patients randomized, 55.9% (risankizumab) vs 5.1% (apremilast) achieved the primary endpoint of PASI 90 response (p < 0.001). Continuation of initially assigned treatment after week 16 resulted in 73.7% of risankizumab patients vs 4.5% of apremilast patients achieving PASI 90 response at week 52.
  - Patients initially assigned to apremilast who were re-randomized to risankizumab were more likely to achieve PASI 90 response at 52-week follow-up (72.3%) than those who continued apremilast (2.6%).

Deucravacitinib (oral)

- The approval of Sotyktu (deucravacitinib) was based on 2 randomized, double-blind, multicenter trials (POETYK PSO-1 and PSO-2) *(Armstrong et al 2023[a], Strober et al 2023[b])*. Adults with moderate to severe PsO who were eligible for systemic therapy or phototherapy were randomized to either deucravacitinib 6 mg once daily, placebo, or apremilast 30 mg twice daily. In both trials, deucravacitinib was superior to placebo for the co-primary endpoints of sPGA 0/1 (PSO-1: 54% vs 7% and PSO-2: 50% vs 9%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 13% and PSO-2: 53% vs 9%, p < 0.0001 for both) responses at week 16. In both trials, deucravacitinib was superior to apremilast for sPGA 0/1 (PSO-1: 54% vs 32% and PSO-2: 50% vs 34%, p < 0.0001 for both) and PASI 75 (PSO-1: 58% vs 35% [p < 0.0001] and PSO-2: 53% vs 40% [p = 0.0004]) responses at week 16. In both trials, efficacy was maintained to week 52. *(Armstrong et al 2023[a], Strober et al 2023[b])*. In a long-term extension study, efficacy of deucravacitinib was maintained for up to 3 years of treatment (*Armstrong et al 2025*).
  - Long-term response rates for deucravaitinib (*Armstrong et al 2025[a]*):
    - PASI 90 at 1 year: 45.6%
    - PASI 90 at 4 years 47.5%
    - DLQI 0/1 at 1 year: 51.5%
    - DLQI 0/1 at 4 years: 49.4%

Bimekizumab

- FDA approval of Bimzelx (bimekizumab-bkzx) for treatment of moderate-to-severe PsO was based on 3 double-blind, placebo-controlled, multicenter, randomized, Phase 3 trials: BE SURE (vs adalimumab; non-inferiority), BE VIVID (vs ustekinumab; non-inferiority), and BE READY (vs placebo only). The co-primary endpoints for all 3 trials were a 90% or greater reduction from baseline in PASI score and IGA score of 0 or 1 (clear or almost clear) (*Gordon et al 2021, Warren et al 2021[a], Reich et al 2021[a]*).
  - BE SURE enrolled 478 adults with a ≥ 6-month history of PsO who had moderate-to-severe disease at screening and had not previously received adalimumab or experienced primary failure of an anti-IL17 biologic or > 1 biologic agent of any other class. Patients were randomized 1:1:1 to receive bimekizumab 320 mg SQ every 4 weeks, bimekizumab 320 mg SQ every 4 weeks for 16 weeks followed by dosing every 8 weeks, or adalimumab. After 24 weeks, patients initially assigned to adalimumab were switched to bimekizumab 320 mg SQ every 4 weeks. The mean age of the patients was 44.9 years; the mean PASI score at baseline was 19.8. At week 16, 86.2% of patients taking bimekizumab had a PASI 90 response vs 47.2% of patients taking adalimumab (adjusted difference, 39.3%; 95% CI, 30.9 to 47.7; p < 0.001 for non-inferiority and superiority). Similarly, 85.3% of patients in the combined bimekizumab groups had an IGA score of 0 or 1 at week 16 (second primary end point) vs 57.2% in the adalimumab group (adjusted risk difference, 28.2%; 95% CI, 19.7 to 36.7; p < 0.001 for noninferiority and superiority). At 56-week follow-up, PASI 90 response rates were similar between patients receiving bimekizumab every 4 weeks throughout follow-up (84.8%) and those who switched to every-8-week dosing after week 16 (82.6%) (*Warren et al 2021[a]*).
  - BE VIVID enrolled 567 adults with a ≥ 6-month history of moderate-to-severe PsO who had not previously received ustekinumab or experienced primary failure of an anti-IL17 biologic or > 1 biologic agent of any other class. Patients were randomized 4:2:1 to receive bimekizumab 320 mg SQ every 4 weeks, ustekinumab 45 mg or 90 mg (weight based) at weeks 0 and 4 followed by dosing every 12 weeks, or placebo every 4 weeks. After 16 weeks, patients initially assigned to placebo were switched to bimekizumab. At 16-week follow-up, 85% of patients taking bimekizumab vs 50% of patients taking ustekinumab experienced a PASI 90 response (difference, 35%; 95% CI, 27 to 43; p < 0.0001) and 5% of those assigned to placebo (difference, 80%; 95% CI, 74 to 86; p < 0.0001). Similarly at week 16, 84% patients taking bimekizumab vs 53% taking ustekinumab had an IGA response (risk difference, 30%; 95% CI, 22 to 39; p<0·0001) and 5% in the placebo group (risk difference, 79%; 95% CI, 73 to 85; p<0·0001). At 52-week, PASI 90 response rates were significantly higher in patients receiving bimekizumab (82%) than those receiving ustekinumab (56%) (difference, 26%; 95% CI, 17 to 34; p < 0.0001) (*Reich et al 2021[a]*)
  - BE READY enrolled 435 adults with a ≥ 6-month history of moderate-to-severe PsO who had not experienced primary failure of an anti-IL17 biologic or > 1 biologic agent of any other class. Patients were randomized 4:1 to bimekizumab 320 mg SQ every 4 weeks or placebo. At week 16, patients initially assigned to bimekizumab who were experiencing a PASI 90 response were re-randomized to continuing bimekizumab every 4 weeks, bimekizumab every 8 weeks, or receive placebo (withdrawal of therapy); patients initially assigned to placebo who were experiencing a PASI 90 response continued to receive placebo, while those not experiencing PASI 90 response entered a 12-week open-label treatment phase with bimekizumab every 4 weeks. Among 435 patients in the primary analysis at 16-week follow-up, 91% of patients taking bimekizumab vs 1% taking placebo experienced a PASI 90 response (difference, 89.8%; 95% CI, 86.1 to 93.4; p < 0.0001). Similarly, an IGA score of 0 or 1 was achieved by

91% of patients taking bimekizumab vs 1% taking placebo (risk difference, 91.5%; 95% CI, 88 to 94.9; p < 0.0001). Durable responses through week 56 were demonstrated with both every 4 week and every 8 week dosing schedules (*Gordon et al 2021*).
  - Participants who were initially randomized to bimekizumab in the BE VIVID, BE READY, and BE SURE trials were eligible to enroll in the BE BRIGHT open-label extension trial. These patients received bimekizumab 320 mg every 4 or 8 weeks according to the dose they were receiving at the end of the prior trial; those who were receiving bimekizumab every 4 weeks from week 16 to the end of the prior trial and were experiencing a PASI 90 response were re-randomized 4:1 to continue treatment every 4 weeks or switch to every-8-week dosing. Among 989 patients enrolled, 87.5% had received bimekizumab and experienced a PASI 90 response at week 16 of the prior trial; among those in this subset who enrolled in the open-label extension, 96.5% and 93% had ongoing PASI 90 response at 1- and 3-year follow-up, respectively (*Strober et al 2023[a]).*
- BE RADIANT was a Phase 3b, double-blind, multicenter, randomized trial that evaluated the efficacy of bimekizumab vs secukinumab in 743 adults moderate to severe PsO without primary failure of an anti-IL17 biologic nor > 1 biologic agent of any other class. Patients were randomized 1:1 to receive bimekizumab 320 mg every 4 weeks or secukinumab 300 mg every 4 weeks (after weekly dosing for the first 4 weeks). After 16 weeks, patients initially assigned to bimekizumab were rerandomized 1:2 to continue bimekizumab every 4 weeks or switch to every-8-week dosing; patients initially assigned to secukinumab received it every 4 weeks through the end of the study. The primary endpoint was 100% reduction from baseline in PASI score at week 16. At week 16, 61.7% of patients taking bimekizumab vs 48.9% taking secukinumab had a 100% reduction in PASI (adjusted difference, 12.7%; 95% CI, 5.8 to 19.6; p < 0.001 for non-inferiority and superiority). After 48 weeks, 67% of patients taking bimekizumab vs 46.2% taking secukinumab had PASI 100 (p < 0.001) (*Reich et al 2021[b]).*
  - At week 48 (open-label extension), all patients received bimekizumab. The 3-year PASI 100 response rate for patients who started bimekizumab in the Phase 3b study was 68.8% and those who switched to bimekizumab at week 48 had a 3-year PASI 100 response rate of 68.8% (*Warren et al 2025*)

Icotrokinra (oral)
- The safety and efficacy of Icotyde (icotrokinra) was evaluated in a Phase 3, double-blind, randomized, placebo-controlled trial with 684 adults and adolescents (≥ 12 years old) with moderate to severe PsO. Patients were randomized 2:1 to icotrokinra of 200 mg once daily (n = 456) through week 24 or placebo (n = 228) through week 16 followed by transition to icotrokinra. The co-primary end points were an IGA 0/1 response (IGA score of 0 or 1 with ≥ 2 point reduction from baseline) and a PASI 90 response (≥ 90% reduction from baseline in the PASI score) at week 16.
  - At week 16, IGA 0/1 response was 65% with icotrokinra vs 8% with placebo; p < 0.001.
  - At week 16, PASI 90 response was 50% (icotrokinra) vs 4% (placebo); p < 0.001.

Pediatric Studies
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Thereafter, Stelara (ustekinumab), Taltz (ixekizumab), and Tremfya (guselkumab) were approved for children ≥ 6 years of age with PsO.
  - A 48-week, double-blind, placebo-controlled trial (N = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (p < 0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (N = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
  - A 52-week, double-blind, placebo-controlled trial (N = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose

(SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) ($p < 0.001$ for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.
  - An open-label, single arm, multicenter, Phase 3 trial evaluated the efficacy and safety of ustekinumab in patients 6 to < 12 years of age with moderate to severe PsO (*Philipp et al 2020*). A total of 44 patients received weight-based ustekinumab at weeks 0 and 4, then every 12 weeks through week 40. At week 12, 77% of patients achieved PGA 0 or 1, 84% achieved PASI 75, and 64% achieved PASI 90. No new safety concerns were identified.
  - The IXORA-PEDS study (N = 171) evaluated the efficacy of Taltz (ixekizumab) in pediatric patients aged 6 to < 18 years with moderate to severe PsO (*Paller et al 2020*). At week 12, weight-based ixekizumab every 4 weeks was superior to placebo for the co-primary endpoints of proportion of patients achieving PASI 75 (89% vs 25%; $p < 0.001$) and proportion of patients achieving PGA 0 or 1 (81% vs 11%; $p < 0.001$). Responses were sustained through week 108 (*Paller et al 2022*).
  - A randomized, placebo-controlled study evaluated Tremfya (guselkumab) in children aged 6 to < 18 years with moderate-to-severe PsO. In part 1 (weeks 0 to 16), 92 children were randomized to guselkumab, placebo, or open-label etanercept; thereafter, participants continued guselkumab, crossed over to guselkumab, or entered a guselkumab withdrawal period through week 52. At week 16, guselkumab demonstrated significantly higher response rates than placebo for IGA 0/1 (66% vs 16%), PASI 75 (76% vs 20%), and PASI 90 (56% vs 16%) (all $p \leq 0.01$), with approximately one-third achieving complete skin clearance (PASI 100: 34% vs 0%). In the open-label extension (part 2), sustained responses were observed at week 52 (IGA 0/1: 86%; PASI 75: 93%; PASI 90: 82%) (*Prajapati et al 2025*).

Multiple Comparative Studies/Meta-analyses

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response ($p < 0.00001$) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo ($p < 0.00001$ for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group ($p < 0.0001$). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥ 24 weeks) for moderate-to-severe PsO (*Nast et al 2015*). A total of 25 randomized trials (N = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept),

MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).

- A network meta-analysis of 41 randomized clinical trials (N = 19,248) assessed the proportion of patients with moderate-to-severe PsO who achieved PASI 100, PASI 90, and PASI 75 at weeks 10, 12, and 16 while using agents such as infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab, or guselkumab. The results revealed higher rates of PASI 100 and PASI 90 with brodalumab, ixekizumab, and risankizumab (*Tada et al 2020*).
- A network meta-analysis used data from 47 RCTs to compare the efficacy of deucravacitinib with other systemic therapies for patients with moderate-to-severe PsO. Deucravacitinib was found to be more likely to produce PASI 75 response in short-term follow up (weeks 10 to 16) compared to etanercept, MTX, and apremilast. At long-term follow up (weeks 44 to 60), deucravacitinib was also more likely to produce PASI 75 response than etanercept, MTX, apremilast, infliximab, adalimumab, and secukinumab 150 mg. However, deucravacitinib was less likely to achieve PASI 75 in short and long term follow up compared to secukinumab 300 mg, brodalumab, ixekizumab, bimekizumab, guselkumab, and risankizumab (*Armstrong et al 2023[b]*).
- A Bayesian network analysis of 86 RCTs (N = 34,476) found that IL-17 and IL-23 antagonists were highly effective in achieving short-term improvement of PsO, with patients on bimekizumab significantly more likely to achieve PASI 90 or PASI 100 within 10 to 16 weeks compared to other biologics (ie, risankizumab, ixekizumab, brodalumab, guselkumab, and secukinumab) (*Armstrong et al 2022*).
- A network meta-analysis of 84 trials compared the effectiveness and safety of biologics (etanercept, infliximab, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab, apremilast, bimekizumab) approved for use in moderate-to-severe PsO. Infliximab 5 mg/kg had the highest probability of achieving PASI 75 in comparison to placebo (RR, 18.76; 95% CI, 12.31 to 28.57). Ixekizumab 80 mg and brodalumab 210 mg had the highest probability at achieving PASI 90 (RR, 37.81; 95% CI, 28.57 to 50.03) and PASI 100 (RR, 81.04; 95% CI, 26.16 to 251.01), respectively, compared to placebo. Risankizumab 150 mg and ustekinumab 90 mg were the only regimens with significantly lower withdrawal rates due to AEs compared to placebo (*Ismail et al 2024*).
- A network meta-analysis of 20 RCTs compared the efficacy and safety of JAK/TYK2 inhibitors with other oral agents in moderate-to-severe PsO. Based on SUCRA, deucravacitinib at all dosages (except for 3 mg every other day) and tofacitinib (10 mg twice daily) ranked best in achieving PGA 0/1 and PASI 75 at 12 to 16 weeks. Tofacitinib (10 mg twice daily) ranked lowest for safety based on treatment-emergent AEs. Comprehensive rankings according to efficacy and safety indicated that deucravacitinib (3 mg daily and 3 mg twice daily) was the best treatment (*Zheng et al 2024*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 204 studies. The network meta-analysis showed that compared to placebo, the most effective induction therapy (outcomes measured from 8 to 24 weeks) for achieving PASI 90 include bimekizumab (high-certainty evidence) and infliximab, xeligekimab, ixekizumab, and risankizumab (moderate certainty evidence) (*Sbidian et al 2025*).

Psoriatic arthritis (PsA)

Adalimumab

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 ($p = 0.012$) in a trial (N = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial ($p < 0.001$) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; $p < 0.001$) (*Mease et al 2005*).

Etanercept

- FDA approval of Enbrel (etanercept) for pediatric patients aged ≥ 2 years with juvenile PsA was based on clinical evidence and pharmacokinetic data from studies of adults with PsA and adult and pediatric studies in other indications (*Enbrel prescribing information 2025*).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with

Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo (p < 0.0001). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients (p = 0.001). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; p < 0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; p < 0.001) (*Mease et al 2004*).

- A 24-week trial of adult patients with PsA randomized 851 patients to oral MTX monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to MTX monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).

Golimumab

- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (N = 405). Golimumab with or without MTX, compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
  - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥ 5 of 7 PsA outcomes measures [≤ 1 swollen joint, ≤ 1 tender joint, PASI ≤ 1, patient pain score ≤ 15, patient global disease activity score ≤ 20, HAQ DI ≤ 0.5, and ≤ 1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).

Infliximab

- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (p < 0.001) (*Antoni et al 2005*).

Certolizumab

- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (N = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).

Ustekinumab

- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (N = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; p < 0.0001 for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (N = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (p < 0.001) (*Ritchlin et al 2014*).
  - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and HRQoL were

sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
  - The approval of ustekinumab for PsA in patients aged 6 to 17 years was based on evidence from adequate and well-controlled studies in adults with PsO and PsA, along with pharmacokinetic data and safety data from 2 clinical studies in 44 patients aged 6 to 11 years with PsO and 110 patients aged 12 to 17 years with PsO (*Stelara prescribing information 2025*).

Secukinumab

- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled RCTs – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to SQ secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
  - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
  - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
  - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
  - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).
  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- An additional RCT (CHOICE) compared secukinumab at 2 doses to placebo in biologic-naïve patients with PsA and found that secukinumab 300 mg every 4 weeks was associated with a higher ACR 20 response rate than placebo at week 16 (51.5% vs 23.1%; $p = 0.001$) (*Nguyen et al 2022*). Secukinumab 150 mg every 4 weeks had a numerically higher ACR 20 response rate than placebo (36.9%) but the difference did not reach statistical significance.
- The randomized, placebo-controlled, INVIGORATE-2 trial evaluated the efficacy and safety of IV secukinumab in adults with active PsA. Patients were randomized 1:1 to receive IV secukinumab (6 mg/kg at baseline, followed by 3 mg/kg every 4 weeks [n = 191]) or placebo (n = 190). At week 16, the placebo group switched to IV secukinumab, while the secukinumab group continued treatment through week 52. At week 16, significantly more patients receiving IV secukinumab achieved ACR 50 (primary outcome) compared to placebo (31.4% vs 6.3%; $p < 0.0001$). Following crossover, patients initially on placebo demonstrated rapid improvement, with both groups exhibiting comparable efficacy outcomes by week 52. The safety profile of IV secukinumab was consistent with the known SQ formulation (*Kivitz et al 2025*).

Apremilast

- The efficacy of Otezla (apremilast) was demonstrated in 4 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a, Wells et al 2018*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b, Wells et al 2018*). In a long-term extension study, clinical improvements with Otezla were sustained up to 260 weeks (*Wells et al 2022*). In addition, a Phase 4 RCT (FOREMOST) found that apremilast improves clinical and patient-reported outcomes at 16 weeks in patients with early oligoarticular PsA (*Gossec et al 2024*).

Abatacept

- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a Phase 2 dose-finding trial (N = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo

(19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p = 0.006) and 30/10 mg/kg (42%; p = 0.022) but not 3 mg/kg (33%). A Phase 3 trial (N = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p < 0.001).

Upadacitinib

- Rinvoq (upadacitinib) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies in adults with moderately to severely active PsA (SELECT-PsA 1 and SELECT-PsA 2) *(McInnis et al 2021, Mease et al 2020[a])*. Patients with a previous inadequate response or intolerance to ≥ 1 non-biologic DMARD (SELECT-PsA 1) or ≥ 1 biologic DMARD (SELECT-PsA 2) were randomized to upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab (SELECT-PsA 1), or placebo as monotherapy or in combination with ≤ 2 non-biologic DMARDs for 24 weeks. The primary endpoint of both studies, ACR 20 at week 12, was significantly improved with upadacitinib 15 mg once daily (FDA-approved dose) compared with placebo in SELECT-PsA 1 (70.6% vs 36.2%; difference, 34.5%; 95% CI, 28.2 to 40.7; p < 0.001) and SELECT-PsA 2 (56.9% vs 24.1%; difference, 32.8%; 95% CI, 24.0 to 41.6; p < 0.001).
  - The approval of Rinvoq/Rinvoq LQ (upadacitinib) for the treatment of PsA in pediatric patients aged 2 years and older was based on evidence from well-controlled studies and pharmacokinetic data in adults with RA and PsA (*Rinvoq/Rinvoq LQ prescribing information 2024*).

Risankizumab

- Skyrizi (risankizumab) received FDA approval for the treatment of PsA based on the results of 2 randomized, double-blind, placebo-controlled studies, KEEPsAKE 1 and KEEPsAKE 2, in patients with active PsA (*Kristensen et al 2022*, *Östör et al 2022*). In KEEPsAKE 1, all patients had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic-naïve. In KEEPsAKE 2, patients had an inadequate response or intolerance to ≤ 2 biologic therapies and/or ≥ 1 non-biologic DMARD therapy. Risankizumab was associated with significantly higher rates of the primary endpoint of ACR 20 response at week 24 in KEEPsAKE 1 (57.3% vs 33.5%; p < 0.001) and KEEPsAKE 2 (51.3% vs 26.5%; p < 0.001). Significant improvements were reported in both trials for ACR 50 and ACR 70 response at week 24. Results at 52 weeks of treatment in both KEEPsAKE 1 and KEEPsAKE 2 indicated no new safety concerns *(Kristensen et al 2022, Östör et al 2022)*.

Ixekizumab

- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; p ≤ 0.001). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; p < 0.0001) (*Nash et al 2017*).
  - An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 response rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018[b]*).
  - An additional open-label extension of the SPIRIT-P1 trial followed patients through week 156. The ACR 20, ACR 50, and ACR 70 response rate for the every 2 weeks and every 4 weeks groups were 62.5% and 69.8%, 56.1% and 51.8%, and 43.8% and 33.4%, respectively (*Chandran et al 2020*).
- SPIRIT-H2H is a 52-week multicenter, open-label study comparing ixekizumab with adalimumab in patients with PsA and without prior use of biologic DMARDs. At week 52, a higher proportion of patients treated with ixekizumab achieved the combined ACR 50 and PASI 100 response (39% vs 26%, p < 0.001) and PASI 100 response (64% vs 41%, p <

0.001) compared with the patients treated with adalimumab. Both agents yielded similar outcomes for ACR 50 (49.8% vs 49.8%, p = 0.924) (*Smolen et al 2020[b]*).

Tofacitinib

- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group (p = 0.01 vs 5 mg; p < 0.001 vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group (p < 0.001 for both comparisons) (*Gladman et al 2017*).
- The approval of Xeljanz (tofacitinib) tablets and oral solution for PsA in children ≥ 2 year of age was supported by evidence from studies of tofacitinib tablets in adults with PsA, pharmacokinetic data from adults with PsA, and pharmacokinetic data from a clinical trial of tofacitinib in 225 pediatric patients with JIA, and safety data from 280 pediatric patients ≥ 2 years with JIA (*Xeljanz Prescribing Information 2026*).

Guselkumab

- Tremfya (guselkumab) received FDA approval for the treatment of PsA based on 2 randomized, double-blind, placebo controlled trials (*Deodhar et al 2020[c], Mease et al 2020[b]*). The DISCOVER-1 trial randomized 381 patients with active PsA despite standard therapies to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 59% and 52%, respectively, which was significantly greater than the ACR 20 response rate with placebo (22%; p < 0.0001) (*Deodhar et al 2020[c]*). The DISCOVER-2 trial randomized 741 biologic-naïve patients with PsA to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 64% and 64%, respectively, which was significantly greater than the ACR 20 response rate with placebo (33%; p < 0.0001) (*Mease et al 2020[b]*). Clinical improvements were maintained through 2 years of treatment (*McInnes et al 2022*). An additional placebo-controlled trial (COSMOS) in patients with inadequate response to TNF inhibitors found that guselkumab significantly improved ACR 20 response rates at week 24 in these patients (44.4% vs 19.8% with placebo; p < 0.001) (*Coates et al 2022[a]*).
- The ongoing APEX study is a phase 3b, multicenter, randomized, placebo-controlled, double-blind trial evaluating the impact of every 4-week (n=273) and every 8-week (n=371) guselkumab regimens on signs, symptoms, and radiographic progression of PsA compared to placebo (n=376). The 24-week ACR 20 response rate was 66.6%, 68.3%, and 47% for patients receiving guselkumab every 4 weeks, every 8 weeks, and placebo, respectively. Radiographic progression was significantly less with both regimens compared to placebo (*Mease et al 2025*).
- The approval of Tremfya (guselkumab) in children ≥ 6 years of age with PsA was supported by evidence from studies of guselkumab in adults with PsO and PsA, pharmacokinetic data from adults with PsO and PsA and children with PsO, and safety data from a clinical trial in 120 children 6 to 17 years of age with PsO (*Tremfya Prescribing Information 2025*).

Bimekizumab

- The approval of Bimzelx (bimekizumab) for the treatment of PsA was supported by evidence from 2 multicenter, double-blind, placebo-controlled RCTs, BE OPTIMAL and BE COMPLETE *(McInnes et al 2023, Merola et al 2023*).
  - In BE OPTIMAL, DMARD-naïve patients with active PsA were randomly assigned to bimekizumab 160 mg every 4 weeks, placebo every 2 weeks, or adalimumab 40 mg every 2 weeks, all administered SQ, for 52 weeks. At week 16, patients randomly assigned to placebo switched to bimekizumab 160 mg every 4 weeks. For the primary endpoint at week 16, significantly more patients receiving bimekizumab reached ACR 50 response versus placebo (44% vs 10%; p < 0.0001; 46% with adalimumab) *(McInnes et al 2023)*.
    - The efficacy and safety of bimekizumab were sustained from week 16 to week 52 *(Ritchlin et al 2023)*.

- In BE COMPLETE, patients with active PsA and previous inadequate response or intolerance to TNF inhibitors were randomized to receive bimekizumab 160 mg SQ every 4 weeks or placebo. At week 16, significantly more patients receiving bimekizumab reached ACR 50 response versus placebo (43% vs 7%; p < 0.0001) *(Merola et al 2023)*.
  - Sustained efficacy was observed from week 16 to 52 *(Coates et al 2024)*.
  - Patients completing the 16-week BE COMPLETE study entered the open-label extension, BE VITAL. Sustained efficacy and safety were observed up to 2 years in biologic DMARD-naïve patients and patients with prior anti-TNF inadequate response/intolerance *(Mease et al 2024[a])*.

deucravacitinib

- The approval of Sotyktu (deucravacitinib) for the treatment of PsA was supported by evidence from the pivotal POETYK PsA-1 (N = 670) and POETYK PsA-2 (N = 624) trials. Patients in both studies were randomized to deucravacitinib 6 mg daily or placebo for 16 weeks; 105 patients were randomized to apremilast 30 mg twice daily in the PsA-2 trial. In both trials, treatment with deucravacitinib resulted in statistically significant improvement in disease activity, as measured by ACR 20, compared to placebo at week 16 (*Sotyktu prescribing information 2026*):
  - PsA-1: 54% vs 34% (difference, 20%; 95% CI, 13 to 27; p < 0.0002)
  - PsA-2: 54% cs 39% (difference, 15%; 95% CI, 7 to 23; p < 0.0002)

Multiple Comparative Studies/Meta-analyses

- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- The multicenter, randomized, double-blind EXCEED study compared Cosentyx (secukinumab) to Humira (adalimumab) in 853 biologic-naïve patients with active PsA and an inadequate response to DMARDs (*McInnes et al 2020*). The ACR 20 response rates at week 52 were 67% with secukinumab and 62% with adalimumab (p = 0.0719). Secukinumab did not show statistical superiority over adalimumab.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 RCTs and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept, and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR 70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR 20 and ACR 50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR 20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.

  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016[b]*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.
- A network meta-analysis of 30 randomized trials (N = 10,191) compared the efficacy of infliximab, apremilast, adalimumab, tofacitinib, ustekinumab, golimumab, abatacept, secukinumab, certolizumab, brodalumab, etanercept, and ixekizumab in PsA (*Qiu et al 2020*). Direct and indirect comparisons were performed. In direct comparisons, most agents were better than placebo in terms of ACR 20 response rate (except adalimumab, tofacitinib, and abatacept), and no agent was significantly different from placebo in terms of serious adverse events. In the network meta-analysis, etanercept and infliximab were more effective than golimumab for ACR 20 response, and infliximab was more effective than certolizumab for PASI 75 response. Etanercept and infliximab were ranked as the most effective treatments.
- A network meta-analysis of 30 randomized trials (only 12 randomized trials for peripheral arthritis outcome) assessed the efficacy of adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, risankizumab, and tildrakizumab on peripheral arthritis by using ACR 70 criteria and on skin by reporting PASI 100 (*Torres et al 2021*). Secukinumab and ixekizumab had the highest probability for reaching both ACR 70 and PASI 100 responses.
- A meta-analysis of 11 randomized studies (N = 5382) revealed that TNF inhibitors, IL inhibitors, and abatacept are more likely to achieve radiographic non-progression compared with placebo (*Wu et al 2020*). Ixekizumab and adalimumab had a similar proportion of non-progressors.
- A meta-analysis of 33 trials in patients with PsA found that guselkumab was comparable to IL-17A inhibitors and TNF inhibitors for achievement of ACR 20, ACR 50, and ACR 70 (*Mease et al 2022*). There was a trend of benefit for guselkumab vs most other active agents for achievement of PASI 90. For PASI 100, van der Heijde-Sharp score, and serious adverse events, guselkumab was comparable to other active agents.
- A network meta-analysis of 11 trials evaluated the comparative efficacy in prevention of radiographic progression PsA of biologic DMARDs, including abatacept, adalimumab, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab *(Wang et al 2022)*. All interventions were more effective than placebo in achieving radiographic non-progression except for secukinumab 150 mg, ustekinumab, and guselkumab. SUCRA values indicated that adalimumab, certolizumab, and etanercept may be most effective in achievement of radiographic non-progression. SUCRA analysis showed that infliximab ranked the best in reducing the total radiographic score, followed by etanercept.
- A network meta-analysis of 41 RCTs evaluated the relative efficacy and safety of bimekizumab (160 mg every 4 weeks) vs other biologic and targeted synthetic DMARDs (secukinumab, ixekizumab, guselkumab, risankizumab, ustekinumab, adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept, tofacitinib, upadacitinib, apremilast) for PsA. Overall, bimekizumab ranked favorably based on SUCRA values among the agents studied for efficacy in joint, skin, and disease activity outcomes across both DMARD-naive and TNF inhibitor-experienced populations. The safety of bimekizumab was similar to the other DMARDs (*Mease et al 2024[b]*).

- A Cochrane review of 25 RCTs (N = 7857) examined the efficacy of TNF inhibitors for PsA and found that, among patients with an inadequate response to conventional synthetic DMARDs (csDMARD), TNF inhibitors probably result in a large clinical improvement, lower disease activity, a small decrease in radiographic progression, and better quality of life compared to placebo (*Cagnotto et al 2025b*).

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
  - VISUAL I (N = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥ 2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - VISUAL II (N = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [> 18 months] vs 8.3 months; hazard ratio, 0.57; 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.
- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated UV. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was TTF. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Alopecia areata

- The efficacy and safety of baricitinib for alopecia areata were assessed in 2 randomized, placebo-controlled, Phase 3 trials (BRAVE-AA1 and BRAVE-AA2) (*King et al 2022*). Both trials enrolled adults with severe alopecia areata and randomized patients to receive either baricitinib 4 mg daily, baricitinib 2 mg daily, or placebo. The primary outcome was a Severity of Alopecia Tool (SALT) score of 20 or less at week 36. In BRAVE-AA1 (N = 654), the primary outcome was achieved in 38.8%, 22.8%, and 6.2% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively (p < 0.001 for both doses vs placebo). In BRAVE-AA2 (N = 546), the primary outcome was achieved in 35.9%, 19.4%, and 3.3% of patients assigned to baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively (p < 0.001 for both doses vs placebo). Continuous therapy of up to 52 weeks resulted in improved response rates of with both baricitinib 4 mg and 2 mg, respectively; 40.9% and 21.2% (BRAVE-AA1) and 36.8% and 24.4% (BRAVE-AA2) achieved a SALT score ≤ 20 at Week 52 (*Kwon et al 2023*). Among the week 52 responders, 90.7% of the 4 mg group, and 89.2% of the 2 mg group maintained a SALT score ≤ 20 by week 104 (*Senna et al 2024*).
- The efficacy and safety of ritlecitinib were evaluated in a randomized, multicenter, Phase 2b-3 trial (ALLEGRO-2b/3) (*King et al 2023*). Patients (N = 718) 12 years of age and older with alopecia areata and at least 50% scalp hair loss were randomly assigned to received either ritlecitinib or placebo, with or without a 4-week loading dose: 50 mg, 30 mg, 10 mg, 200 mg loading dose followed by 50 mg, or 200 mg loading dose followed by 30 mg. The primary outcome assessed was SALT score 20 or less at week 24. At week 24, 31% (38/124) of patients in the ritlecitinib 200 mg + 50 mg group, 22% (27/121) of patients in the 200 mg + 30 mg group, 23% (29/124) of patients in the 50 mg group, 14% (17/119) of patients in the 30 mg group, and 2% (2/130) of patients in the placebo group had a response based on SALT score 20 or less. In an open-label, long-term extension study (ALLEGRO-LT), ritlecitinib 50 mg (with or without a 200-mg 4-week daily loading dose) maintained efficacy for up to 2 years (*Piliang et al 2025*). In adults and adolescents with ≥ 25% scalp hair loss, who received the loading dose, 73.5% achieved a SALT score ≤ 20 and 66.4% achieve a SALT score ≤10 at 24 weeks (*Tziotzios et al 2025*). Moderate or great improvement on the Patient Global Impression of Change (PGI-C) score was achieved in 82.4% of patients.

- In an indirect treatment comparison, there was no statistically significant difference between ritlecitinib 50 mg and baricitinib 4 mg in achievement of SALT ≤ 10 (OR, 0.96; 95% CrI, 0.18 to 7.21) and SALT ≤ 20 (OR, 2.16, 95% CrI, 0.48 to 16.46) at Week 24 in patients with alopecia areata (*Aceituno et al 2024*).
- The efficacy and safety of deuruxolitinib (Leqselvi) for alopecia areata was assessed in a Phase 3, multicenter, randomized, double-blind, placebo- controlled trial (THRIVE-AA1). Adults aged 18 to 65 years old with ≥ 50% scalp hair loss (defined as SALT score ≥ 50 at screening and baseline) with a total disease duration of > 10 years were eligible for inclusion. Patients were randomized in a 3:5:2 ratio to receive oral deuruxolitinib 12 mg twice daily, deuruxolitinib 8 mg twice daily, or placebo. The primary efficacy end point was the percentage of patients who achieved a SALT score ≤ 20 at week 24 (*King et al 2024*).
  - Both doses of deuruxolitinib had a higher proportion of patients achieving a SALT score ≤ 20 at 24 weeks; 94 patients in the 8 mg group (29.6%), 83 patients in the 12 mg group (41.5%), and 1 patient in the placebo group (0.8%). Both deuruxolitinib doses also demonstrated improvements in satisfaction of hair patient-reported outcome (8 mg 42.1%; 12 mg 53.0% versus placebo 4.7%).
- A Cochrane review of 63 RCTs found that baricitinib produced significantly greater short- and long-term hair regrowth than placebo, whereas the effect of other included treatments was very uncertain. Data for ritlecitinib were not included in the analysis (*Mateos-Haro et al 2023*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (N = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

Other conditions: Behçet disease, CAPS, CRS, DIRA, ERA, FMF, GCA, GVHD, HIDS/MKD, NOMID, NRAS, SSc-ILD, TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ($p < 0.001$). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2024*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy of Kineret (anakinra) for DIRA was evaluated in a long-term natural history study of 9 patients (ages 1 months to 9 years) with genetically-confirmed DIRA who were treated with anakinra for up to 10 years. All patients achieved inflammatory remission (defined as CRP ≤ 5 mg/dL and absence of pustulosis, inflammatory bone disease, or glucocorticoid use) (*Kineret prescribing information 2024*).
- Cosentyx (secukinumab) was evaluated in a double-blind, placebo-controlled trial in 86 patients 2 to < 18 years of age with active ERA or juvenile PsA *(Ruperto et al 2021[c], Brunner et al 2023)*. The JIA subtypes at baseline were 60.5% ERA and 39.5% juvenile PsA. Patients were treated with secukinumab during an open-label portion, followed by a randomized withdrawal phase and then open-label treatment. In patients with ERA, the primary endpoint of time to disease flare during the randomized withdrawal period demonstrated reduced risk in patients treated with secukinumab compared with placebo (hazard ratio, 0.45; 95% CI, 0.16 to 1.28).
- The efficacy of Cimzia (certolizumab) was evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg

every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2-point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b])*.

- The efficacy and safety of Rinvoq (upadacitinib) were evaluated in a Phase 3, randomized, double-blind, placebo-controlled trial in adults with active NRAS and inadequate response to at least 2 NSAIDs or intolerance or contraindication to NSAIDs. Patients were randomized to upadacitinib (15 mg daily; n = 156) or placebo (n = 157). At 14 weeks, the primary endpoint of ASAS 40 response was significantly improved with upadacitinib compared with placebo (44.9% vs 22.3%, respectively; difference, 22.5%; 95% CI, 12.4 to 32.5; p < 0.0001) *(Deodhar et al 2022[a])*. Upadacitinib efficacy was maintained for up to 2 years of treatment (*Van den Bosch et al 2025*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in NRAS in the 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020[a]*). In COAST-X, 303 adults with NRAS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent AEs were nasopharyngitis and injection site reaction.
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in NRAS in the randomized, double-blind, placebo-controlled, Phase 3 PREVENT study (*Deodhar et al 2020[b]*). In this trial, 555 adults with NRAS were randomized to receive secukinumab with a loading dose, secukinumab without a loading dose, or placebo (secukinumab was dosed as 150 mg at weeks 0, 1, 2, and 3, then every 4 weeks starting at week 4). The primary analyses were performed in TNF inhibitor-naïve patients (n = 501). Both primary endpoints were met. At week 16, more patients in the secukinumab plus loading dose group achieved ASAS 40 compared with placebo (41.5% vs 29.2%; p < 0.05). At week 52, more patients in the secukinumab without loading dose group achieved ASAS 40 compared with placebo (39.8% vs 19.9%; p < 0.05).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, FMF, and adult-onset Still's disease.
  - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2024*). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
  - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs 6%, respectively). Resolution of the flare was defined as a PGA score < 2 (minimal or no disease) and CRP within normal range (or reduction ≥ 70% from baseline) (*De Benedetti et al 2018*). In the open-label extension phase of this trial, canakinumab was effective for controlling disease activity and flares over 72 weeks; 64% of patients experienced no flares during the 72-week trial period, and 20% had 1 flare, as compared with a median of 12 flares per year reported at baseline (*Jeyaratnam et al 2022*).
  - Efficacy and safety in adult-onset Still's disease were evaluated in a randomized, double-blind, placebo-controlled study of 36 patients with adult-onset Still's disease and active joint involvement. The primary endpoint, proportion of patients achieving a significant reduction in DAS28 at week 12, was achieved in 67% of canakinumab-treated patients and 41% of placebo-treated patients (p = 0.18). Proportions of patients achieving the secondary endpoints of ACR 30, 50, and 70 were significantly greater in the canakinumab group (61%, 50%, and 28% with canakinumab vs 20%, 6.7%, and 0% with placebo; p = 0.033, 0.009, and 0.049 for canakinumab vs placebo, respectively). The study was terminated prematurely due to recruitment difficulties (*Kedor et al 2020*).
- The efficacy and safety of Actemra (tocilizumab) have been evaluated for treatment of GCA, CRS, and SSc-ILD.
  - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled Phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo (p < 0.01).

- The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2024*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.
- The efficacy of tocilizumab in SSc-ILD was evaluated in a randomized, double-blind, placebo-controlled clinical trial of 210 adults with SSc-ILD (*Khanna et al 2020*). While this trial did not meet its primary endpoint (change from baseline to week 48 in the modified Rodnan Skin Score [mRSS], a standard outcome measure for skin fibrosis in SSc-ILD), there was a trend of benefit in favor of tocilizumab for preservation of lung function (a > 10% decrease in FVC% predicted occurred in 24% of patients in the placebo group and only 13% of patients in the tocilizumab group; HR, 0.55; 95% CI, 0.3 to 1.11; p = 0.08). Treatment failure was also less likely with tocilizumab (22%) vs placebo (35%; p = 0.08). Benefits in preservation of lung function were maintained through week 96 in an open-label extension of this study (*Khanna et al 2022*).

- The efficacy of Rinvoq (upadacitinib) for the treatment of GCA was assessed in a randomized, double-blind, placebo-controlled Phase 3 trial of patients ≥ 50 years old with new-onset or relapsing GCA. Patients were randomized in a 2:1:1 ratio to receive upadacitinib 15 mg daily, upadacitinib 7.5 mg daily, or placebo; all patients were simultaneously treated with a glucocorticoid taper (26-week taper for the upadacitinib groups or 52-week taper for the placebo group). The primary endpoint was sustained remission at week 52, defined as the absence of signs or symptoms of GCA from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper. Upadacitinib 15 mg daily was superior to placebo with respect to the proportion of patients achieving sustained remission at week 52 (46.4% vs 29%; p = 0.002); upadacitinib 7.5 mg daily was not associated with a significantly higher rate of sustained remission compared to placebo (*Blockmans et al 2025*).
- The efficacy and safety of Orencia (abatacept) in the prophylaxis of acute GVHD was assessed in a Phase 2 trial of adults and children with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor *(Watkins et al 2021)*. A cohort of patients with 8/8 HLA-matched HSCT (N = 142) were randomized to blinded abatacept or placebo, each in addition to a calcineurin inhibitor (CNI) and MTX. At day 100, abatacept was associated with numeric improvements in the primary endpoint of severe (grade 3 to 4) acute GVHD (hazard ratio, 0.45; 95% CI, 0.22 to 0.90). At day 180, severe acute GVHD-free-survival (SGFS) was 93.2% for CNI/MTX plus abatacept vs 82% for CNI/MTX plus placebo (p = 0.05). In an open-label single-arm cohort of patients undergoing 7/8 HLA-matched HSCT (N = 43), grade 3 to 4 acute GVHD was 2.3% for CNI/MTX plus abatacept, which compared favorably with a nonrandomized matched cohort of CNI/MTX (30.2%, p < 0.001); the SGFS was also better (97.7% vs 58.7%, p < 0.001).
  - A study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) of patients 6 years and older who underwent HSCT from a 1 allele-mismatched unrelated donor demonstrated that treatment with abatacept in addition to CNI and MTX was associated with greater overall survival at day 180 post-HSCT compared with patients not treated with abatacept (98% vs 75%) (*Orencia prescribing information 2024*).
- A systematic literature review of 38 studies determined that anakinra, canakinumab, and etanercept are the most commonly studied biologics for treating familial Mediterranean fever, while studies with adalimumab, tocilizumab, rilonacept, and infliximab remain limited (*Kuemmerle-Deschner et al 2020*). The available evidence suggests that anakinra and canakinumab are effective in treating familial Mediterranean fever.

Clinical Guidelines

RA:

- The 2021 America College of Rheumatology (ACR) recommends the use of conventional DMARDs (eg, hydroxychloroquine, sulfasalazine, MTX, leflunomide), a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). For patients who are not at target, switching to a medication in a different class is conditionally recommended over switching to a medication in the same class for patients receiving a biologic or JAK inhibitor. Biosimilars are considered equivalent to FDA-approved originator biologics. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Fraenkel et al 2021*).
- The 2023 EULAR guidelines for RA management recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in

every patient. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered. If poor prognostic factors are present with csDMARD failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors should be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biologic or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor (*Smolen et al 2023*).

- An ACR position statement on biosimilars states that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber and the patient. The ACR "supports the use of biosimilars to increase patients' access to biologics" and "opposes insurer-mandated force switching to biosimilars" (*ACR 2024*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
- EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that all TNF inhibitors may be used throughout pregnancy. The following non-TNF inhibitor biologics may also be used during pregnancy if needed to effectively control disease: abatacept, anakinra, canakinumab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab. Due to a lack of data, guselkumab and risankizumab should only be used in pregnancy if no other pregnancy-compatible medication options can effectively control disease. Apremilast, baricitinib, tofacitinib, and upadacitinib should not be used during pregnancy until further evidence is available (*Rüegg et al 2025*).
- The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommend against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).

JIA:

- The 2019 ACR and Arthritis Foundation guideline for the treatment of JIA focuses on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. Recommendations for initial therapy include the use of DMARDs (MTX, lefunomide, or sulfasalazine); the preference for MTX over other agents is conditionally recommended. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic to DMARD (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy (*Ringold et al 2019*).
- A 2021 guideline from the ACR addresses the treatment of oligoarthritis, temporomandibular joint arthritis, and SJIA (*Onel et al 2022*). For SJIA, an IL-1 inhibitor or IL-6 inhibitor is conditionally recommended for initial treatment; no specific agent is preferred. Monotherapy with an NSAID may also be considered for initial treatment of SJIA without macrophage activation syndrome. Systemic glucocorticoids are conditionally recommended as part of initial therapy for patients with macrophage activation syndrome. If residual arthritis is present despite these therapies, a conventional synthetic DMARD may be added or a different biologic therapy may be tried. Patients without macrophage activation syndrome who experience incomplete response or intolerance to an initial IL-1 or IL-6 inhibitor may be switched to an alternative IL-1 or IL-6 inhibitor.

PsO and PsA:

- Joint guidelines from the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) state that topical medications (eg, corticosteroids, vitamin D analogues) are the most common agents used to treat mild to moderate PsO. They are commonly used as adjunctive therapy to phototherapy, systemic agents, and biologics (*Elmets et al 2021*). Phototherapy is viewed as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications (*Elmets et al 2019*). Although biologic therapies have changed the treatment landscape, non-biologic systemic agents (eg, MTX) either as monotherapy or in combination with biologics, are still widely used due to benefit for widespread disease, comparatively low cost, increased availability, and ease of administration. Methotrexate and apremilast are recommended for moderate to severe psoriasis in adults, however, MTX is considered less effective than adalimumab and infliximab for cutaneous psoriasis (*Menter et al 2020[a]*).
- Joint guidelines from the AAD/NPF on the treatment of psoriasis with biologics address the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can all be

recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).

- The AAD/NPF guideline on PsO in pediatric patients states that etanercept, adalimumab, and ustekinumab are effective biologic therapies for moderate to severe pediatric psoriasis. Infliximab can be recommended as monotherapy or in combination with MTX for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening (*Menter et al 2020[b]*).
- The EULAR 2023 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate. The choice of the mechanism of action should be based on musculoskeletal manifestations related to PsA; for patients with clinically relevant skin involvement, an IL-17A inhibitor (ixekizumab, secukinumab), IL-17A/F inhibitor (bimekizumab), IL-23 inhibitor (guselkumab, risankizumab), or IL-12/23 inhibitor (ustekinumab) is preferred; for patients with uveitis, TNF inhibitors (adalimumab, certolizumab, etanercept, infliximab, and golimumab) are preferred. In patients with inadequate response or intolerance to a biologic DMARD or JAK inhibitor, switching to another biologic DMARD or JAK inhibitor should be considered, including one switch within a class (*Gossec et al 2024).*
- The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, inhibitors of IL-12/23 or IL-23, a JAK inhibitor, or a PDE-4 inhibitor (*Coates et al 2022[b]*).
- The ACR/NPF guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).
- In 2020, the International Psoriasis Council Biosimilar Working Group published a consensus statement for the use of biosimilars in the treatment of patients with psoriasis (*Cohen et al 2020*). There was consensus from the Group that prescribing biosimilars to biologic-naïve patients or switching a stable patient from a reference product to a biosimilar product is appropriate if the patient and physician agree to do so. Furthermore, switching between different biosimilars should be performed with caution, until more evidence is generated supporting this practice, and multiple switches between various biosimilars and reference biologics is not the preferred option but is acceptable. Lastly, treatment switches should not occur in less than an adequate period of time (usually 6 months) from initiation of the reference product, allowing full assessment of its therapeutic effect.
- In 2024, the NPF published a Delphi consensus on vaccination recommendations for adults receiving biologics and oral therapies for psoriasis and PsA. For patients receiving nonlive vaccines, the NPF recommends continuing oral and biologic therapies for the treatment of psoriasis and/or PsA without modification in most cases. For patients receiving live vaccines, the NPF recommends temporarily discontinuing most oral and biologic therapies for the treatment of psoriasis and/or PsA before and after vaccination (*Chat et al 2024*).

AS:

- The ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended. Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In

patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar (*Ward et al 2019*).

- Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR and were updated in 2022. The guideline notes that radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis are part of the same disease spectrum, and therefore uses the term axial spondyloarthritis in recommendations. The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered, but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor. In patients with a history of recurrent UV or active IBD, preference should be given to a monoclonal antibody against TNF. In patients with significant psoriasis, an IL-17 inhibitor may be preferred. Following failure of the first biologic or targeted synthetic DMARD, switching to another biologic DMARD (TNF inhibitor or IL-17A inhibitor) or a JAK inhibitor should be considered. For patients in sustained remission, tapering of a biologic DMARD can be considered (*Ramiro et al 2023*).

Ocular inflammatory disorders:

- Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- A 2019 guideline by the ACR and Arthritis Foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options (*Angeles-Han et al 2019*).
- A 2018 guideline by the Fundamentals of Care for Uveitis (FOCUS) International Consensus Group published guidance for non-corticosteroid systemic immunomodulatory therapy in noninfectious UV (*Dick et al 2018*). For the treatment of noninfectious uveitis, the consensus group recommends use of adalimumab (evidence level 1B) and infliximab (evidence level 2B); Grade A recommendation.

Additional indications:

- National guidelines for alopecia areata were not identified. In a guideline from the British Association of Dermatologists, oral JAK inhibitors are mentioned for treatment in adults and young people with severe disease (*Harries et al 2025*).

- Based upon guidelines from the European Dermatology Forum, adalimumab, secukinumab, and bimekizumab are recommended as first-line therapies for moderate-to-severe HS in patients with inadequate response to conventional systemic therapies. Infliximab may be recommended as a second-line option if first-line biologic treatment is unsatisfactory; brodalumab, ustekinumab, anakinra, or ustekinumab could also be considered in this setting (*Zouboulis et al 2025*).
- The North American clinical management guidelines for HS indicate that immunomodulators are rapidly becoming the cornerstone of therapy for moderate to severe disease. Recommendations for the use of biologics includes adalimumab at the approved HS dose to improve disease severity and quality of life in patients with moderate to severe HS; infliximab is also recommended for moderate to severe disease, however optimal dosage was not noted. Anakinra and ustekinumab are noted to be possibly effective, while limited available evidence does not support the use of etanercept for HS (*Alikhan et al 2019*). A newer guideline on HS treatment in special populations recommends adalimumab in pregnant patients with HS who require biologics; infliximab and secukinumab can also be considered in this patient

population, and certolizumab may be considered as an alternative option in select patients planning a pregnancy who have a compelling reason to be concerned about in-utero biologic exposure (*Alhusayen et al 2025*).

- For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine (*Ozen et al 2025*).

- For the management of GCA, EULAR recommendations state that tocilizumab (or MTX as an alternative) should be used as an adjunctive therapy in patients who have refractory or relapsing disease or who are at an increased risk of glucocorticoid-related AEs or complications (*Hellmich et al 2020*). A joint guideline from the ACR and Vasculitis Foundation recommends the use of oral or IV glucocorticoids, tocilizumab, and other non-glucocorticoid immunosuppressive drugs (eg, methotrexate, abatacept); specific recommendations depend on various factors such as the patient's clinical presentation, comorbidities, and prior therapies (*Maz et al 2021*).

- An ACR guideline conditionally recommends tocilizumab and nintedanib as first-line treatment options for SSc-ILD; tocilizumab is also conditionally recommended as a second-line treatment option for patients with progression despite first SSc-ILD treatment (*Johnson et al 2024*).
- A guideline from the American Thoracic Society (ATS) strongly recommends mycophenolate for the treatment of SSc-ILD, and conditionally recommends cyclophosphamide, rituximab, tocilizumab, and nintedanib (*Raghu et al 2024*).
- A EULAR guideline recommends the following agents for the treatment of SSc-ILD: mycophenolate mofetil, cyclophosphamide, rituximab, nintedanib (alone or in combination with mycophenolate mofetil), or tocilizumab (*Del Galdo et al 2024*).

- In children and adolescents with JIA and active enthesitis, ACR guidelines conditionally recommend TNF inhibitor therapy over methotrexate or sulfasalazine (*Ringold et al 2019*).

- A EULAR guideline for the management of IL-1-mediated autoinflammatory disorders provides recommendations for the management of CAPS, TRAPS, MKD, and DIRA (*Romano et al 2022*). The guideline states that IL-1 inhibitor therapy has become the preferred treatment for these disease states; a therapeutic trial with an IL-1 inhibitor may be started when strong clinical suspicion of CAPS, TRAPS, MKD, or DIRA exists. For CAPS, IL-1 inhibitors (anakinra, canakinumab, and rilonacept) are considered standard of care; anakinra may be the most effective treatment for CNS disease. For TRAPS, IL-1 inhibitors are more effective than traditional DMARDs or other biologic DMARDs. For MKD, IL-1 inhibitors are first-line; if these therapies are not effective or available, TNF inhibitors may be considered. For DIRA, anakinra and rilonacept are recommended.

- The 2024 EULAR/Pediatric Rheumatology European Society guideline on Still's disease recommends that an IL-1 or an IL-6 inhibitor should be initiated as early as possible when the diagnosis is established (*Fautrel et al 2024*). The use of an IL-1 or IL-6 inhibitor should be prioritized to avoid prolonged systemic glucocorticoid use. When bacterial infection remains on the differential diagnosis, an IL-1 inhibitor is preferred. Short duration glucocorticoids (high dose) are indicated in patients with high disease severity; glucocorticoids (at low or intermediate doses) may also be used in milder presentations but are not required. Maintenance of clinically inactive disease (absence of Still's disease-related symptoms and normal ESR or CRP) for 3 to 6 months without glucocorticoids should be achieved before initiating tapering of the biological DMARD.

- A 2015 EULAR/ACR guideline for the management of PMR indicates that glucocorticoids (instead of NSAIDs) are currently the standard of care for treatment. The early introduction of MTX is recommended with glucocorticoids in patients at a high risk of relapse or prolonged therapy. The guideline strongly recommends against the use of TNF inhibitors (*Dejaco et al 2015*).

Safety Summary

- Contraindications:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Avtozma (tocilizumab-anoh), Cimzia (certolizumab), Cosentyx (secukinumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Imuldosa (ustekinumab-srlf), Inflectra (infliximab-

dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Otulfi (ustekinumab-aauz), Pyzchiva (ustekinumab-ttwe), Remicade (infliximab), Renflexis (infliximab-abda), Selarsdi (ustekinumab-aekn), Siliq (brodalumab), Skyrizi (risankizumab), Stelara (ustekinumab), Starjemza (ustekinumab-hmny), Steqeyma (ustekinumab-stba), Taltz (ixekizumab), Tofidence (tocilizumab-bavi), Tyenne (tocilizumab-aazg), Wezlana (ustekinumab-auub), and Yesintek (ustekinumab-kfce), in patients with hypersensitivity to any component of the product.
  - Enbrel (etanercept) in patients with sepsis.
  - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - Leqselvi (deuruxolitinib) is contraindicated in patients who are poor cytochrome P450 (CYP) 2C9 metabolizers and in patients using moderate to strong CYP2C9 inhibitors.
  - Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses > 5 mg/kg in patients with moderate to severe heart failure.
  - Siliq (brodalumab) in patients with CD since the drug may cause worsening of the disease.
- Boxed Warnings:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), adalimumab-aacf, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simlandi (adalimumab-ryvk), Simponi / Simponi Aria (golimumab), Avtozma (tocilizumab-anoh),Tofidence (tocilizumab-bavi), Tyenne (tocilizumab-aazg), Xeljanz / Xeljanz XR/Xeljanz oral solution (tofacitinib), Yuflyma (adalimumab-aaty) and Yusimry (adalimumab-aqvh) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Avsola (infliximab-axxq), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), adalimumab-aacf, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb Litfulo (ritlecitinib), Leqselvi (deuruxolitinib), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simlandi (adalimumab-ryvk), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib),Yuflyma (adalimumab-aaty) and Yusimry (adalimumab-aqvh) all have warnings for increased risk of malignancies.
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Rinvoq (upadacitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), and Olumiant (baricitinib) have warnings for increased risk of thrombosis and death, including sudden cardiovascular death.
    - In September 2021, the FDA announced that its review of a large, randomized safety clinical trial comparing Xeljanz (tofacitinib) vs a TNF inhibitor in RA found an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with tofacitinib. The final results showed an increased risk of AEs with the lower dose as well as the higher dose. The FDA believes that baricitinib and upadacitinib have similar risks because they share the same mechanism of action. The FDA has limited all approved uses of baricitinib, tofacitinib, and upadacitinib to certain patients who have not responded or cannot tolerate 1 or more TNF inhibitors.
  - Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
  - Siliq (brodalumab) has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
- Warnings/Precautions (applying to some or all the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections (including tuberculosis)
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Cytopenias and pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome

- Malignancy and lymphoproliferative disorders
- Avoiding live vaccinations and therapeutic infectious agents
- Noninfectious pneumonia with Stelara (ustekinumab), Imuldosa (ustekinumab-srlf), Otulfi (ustekinumab-aauz), Pyzchiva (ustekinumab-ttwe), Selarsdi (ustekinumab-aekn), Starjemza (ustekinumab-hmny), Steqeyma (ustekinumab-stba), Wezlana (ustekinumab-auub), and Yesintek (ustekinumab-kfce)
- Increased lipid parameters and liver function tests with Actemra (tocilizumab), Avtozma (tocilizumab-anoh), Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Kevzara (sarilumab), Bimzelx (bimekizumab-bkzx), Tofidence (tocilizumab-bavi), and Tyenne (tocilizumab-aazg)
- Lipid elevations, anemia, neutropenia, and lymphopenia with Leqselvi (deuruxolitinib)
- Increased incidence of CD and UC with Cosentyx (secukinumab), Taltz (ixekizumab), Bimzelx (bimekizumab-bkzx); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
- Diarrhea, nausea, and vomiting with Otezla (apremilast)
- Depression and weight loss with Otezla (apremilast)
- Suicidal ideation and behavior with Bimzelx (bimekizumab-bkzx)
- Gastrointestinal perforations with Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Avtozma (tocilizumab-anoh), Kevzara (sarilumab), Leqselvi (deuruxolitinib), Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr), Truxima (rituximab-abbs), Tofidence (tocilizumab-bavi), and Tyenne (tocilizumab-aazg)
- Thrombosis with Olumiant (baricitinib)
- Embryo-fetal toxicity with Rinvoq (upadacitinib)
- Hepatotoxicity with Actemra (tocilizumab), Avtozma (tocilizumab-anoh), Tofidence (tocilizumab-bavi), Tyenne (tocilizumab-aazg), and Tremfya (guselkumab)
- Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
- Macrophage activation syndrome with Ilaris (canakinumab)
- Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab), Imuldosa (ustekinumab-srlf), Otulfi (ustekinumab-aauz), Pyzchiva (ustekinumab-ttwe), Selarsdi (ustekinumab-aekn), Starjemza (ustekinumab-hmny), Steqeyma (ustekinumab-stba), Wezlana (ustekinumab-auub), and Yesintek (ustekinumab-kfce)
- Cytomegalovirus and Epstein-Barr Virus reactivation with Orencia (abatacept)
- Severe eczematous eruptions with Taltz (ixekizumab)
- Amyloidosis with Kineret (anakinra)
- Consult prescribing information for other drug-specific warnings/precautions

- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, and headache.
  - Consult prescribing information for other drug-specific AEs and major drug interactions.
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.
    - Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99

events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.

- A randomized controlled noninferiority trial compared tofacitinib to TNF inhibitors in terms of risk for major cardiovascular AEs and malignancy (*Ytterberg et al 2022*). A total of 1455 patients with active RA and at least 1 additional cardiovascular risk factor were randomized to receive tofacinitib 5 or 10 mg twice daily or a TNF inhibitor. During a median follow-up of 4 years, major cardiovascular AEs were more common among patients receiving tofacitinib (3.4% vs 2.5%; hazard ratio, 1.33; 95% CI, 0.91 to 1.94), as were malignancies (4.2% vs 2.9%; hazard ratio, 1.48; 95% CI, 1.04 to 2.09). Noninferiority was not established for tofacitinib vs TNF inhibitors for either endpoint.
- Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 RCTs and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 RCTs and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
- A systematic review and network meta-analysis analyzed 42 RCTs and found no significant difference between the available JAK inhibitors in terms of MACE or venous thromboembolic events (*Alves et al 2022*).
- A network meta-analysis of 18 RCTs (N = 21,432) compared JAK inhibitor or tocilizumab treatment to TNF inhibitor control in terms of MACE and all-cause mortality (*Pugliesi et al 2024*). In this analysis, JAK inhibitors were associated with a non-significant increase in risk of MACE (OR, 1.232; 95% CI, 0.86 to 1.76; p = 0.25) and all-cause mortality (OR, 1.39; 95% CI, 0.94 to 2.07; p = 0.10) compared to TNF inhibitors; although these differences did not reach statistical significance, a Bayesian analysis found a high clinical probability of more frequent MACE and all-cause mortality with JAK inhibitors versus TNF inhibitors. Tocilizumab was not associated with a significant increase in risk of MACE (OR, 1.029; 95% CI, 0.75 to 1.40; p = 0.86) or all-cause mortality (OR, 1.11; 95% CI, 0.82 to 1.52; p = 0.33) compared to TNF inhibitors.
- A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for MACE was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) vs placebo (0 events in 1070 patients) (*Taylor et al 2019*). Another pooled analysis of 10 RA trials including 3770 patients (14,744 patient-years exposure) examined the safety of baricitinib over a median of 4.6 years and a maximum of 9.3 years. In this analysis, the incidence rates for serious infections, herpes zoster, major cardiovascular adverse events, malignancy, and deep vein thrombosis/pulmonary embolism were 2.6, 3.0, 0.5, 1.0, and 0.5 per 100 patient-years, respectively (*Taylor et al 2022*).

- PsO
  - A total of 3117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3), and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95% CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95% CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patient-years, for malignancies was 1.2/100 patient-years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - In a 5-year extension study, 1349 patients treated with guselkumab in VOYAGE 1 and VOYAGE 2 were evaluated for long-term safety; during 7166 patient-years of follow-up, the incidence rates for serious infections, nonmelanoma skin cancer, malignancy other than nonmelanoma skin cancer, and MACE were 0.85, 0.34, 0.45, and 0.29 per 100 patient-years, respectively (*Blauvelt et al 2022*).
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
  - Pooled safety data from the BE VIVID, BE READY, BE SURE, and open-label extension BE BRIGHT trials (described above) did not indicate new safety concerns with long-term use of Bimzelx (bimekizumab-bkzx) (*Gordon et al 2023*). The most commonly reported treatment-emergent AEs were nasopharyngitis (15 per 100 patient-years), oral candidiasis (10.1 per 100 patient-years), and upper respiratory tract infection (6.5 per 100 patient-years). Nearly all cases of oral candidiasis were mild or moderate; treatment with an antifungal agent lasted a median of 12 days. Exposure-adjusted incidence rates of overall treatment-emergent AEs decreased over time and were lower in patients receiving bimekizumab every 8 weeks than those receiving it every 4 weeks.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
  - An integrated safety analysis of 4 clinical trials examined the safety of ixekizumab in 1401 patients with PsA (2247.7 patient-years of exposure) (*Deodhar et al 2022[b]*). In this study, the exposure-adjusted incidence rates of

serious infections, malignancies, inflammatory bowel disease, depression, and major cerebrocardiovascular events were 1.2, 0.7, 0.1, 1.6, and 0.5 per 100 patient-years, respectively. No new safety signals were observed.

- AS
  - A meta-analysis of 25 RCTs with 2403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
  - Another meta-analysis of 14 RCTs with 2032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious AEs (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to AEs (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).
- Alopecia Areata
  - The safety of baricitinib in 1303 adults with severe alopecia areata was evaluated using data from 2 phase III trials over a median of 2.3 years and up to 4 years of treatment. Through 152 weeks of follow-up, incidence rates for serious adverse events and discontinuation due to adverse events were 2.6 and 1.6, similar to results seen at 104 weeks. Additional follow-up did not reveal new cases of serious infections, opportunistic infections, major adverse cardiovascular events (MACE), deep vein thromboses, or pulmonary embolism. Incidence ratios for non-melanoma skin cancer, other malignancies, and herpes zoster were 0.1, 0.2, and 1.9, respectively. No deaths were reported (*King et al 2025*).
  - The safety of 2-year exposure of ritlectinib in adults and adolescents (n=449) for alopecia areata treatment demonstrated 86.1% of patients with treatment-emergent adverse events (TEAEs) with most being mild to moderate in severity. The most common adverse events (AEs) were positive SARS-CoV-2 test (24.2%), headache (20.8%), and pyrexia (13%). Rates of serious AEs, severe AEs, and treatment discontinuation were 4.9%, 6%, 6.5%, respectively. Other AEs included herpes zoster infection (n=6), serious infection (n=4), malignancy (excluding nonmelanoma skin cancer, n=3) and MACE (n=3) (*Tziotzios et al 2025*).
- SJIA
  - The 5-year safety of canakinumab in patients with SJIA was reported from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry in patients between 2 and 18 years old. Of the 177 patients evaluated 90 received canakinumab and 87 received alternate treatment; the median patient age at time of treatment initiation was 8 years in the canakinumab group. The incidence rates of serious adverse events (SAEs) per 100 patient-years was 3.62. Macrophage activation syndrome was reported in 5 patients and 1 patient experienced infection requiring IV antibiotics. The authors concluded no change in frequency of known AEs and no identification of new risks with canakinumab treatment (*Correll et al 2025*)
- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
  - Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, RCTs evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.

- The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 patient-years. Respective incidences per 100 patient-years of infections (125.4 vs 129.4), major cardiovascular AEs (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
- Several meta-analyses evaluated the safety of TNF inhibitors.
  - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
  - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.
- A meta-analysis evaluated the risk of malignancy in patients treated with ixekizumab for PsA or AS using data from 4 RCTs, 4 long-term extension studies, and 8 pooled analyses (*Maneiro et al 2025*). In this analysis, ixekizumab was associated with low incidence rates of malignancy at week 52 (0.31 per 100 patient-years) and week 156 (0.58 per 100 patient-years).

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), adjust dose with potent inhibitors of CYP3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
  - For Olumiant (baricitinib), adjust dose when used with potent inhibitors of organic anion transporter (OAT) 3.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.
    - Patients must enroll in the program.
    - Pharmacies must be certified with the program and must only dispense to patients who are enrolled in the program.

Dosing and Administration

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: < 100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥ 100 kg,	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement,	Give as a single 60-minute IV infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		162 mg administered SQ every week. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. SQ: < 30 kg, 162 mg SQ every 3 weeks; ≥ 30 kg, 162 mg SQ every 2 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks SQ: < 30 kg, 162 mg SQ every 2 weeks; ≥ 30 kg, 162 mg SQ once weekly. **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids. SQ: 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** < 30 kg, 12 mg/kg IV; ≥ 30 kg, 8 mg/kg IV; maximum, 800 mg per infusion. **SSc-ILD:** 162 mg SQ once weekly **COVID-19**: IV infusion: < 30 kg, 12 mg/kg; ≥ 30 kg, 8 mg/kg	with at least 8 hours between doses. **RA, PJIA, and SJIA, SSc-ILD, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count, infection, and low ANC. **PJIA**: Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.	Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites. SQ administration with the prefilled autoinjector has not been studied in SSc-ILD. IV administration is not approved for SSc-ILD. Laboratory abnormalities in patients with GCA may warrant dose interruption with IV administration and dose interruption or reduction with SQ administration. Doses > 600 mg per infusion not recommended in GCA. Doses > 800 mg per infusion not recommended in COVID-19.
Adalimumab-aacf	Single-dose prefilled pen: 40 mg/0.8 mL Single-dose prefilled syringe: 40 mg/0.8 mL Single-use vial: 40 mg/0.8 mL Single-dose prefilled pen starter package for CD, UC, or HS: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA:** 10 kg to < 15 kg: 10 mg SQ every other week; 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week.	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Single-dose prefilled pen starter package for PsO or UV: 40 mg/0.8 mL	**PsO and adult UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **HS:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week.		
Avsola (infliximab-axxq)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen, and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Avtozma (tocilizumab-anoh)	Vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA**: IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: < 100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥ 100 kg,	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. **GCA:** Can use alone after discontinuation of glucocorticoids.	Not recommended for concomitant use with biological DMARDs. Give as a single 60-minute IV infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		162 mg administered SQ every week. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. SQ: < 30 kg, 162 mg SQ every 3 weeks; ≥ 30 kg, 162 mg SQ every 2 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks SQ: < 30 kg, 162 mg SQ every 2 weeks; ≥ 30 kg, 162 mg SQ once weekly. **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids. SQ: 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** < 30 kg, 12 mg/kg IV; ≥ 30 kg, 8 mg/kg IV; maximum, 800 mg per infusion. **COVID-19**: IV infusion: < 30 kg, 12 mg/kg; ≥ 30 kg, 8 mg/kg	**CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, SJIA, and GCA:** Adjust dose for liver enzyme abnormalities, low platelet count, and low ANC.	Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites. Laboratory abnormalities in patients with RA and GCA may warrant dose interruption with IV administration and dose interruption or reduction with SQ administration. Doses > 600 mg per infusion not recommended in GCA. Doses > 800 mg per infusion not recommended in COVID-19.
Bimzelx (bimekizumab-bkzx)	Autoinjector: 160 mg/mL, 320 mg/2 mL Prefilled syringe: 160 mg/mL, 320 mg/2 mL	**PsO:** 320 mg SQ at 0, 4, 8, 12, and 16 weeks, then every 8 weeks. **PsA, AS, NRAS:** 160 mg SQ every 4 weeks. **HS**: 320 mg SQ at 0, 2, 4, 6, 8, 10, 12, 14, and 16 weeks, then every 4 weeks.	For patients with PsO weighing ≥ 120 kg, consider continuous every-4-week dosing. For patients with PsA with coexistent moderate to severe PsO, use the dosing regimen for adults with PsO.	Each 320 mg SQ dose may be given as 2 SQ injections of 160 mg. Patients and/or caregivers may self-administer the SQ injection.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **PsO:** 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week (for body weight ≤ 90 kg). **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks. **PJIA in pediatric patients ≥ 2 years of age:** 10 kg to < 20 kg: 100 mg at week 0, 2, and 4 (loading dose), then 50 mg every 2 weeks (maintenance dose beginning at week 6); 20 kg to < 40 kg, 200 mg at week 0, 2, and 4 (loading dose), then 100 mg every 2 weeks (maintenance dose beginning at week 6); ≥ 40 kg: 400 mg at week 0, 2, and 4 (loading dose), then 200 mg every 2 weeks (maintenance dose beginning at week 6).	Patients can self-inject with the prefilled syringe. Doses < 200 mg require administration by a health care professional using the vial kit.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 300 mg/2 mL, 150 mg/mL, 75 mg/0.5 mL Unoready pen: 300 mg/2 mL	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks; for some patients, 150 mg may be acceptable. **PsO in pediatric patients ≥ 6 years of age:** Dose is based on weight (< 50 kg, 75 mg;	**PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA or AS continues in adults,	Each 300 mg SQ dose is given as 1 SQ injection of 300 mg or 2 SQ injections of 150 mg. Patients may self-administer SQ with the pen or prefilled syringe, or they may

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Solution for IV infusion: 125 mg/5 mL	≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed every 4 weeks. **PsA, AS, NRAS:** With a loading dose (not required): 150 mg SQ or IV at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks. **PsA in pediatric patients:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed by every 4 weeks. **ERA:** Dose is based on weight (≥ 15 kg and < 50 kg, 75 mg; ≥ 50 kg, 150 mg) and administered at weeks 0, 1, 2, 3 and 4, followed by every 4 weeks. **HS adults:** 300 mg SQ weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks. **HS in adolescent patients ≥ 12 years and older:** weight based administered at weeks 0, 1, 2, 3, 4 and then every 4 weeks; 150 mg (≥ 30 kg and < 90 kg) or 300 mg (≥ 90 kg).	consider 300 mg dose every 4 weeks. **HS:** If a patient does not adequately respond, consider increasing the dosage to 300 mg every 2 weeks.	be administered by a caregiver. The IV formulation is indicated for adults with PsA, AS, or NRAS, and must be administered by a healthcare professional in a healthcare setting.
Enbrel (etanercept)	Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder	**RA, AS, PsA (adults):** 50 mg SQ weekly. **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly. **PJIA, juvenile PsA, and PsO (pediatrics):**	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued. **JIA:** NSAIDs glucocorticoids, or	Patients may be taught to self-inject. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only Single-dose vial: 25 mg/0.5 mL	≥ 63 kg, 50 mg SQ weekly; < 63 kg, 0.8 mg/kg SQ weekly.	analgesics may be continued.	
Humira (adalimumab), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Abrilada (adalimumab-afzb), Simlandi (adalimumab-ryvk), Yuflyma (adalimumab-aaty)	Humira prefilled syringe: 10 mg/0.1 mL 20 mg/0.2 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Amjevita prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL Cyltezo prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL Hadlima prefilled syringe: 40 mg/0.8mL 40 mg/0.4 mL Hulio prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Hyrimoz prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL Hyrimoz single-dose prefilled syringe (with BD UltraSafe Passive Needle Guard): 20 mg/0.4 mL 40 mg/0.8 mL 40 mg/0.4 mL 80 mg/0.8 mL Abrilada prefilled syringe:	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **HS:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week. **PsO and adult UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **Pediatric JIA:** 10 kg to < 15 kg: 10 mg SQ every other week; 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **Pediatric UV:** 10 kg to < 15 kg: 10 mg SQ every other week; 15 kg to < 30 kg: 20 mg SQ every other week; ≥ 30 kg, 40 mg SQ every other week **HS in adolescent patients ≥ 12 years and older:** 30 kg to < 60 kg: 80 mg on day 1, 40 mg on day 8; maintenance dose is 40 mg every other week. ≥ 60 kg: 160 mg on day 1, 80 mg on day 15, 40 mg on day	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL Simlandi single-dose prefilled syringe: 20 mg/0.2 mL 40 mg/0.4 mL 80 mg/0.8 mL Yuflyma single-dose prefilled syringe: 20 mg/0.2 mL 40 mg/0.4 mL 80 mg/0.8 mL Yuflyma single-dose prefilled syringe with safety guard: 40 mg/0.4 mL 80 mg/0.8 mL Humira single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Cyltezo prefilled pen: 40 mg/0.8mL Hulio single-use pen: 40 mg/0.8 mL Hyrimoz Sensoready Pen: 40 mg/0.8 mL 40 mg/0.4 mL 80 mg/0.8 mL Abrilada single-use pen: 40 mg/0.8 mL Amjevita prefilled autoinjector: 40 mg/0.8 mL Hadlima PushTouch autoinjector: 40 mg/0.8 mL 40 mg/0.4 mL	29; maintenance dose is 40 mg every week.		

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Simlandi single dose auto injector: 80 mg/0.8 mL 40 mg/0.4 mL Yuflyma single-dose prefilled auto-injector: 40 mg/0.4 mL 80 mg/0.8 mL Humira single-use vial: 40 mg/0.8 mL Abrilada single-use vial: 40 mg/0.8 mL Hadlima single-dose vial: 40 mg/0.8 mL Humira single-use pen starter package for CD, UC, or HS: 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Humira single-use pen starter package for psoriasis, UV, or adolescent HS: 40 mg/0.4 mL 40 mg/0.8 mL 40 mg/0.4 mL 80 mg/0.8 mL Cyltezo prefilled pen starter package for CD, UC, or HS: 40 mg/0.8 mL Cyltezo prefilled pen starter package for psoriasis or UV: 40 mg/0.8 mL Hyrimoz single-dose prefilled pen starter package for CD, UC, or HS: 40 mg/0.4 mL			

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	80 mg/0.8 mL Hyrimoz single-dose prefilled pen starter package for PsO or UV: 40 mg/0.4 mL 80 mg/0.8 mL Yuflyma single-dose prefilled auto-injector starter package for PsO: 40 mg/0.4 mL 40 mg/0.4 mL and 80 mg/0.8 mL Yuflyma single-dose prefilled auto-injector starter package for CD, UC, or HS: 40 mg/0.4 mL 80 mg/0.8 mL			
Icotyde (icotrokinra)	200 mg tablet	**PsO**: Once daily		Should be taken on an empty stomach with water upon waking; Wait at least 30 minutes after taking dose before eating food. For patients who have difficulty swallowing tablets, tablet can be dispersed in water. Monitor patients with moderate to severe renal impairment (GFR < 60 mL/min).

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ilaris (canakinumab)	Single-dose vial: 150 mg injection solution	**SJIA and adult-onset Still's disease:** ≥ 7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥ 15 to ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 8 weeks. **TRAPS, HIDS/MKD, and FMF**: ≤ 40 kg, 2 mg/kg SQ; > 40 kg, 150 mg SQ; frequency every 4 weeks.	**For CAPS:** children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg. **For TRAPS, HIDS/MKD, and FMF:** If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤ 40 kg) or 300 mg (weight > 40 kg).	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks.		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Imuldosa (ustekinumab-srlf)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg;	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		administer recommended dose initially, 4 weeks later, then every 12 weeks.		
Inflectra (infliximab-dyyb)	Single-dose vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks. **PMR:** 200 mg SQ every 2 weeks **PJIA in patients who weigh ≥ 63 kg:** 200 mg SQ every 2 weeks	**RA:** give with or without MTX or other conventional DMARDs. **PMR:** give in combination with tapering course of corticosteroids; can be used as monotherapy following corticosteroid discontinuation. **PJIA:** use alone or in combination with conventional DMARDs. Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID) and DIRA:** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily. CrCl < 30 mL/min: give dose every other day	Patients may be taught to self-inject. A new syringe must be used for each dose. Rotate injection sites.
Leqselvi (deuruxolitinib)	Tablet: 8 mg	**Alopecia areata:** 8 mg twice daily	Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as cyclosporine.	Perform CYP2C9 genotype determination prior to administration.
Litfulo (ritlecitinib)	Capsule: 50 mg	**Alopecia areata:** 50 mg orally once daily	**Alopecia areata**: use is not recommended in patients with severe (Child Pugh C) hepatic impairment. Treatment should be discontinued if platelet count is < 50,000/mm^3. Treatment should be interrupted if ALC is < 500/mm^3 and can be restarted once ALC is above this value. Coadministration with strong CYP3A inducers not recommended. Additional monitoring and dose adjustment may be required with coadministration with certain CYP3A and CYP1A2 substrates.	May be taken with or without food. Capsules should be swallowed whole. Do not crush, split, or chew.
Olumiant (baricitinib)	Tablet: 1 mg, 2 mg, and 4 mg	**RA:** 2 mg once daily. **Alopecia areata:** 2 mg once daily; increase to 4 mg once daily if response is inadequate.	**Alopecia areata**: for patients with nearly complete or complete scalp hair loss, consider treating with 4 mg once daily; once	May be taken with or without food. Tablets may be crushed and dispersed in water for patients

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			patients achieve an adequate response to treatment with 4 mg, decrease the dosage to 2 mg daily. Dosage modification may be required for cytopenias or anemia, or when used concomitantly with potent OAT3 inhibitors. Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine. Renal: Use not recommended in patients with estimated glomerular filtration rate < 30 mL/min/1.73m^2; adjust dosage in patients with estimated glomerular filtration rate between 30 and 60 mL/min/1.73 m^2.	unable to swallow whole tablets.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: < 60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; > 100 kg, 1000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first	Before administering for treatment of GVHD, administer recommended antiviral prophylaxis.	IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients or caregivers may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and < 75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. > 75 kg, follow adult RA IV schedule; maximum dose = 1000 mg. SQ: 2 to 17 years, 10 to < 25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA (adults):** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose. **PsA (pediatric):** SQ: 10 to < 25 kg: 50 mg once weekly; 25 to < 50 kg: 87.5 mg once weekly; ≥ 50 kg: 125 mg once weekly. **GVHD:** IV: ≥ 6 years: 10 mg/kg (maximum 1000 mg) on the day before transplantation, then administration on days 5, 14, and 28 after transplantation. ≥ 2 to < 6 years: 15 mg/kg (maximum 1000 mg) on the day before transplantation, then 12 mg/kg on days 5, 14, and 28 after transplantation.		
Otezla, Otezla XR (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg Extended-release tablet: 75 mg	**PsA, PsO, Behçet's in adults:** (Days 1 to 5, use Otezla only; Day 6, use Otezla or Otezla XR)	Titrate according to the labeling when initiating therapy to reduce	May be taken with or without food. Do not crush, split, or chew the tablets.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: Otezla - 30 mg twice daily Otezla XR – 75 mg once daily **PsA, PsO in pediatric patients:** (Days 1 to 5, use Otezla only; Day 6, use Otezla or Otezla XR depending on weight) Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 to < 50 kg: 20 mg in the morning and 20 mg in the evening ≥ 50 kg: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 20 to < 50 kg: 20 mg twice daily ≥50 kg: 30 mg twice daily (Otezla) or 75 mg once daily (Otezla XR)	gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in adult patients with severe renal impairment (CrCl < 30 mL/min as estimated by the Cockcroft-Gault equation). Otezla XR is not recommended in these patients. In pediatric patients with severe renal impairment (CrCl < 30 mL/min as estimated by the Cockcroft-Gault equation), dosage should be reduced to 20 mg once daily (20 to < 50 kg) or 30 mg once daily (≥ 50 kg) in patients with severe renal impairment (CrCl < 30 mL/min as estimated by the Cockcroft-Gault equation). Otezla XR is not recommended in these patients. For initial dosing in patients with severe renal impairment, use only the morning titration schedule listed above (evening doses should be excluded). Patients treated with Otezla 30 mg twice daily may be switched to Otezla XR 75 mg once daily the day following the	

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			last dose of Otezla 30 mg. Patients treated with Otezla XR 75 mg once daily may be switched to Otezla 30 mg twice daily the day following the last dose of Otezla XR 75 mg.	
Otulfi (ustekinumab-aauz)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Pyzchiva (ustekinumab-ttwe)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks.	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Vial: 45 mg/0.5 mL and 130 mg/26 mL	> 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	and 4 weeks later, followed by 90 mg every 12 weeks.	recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Remicade (infliximab)	Vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Renflexis (infliximab-abda)	Single-dose vial: 100 mg	**PsA, PsO**: 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg every 8 weeks or treat as often as every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Riabni (rituximab-arrx)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Rinvoq/Rinvoq LQ (upadacitinib)	Extended-release tablet: 15 mg, 30 mg, and 45 mg Oral solution: 1 mg/mL	**RA, PsA, AS, NRAS, GCA in adults:** 15 mg once daily. **PJIA and PsA in pediatric patients:** 3 mg (3 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg; 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 30 kg; and 6 mg oral solution (6 mL) twice daily or 15 mg ER tablet once daily if weight ≥ 30 kg.	**GCA**: use in combination with a tapering course of corticosteroids; may be used as monotherapy following discontinuation of corticosteroids.	Extended-release tablets and oral solution are not interchangeable. May be administered with or without food. Swallow tablets whole; do not crush, split, or chew. Administer oral solution with the included press-in bottle adapter and oral dosing syringe.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.		reduce the incidence and severity of infusion reactions.
Ruxience (rituximab-pvvr)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Selarsdi (ustekinumab-aekn)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks.	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation.	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/Simponi Aria (golimumab)	SmartJect autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Simponi Aria, single-dose vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. **Aria (PJIA):** 80 mg/m^2 IV at weeks 0 and 4, and then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX. Efficacy and safety of switching between IV and SQ formulations have not been established.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 90 mg/mL,150 mg/mL, 180 mg/1.2 mL Prefilled pen (autoinjector): 150 mg/mL Prefilled cartridge with on-body injector (for CD only): 180 mg/1.2 mL, 360 mg/2.4 mL Single dose vial (for IV infusion in CD only): 600 mg/10 mL	**PsO, PsA:** 150 mg SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex. **PsA**: give with or without non-biologic DMARD.	Each dose must be administered in different anatomic locations. Patients may be taught to self-inject using the prefilled syringes or pen.
Sotyktu (deucravacitinib)	Tablet: 6 mg	**PsO, PsA:** 6 mg once daily	Not recommended in severe hepatic impairment.	May take with or without food.
Stelara (ustekinumab), Wezlana	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**:	Patients may be taught to self-inject using the prefilled syringes. In pediatric

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
(ustekinumab-auub)	Vial: 45 mg/0.5 mL and 130 mg/26 mL	by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. Needle cover of the syringe for Stelara contains dry rubber (latex).	patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Starjemza (ustekinumab-hmny)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO (adults)**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. Needle cover of the syringe for Starjemza contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		PsA (adults): 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.		
Steqeyma (ustekinumab-stba)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10,		Patients weighing > 50 kg may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Autoinjector: 20 mg/0.25 mL, 40 mg/0.5 mL, 80 mg/mL	and 12, then 80 mg every 4 weeks. **PsO (6 to < 18 years old):** < 25 kg, 40 mg SQ at week 0 then 20 mg every 4 weeks; 25 to 50 kg, 80 mg SQ at week 0 then 40 mg every 4 weeks; > 50 kg, 160 mg SQ at week 0, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. **NRAS:** 80 mg by SQ injection every 4 weeks. NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		to room temperature prior to injecting. Rotate injection sites. Doses for patients weighing ≤ 50 kg must be administered by a healthcare professional. Contents of a prefilled syringe should be transferred to a sterile vial, and the appropriate dose drawn out of the vial into a new syringe. 20 mg and 40 mg doses prepared from the 80 mg/mL prefilled syringe should only be administered by a qualified healthcare professional.
Tremfya (guselkumab)	Prefilled syringe: 100 mg/mL, 200 mg/2 mL Prefilled pen: 100 mg/mL, 200 mg/2 mL Single-dose patient-controlled autoinjector: 100 mg/mL Vial: 200 mg/20 mL (for UC)	**PsO, PsA (adults and pediatrics):** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks	For **PsA**, Tremfya may be used alone or in combination with MTX.	Patients may be taught to self-inject SQ. Bring to room temperature (30 minutes) prior to injecting.
Truxima (rituximab-abbs)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg (or equivalent glucocorticoid) IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Tofidence (tocilizumab-bavi)	Vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	**RA**: IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks.	**RA:** Can give with MTX or other non-DMARDs.	Not recommended for concomitant use with biological DMARDs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Maximum dose = 800 mg. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids	**PJIA and SJIA:** Can give with MTX. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. **GCA:** Can be used alone following discontinuation of glucocorticoids.	Give as a single 60-minute IV infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Laboratory abnormalities in patients with RA and GCA may warrant dose interruption. Doses > 600 mg per infusion not recommended in GCA.
Tyenne (tocilizumab-aazg)	Vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA**: IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: < 100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥ 100 kg, 162 mg administered SQ every week. **PJIA:** IV: < 30 kg, 10 mg/kg IV every 4 weeks; ≥ 30 kg, 8 mg/kg IV every 4 weeks. SQ: < 30 kg, 162 mg SQ every 3 weeks; ≥ 30 kg, 162 mg SQ every 2 weeks. **SJIA:** IV: < 30 kg, 12 mg/kg IV every 2 weeks; ≥ 30 kg, 8 mg/kg IV every 2 weeks	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, SJIA, and GCA:** Adjust dose for liver enzyme abnormalities, low platelet count, and low ANC.	Not recommended for concomitant use with biological DMARDs. Give as a single 60-minute IV infusion. < 30 kg, use a 50 mL infusion bag. ≥ 30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites. Laboratory abnormalities in patients with RA and GCA may warrant dose interruption with IV administration and dose interruption or reduction with SQ administration.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		SQ: < 30 kg, 162 mg SQ every 2 weeks; ≥ 30 kg, 162 mg SQ once weekly. **GCA:** IV: 6 mg/kg IV every 4 weeks with tapering glucocorticoids. SQ: 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** < 30 kg, 12 mg/kg IV; ≥ 30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.		Doses > 600 mg per infusion not recommended in GCA.
Xeljanz/Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended-release tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	**RA, AS:** 5 mg PO twice daily or 11 mg PO once daily. **PsA:** 5 mg PO twice daily or 11 mg once daily used in combination with nonbiologic DMARDs. **PsA/PJIA (≥2 years old):** 3.2 mg (3.2 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg; 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 40 kg; and 5 mg (tablet or 5 mL oral solution) twice daily if weight ≥ 40 kg.	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Xeljanz XR is not interchangeable or substitutable with Xeljanz oral solution. Dose adjustment needed in patients taking CYP450 inhibitors, and with moderate or severe renal impairment, moderate hepatic impairment, lymphopenia, neutropenia, and anemia. Moderate to severe renal impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew. Xeljanz should not be initiated in patients with absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or hemoglobin < 9 g/dL. Administer Xeljanz oral solution with the included press-in bottle adapter and oral dosing syringe.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. For patients on hemodialysis, administer doses after the dialysis session. Do not take supplemental doses if a dose was taken before dialysis. Hepatic impairment: Patients with RA, PsA, or AS receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. Not recommended in severe hepatic impairment.	
Yesintek (ustekinumab-kfce)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤ 100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. > 100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):**	**Co-existent moderate-to-severe PsO with PsA weighing > 100 kg**: 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks.	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that the drug be administered by a healthcare provider. When administered via IV infusion, the drug must be diluted, prepared

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		< 60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg > 100 kg, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **PsA (≥ 6 years):** < 60 kg, 0.75 mg/kg (injection volume based on weight) 60 kg or more, 45 mg > 100 kg with concomitant moderate-to-severe PsO, 90 mg; administer recommended dose initially, 4 weeks later, then every 12 weeks.		and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Yusimry (adalimumab-aqvh)	Single-dose prefilled pen: 40 mg/0.8 mL Single-dose prefilled syringe: 40 mg/0.8 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA:** ≥ 30 kg, 40 mg SQ every other week **PsO, UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **HS:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations

ALC=absolute lymphocyte count; ANC=absolute neutrophil count; AS = ankylosing spondylitis; CD = Crohn's disease; CRS = cytokine release syndrome; DIRA = deficiency of interleukin-1 receptor antagonist; DMARD = disease-modifying anti-rheumatic drug; ERA = enthesitis-related arthritis; GCA = giant cell arteritis; GVHD: graft-vs-host disease; HS = hidradenitis suppurative; IV = intravenous infusion; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NOMID = neonatal-onset multisystem inflammatory disease; NRAS = nonradiographic axial spondyloarthritis; NSAID = non-steroidal anti-inflammatory drug; PJIA = polyarticular juvenile idiopathic arthritis; PMR = polymyalgia rheumatica; PO = orally; PsA = psoriatic arthritis; PsO = plaque psoriasis; RA = rheumatoid arthritis; SJIA = systemic juvenile idiopathic arthritis; SQ = subcutaneously; SSc-ILD = systemic sclerosis-associated interstitial lung disease; UC = ulcerative colitis; UV = uveitis.
See the current prescribing information for full details.

Conclusion

- Immunomodulators are available for a variety of conditions associated with inflammation. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Some head-to-head clinical trials between the agents have been completed.
  - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
  - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
  - In patients with RA, upadacitinib was superior to abatacept for changes in the DAS28-CRP and the achievement of remission (*Rubbert-Roth et al 2020*).
  - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
  - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
  - In patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 responses compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
  - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have noninferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
  - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
  - Persistence of efficacy at 5 years in patients with RA was evaluated in an exploratory meta-analysis of 29 studies of second-line treatment with biological DMARDs including adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, tocilizumab, abatacept, rituximab, sarilumab, and infliximab-dyyb. Tocilizumab had the highest persistence (66%, 95% CI 60 to 72), followed by golimumab (62%, 95% CI 47 to 75) and abatacept (59%, 95% CI 38 to 77) (*Schneeberger et al 2026*)
  - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, RCTs in 676 and 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, $p < 0.0001$; CLARITY: 66.5% vs 47.9%, $p < 0.0001$) at week 16 in CLEAR and at week 12 in CLARITY.
  - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017[b]).*

- In the IXORA-R study, ixekizumab was found noninferior to guselkumab for achievement of PASI 100 at week 24 (50% vs 52%, respectively); statistical significance was not reached for this comparison (p = 0.41) (*Blauvelt et al 2021).*
- A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
- In the FIXTURE study in patients with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
- In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
- In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
- In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
- In 2 trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.
- In the IMMerge trial, risankizumab was noninferior to secukinumab for the proportion of patients achieving PASI 90 at week 16 (73.8% vs 65.6%, respectively) and was superior to secukinumab at week 52 (86.6% vs 57.1%, respectively; p < 0.001) (*Warren et al 2021[b]*).
- In the IMMPulse trial, risankizumab produced significantly greater rates of PASI 90 response at short- and long-term follow-up than apremilast in adults with moderate PsO (*Stein Gold et al 2023*).
- In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; p < 0.0001).
- Four trials, BE READY, BE SURE, BE VIVID, and BE RADIANT, demonstrated superiority of bimekizumab over placebo, adalimumab, ustekinumab, and secukinumab (respectively) for the treatment of adults with moderate-to-severe PsO based on PASI and IGA endpoints (*Gordon et al 2021*, *Reich et al 2021[a]*, *Reich et al 2021[b]*, *Warren et al 2021[a]*).
- No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
- In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
- In the SPIRIT-H2H study, ixekizumab led to a higher proportion of patients with PsA achieving the combined ACR 50 and PASI 100 and PASI 100 alone compared with adalimumab (*Smolen et al 2020[b]*).

- For RA, the ACR recommends the use of conventional DMARDs, a TNF inhibitor, a non-TNF inhibitor biologic (tocilizumab, sarilumab, abatacept, or rituximab [only in patients that have had an inadequate response to TNF inhibitors or have a history of lymphoproliferative disorder]), or a JAK inhibitor (tofacitinib, baricitinib, upadacitinib). Biosimilars are considered equivalent to FDA-approved originator biologics (*Fraenkel et al 2021*). EULAR guidelines for RA management were recently updated (*Smolen et al 2023*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological DMARD should be added; JAK inhibitors may be considered, but pertinent risk factors must be taken into account. In patients who cannot use csDMARDs as a comedication, IL-6 inhibitors and targeted synthetic DMARDs may have some advantages compared with other biologic DMARDs. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF or IL-6 inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF or IL-6 inhibitor.

- The EULAR 2023 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, such as MTX (*Gossec et al 2024*). In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate. The choice of the mechanism of action should be based on musculoskeletal manifestations related to PsA; for patients with clinically relevant skin involvement, an IL-17A inhibitor (ixekizumab, secukinumab), IL-17A/F inhibitor (bimekizumab), IL-23 inhibitor (guselkumab, risankizumab), or IL-12/23 inhibitor (ustekinumab) is preferred; for patients with uveitis, TNF inhibitors (adalimumab, certolizumab, etanercept, infliximab, and golimumab) are preferred; and in patients with inflammatory bowel disease, TNF inhibitors, an IL-23 inhibitor, ustekinumab, or a JAK inhibitor (tofacitinib or upadacitinib) is preferred. In patients with inadequate response or intolerance to a biologic DMARD or JAK inhibitor, switching to another biologic DMARD or JAK inhibitor should be considered, including one switch within a class.
- Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, JAK inhibitors, and PDE-4 inhibitors (*Coates et al 2022[b]*). Joint guidelines from the AAD/NPF on the treatment of PsO with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*). Icotyde (icotrokinra) is the first oral IL-23 for the treatment of PsO approved in 2026; it has not yet been incorporated into clinical guidelines.
- The ACR/NPF guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).
- The ACR guideline for SJIA conditionally recommends an IL-1 inhibitor or IL-6 inhibitor for initial treatment; no specific agent is preferred (*Onel et al 2022*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.
- Based upon guidelines from the European Dermatology Forum, adalimumab, secukinumab, and bimekizumab are recommended as first-line therapies for moderate-to-severe HS in patients with inadequate response to conventional systemic therapies. Infliximab may be recommended as a second-line option if first-line biologic treatment is unsatisfactory; brodalumab, ustekinumab, anakinra, or ustekinumab could also be considered in this setting (*Zouboulis et al 2025*).
- Joint guidelines from ASAS and EULAR state that TNF inhibitors, IL-17A inhibitors, or JAK inhibitors should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with a TNF inhibitor or IL-17A inhibitor (*Ramiro et al 2023*). The 2019 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients. Secukinumab or ixekizumab is recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2014*).
- The boxed warnings for various immunomodulator agents discussed in this overview generally highlight the risk of serious infections, malignancies, mortality, major cardiovascular events (MACE), or thrombosis; see safety section for information for specific agents in the class.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, deucravacitinib, deuruxolitinib, tofacitinib, ritlecitinib, and upadacitinib are given by SQ injection and/or IV infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, deucravacitinib, deuruxolitinib, tofacitinib, ritlecitinib, and upadacitinib are given orally.

- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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