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Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, August 6th, 2026 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333.

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	T. Douglass (OHA)
	E. Mental Health Clinical Advisory Group	A. Gibler (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. Quarterly Utilization Reports
B. Oncology Prior Authorization Updates
C. Literature Scans
   1. Drugs for Diabetes
      a. GLP-1 Receptor Agonists and GIP Therapies
      b. Oral Medications for Diabetes
   2. Glaucoma Drugs
   3. Antianginals
   4. Ophthalmic Anti-inflammatory Drugs
   5. Topical Steroids
   6. Antihypertensive Drugs
      a. Combination Antihypertensive
      b. Beta-blockers, Oral
      c. Calcium Channel Blockers
   7. Potassium and Potassium Phosphate, Oral Products
D. Public Comment

1:25 PM	III. DUR ACTIVITIES	
	A. ProDUR Report	L. Starkweather (Gainwell)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)
	1. Update on Targeted Immune Modulators Used to Manage Selected Autoimmune Conditions	

2. Chronic Kidney Disease Pharmacotherapy: Guideline Updates & Practical Application
3. Eating Disorders and Disordered Eating Behaviors in Patients with Diabetes

IV. OLD BUSINESS

A. Healthier Oregon Policy Update — S. Servid (OSU)
1. Antifungals, Oral

V. NEW BUSINESS

1:45 PM — A. Redemplo® (plozasiran) New Drug Evaluation — M. Herink (OSU)
1. New Drug Evaluation/Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:00 PM — B. Newer Drugs for Heart Failure Class Update — D. Moretz (OSU)
1. Class Update ARNI and Diuretics
2. Prior Authorization Criteria
3. Public Comment
4. Discussion and Clinical Recommendations to OHA

2:15 PM — C. Tzield® (teplizumab) Prior Authorization Update — K. Sentena (OSU)
1. Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:20 PM — D. Herpes Simplex Class Update — K. Sentena (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion and Clinical Recommendations to OHA

2:40 PM — E. Enzyme Replacement for Hunter Syndrome Orphan Drug Evaluations — D. Moretz (OSU)
1. Elaprase® (idursulfase) Orphan Evaluation
2. Avlayah™ (tividenofusp alfa) Orphan Evaluation
3. Prior Authorization Criteria
4. Public Comment
5. Discussion and Clinical Recommendations to OHA

2:55 PM — BREAK

3:10 PM — F. Monoclonal Antibodies for Lupus Class Update and New Drug Evaluation — S. Fletcher (OSU)
1. Gazyva® (obinutuzumab) New Drug Evaluation
2. Class Update/Prior Authorization Criteria
3. Public Comment

4. Discussion and Clinical Recommendations to OHA

3:25 PM	G. C-Type Natriuretic Peptides Class Update and New Drug Evaluation 1. Yuviwel® (navepegritide) New Drug Evaluation 2. Class Update/Prior Authorization Criteria 3. Public Comment 4. Discussion and Clinical Recommendations to OHA	D. Moretz (OSU)
3:40 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

Drug Use Research & Management Program
OHA Health Policy & Analytics
Office of Delivery System Innovation
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Bridget Bradley, PharmD, BCPP	Pharmacist	Kaiser Northwest Psychiatry	Beaverton	December 2026
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2026
Samara Stevens, ND	Public	Mental Health Naturopath	Portland	December 2026
F. Douglas Carr, MD, MMM	Physician	Medical Director, Umpqua Health	Roseburg	December 2027
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2027
Eriko Onishi, MD	Physician	OHSU Family Medicine	Portland	December 2027
Edward Saito, PharmD, BCACP	Pharmacist	Clinical Pharmacist, Virginia Garcia Memorial Health Center	Cornelius	December 2027
Patrick DeMartino, MD, MPH	Physician	Pediatric Hematology & Oncology	Portland	December 2028
Jennifer Henderson, DO	Physician	Asante Medical Director	Medford	December 2028
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2028
Bruce Leewiwatanakul, DO, MA	Physician	Child & Adolescent Psychiatry	Portland	December 2029

Drug Use Research & Management Program
OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 4th, 2026
1:05 PM - 3:35 PM
Via Zoom webinar

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence, and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee, and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 in accordance with Oregon Revised Statute 183.333

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Bruce Leewiwatanakul, DO; Eddie Saito, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Dee Weston; Trevor Douglass, DC; Lewis Backus

Audience: Lynda Finch*, Biogen; Rober Konop*, Novartis; Abby Hata, Immedica North America; Rodney Padron Perez, Samaritan; Michele Pannell, Alkermes; Jennie Barlow, Amgen; Jenna Doerr, Artia Solutions; Sandee Merrick, Rocket Pharmaceuticals; Tony Pendergraft; Michael Foster, Ultragenyx; Bill McDougall, Biogen; Herbert Starr, Acadia Pharmaceuticals; Lee Stout, Chiesi; Rosalie Elliott, UHA; Gary Parenteau, Dexcom; Elisha Joseph; Jessica GFarrison, Gainwell Technologies; Sergio M; Shauna Wick, Trillium; Tim Melancon; Jason Morris, Samaritan; Lisa Pulver; Nirmal Ghuman; J&J; Daria Meleshkina, Moda EOCCO; Jeanna Colabianchi; Craig Sexton, Supernus; Joseph Auci; Mark Kantor, AllCare; Gloria Zepeda, AllCare; Ann Nelson; Amanda Howton; Divine Marcelo; Chris Ferrin, IHN; Megan Bell; Mike Donabedian, Sarepta Therapeutics; Georgette Dzwilewski, Indivior

(*) Provided verbal testimony

I. CALL TO ORDER

A. Roll Call & Introductions
- Meeting called to order at approx. 1:05 p.m., introduction of new Committee member Dr. Leewiwatanakul and roll call of Committee and staff

B. Conflict of Interest Declaration – no new conflicts of interest were declared

C. Approval of Agenda and April Minutes presented by Roger Citron, RPh
ACTION: Motion to approve, 2nd, all in favor with one abstention

D. Department Update provided by Dee Weston, JD

E. Mental Health Clinical Advisory Group Update presented by Andrew Gibler, PharmD

DRAFT

II. CONSENT AGENDA TOPICS

A. Inhalers for Asthma/COPD Literature Scan
Recommendation:
- No changes to the PDL are recommended based on the review of the clinical evidence
- Evaluate costs in executive session

B. Oncology Prior Authorization (PA) Updates
Recommendation:
- Add: Kitprozy (carfilzomib); Phyrago (dasatinib anhydrous); Zusduri (mitomycin); Lifyorli (relacorilant); Koselugo (selumetinib) to Table 1 in the Oncology Agents PA criteria

C. Orphan Drug Policy Updates
Recommendation:
-Update Table 1 in the Orphan Drugs PA criteria to support medically appropriate use of: Kygevvi (doxecitine and doxribtimine); Lynavoy (linerixibat); Otarmeni (lunsotogene parvec); Kresladi (marnetegragene autotemcel); Avlayah (tividenofusp alfa)
- Modify PA criteria to include new orphan drugs and carve-out status
- Update renewal criteria to accommodate longer approvals for chronic therapy
ACTION: Motion to approve, 2nd, all in favor

III. PDL OLD BUSINESS

A. Healthier Oregon Policy Update
1. Topical Antifungals
2. Antidiarrheals
3. Antacids, Proton Pump Inhibitors
4. Nasal Allergy Inhalers
5. Ophthalmic Medications for Allergies
6. Laxatives for Chronic Constipation
Recommendation:
-Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

IV. DRUG USE REVIEW (DUR) ACTIVITIES

A. Quarterly Utilization Report: Roger Citron, RPh
B. ProDUR Report: Lan Starkweather, PharmD
C. RetroDUR Report: Dave Engen, PharmD
D. Oregon State Drug Review: Kathy Sentena, PharmD
1. Respiratory Syncytial Virus (RSV) Prevention Update
2. Evaluating the Quality of Evidence from Observational Studies: Lessons from Acetaminophen Use in Pregnancy

DRAFT

V. NEW BUSINESS

A. Topoisomerase II Inhibitors Class Update with New Drug Evaluation: Kathy Sentena, PharmD
Recommendation:
- No changes to the PDL are recommended based on the review of the clinical evidence
- Nonpreferred antibiotics are subject to the **Non-Preferred Drugs in Select PDL Classes** PA criteria
- Maintain zoliflodacin as non-preferred
- Evaluate costs in executive session

ACTION: Motion to approve, 2nd, all in favor

B. Zycubo (Copper Histidinate) Orphan Drug Evaluation: Sara Fletcher, PharmD
Recommendation:
- Implement **Copper histidinate (ZYCUBO)** PA criteria to verify appropriate diagnosis, monitoring and dosing

ACTION: Motion to approve, 2nd, all in favor

C. Benzodiazepines Focused Scan for Catatonia: Dave Engen, PharmD
Recommendations:
- No changes to the PDL are recommended based on the review of the clinical evidence
- Update **Benzodiazepines** PA criteria to align with current evidence for the treatment of catatonia and minimize therapy interruptions for patients with conditions previously approved for long-term use
- Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd, all in favor

D. Cardamyst (etripamil) New Drug Evaluation: Deanna Moretz, PharmD
Recommendations:
- Maintain etripamil as non-preferred on the PDL
- Implement proposed **Etripamil (Cardamyst) Nasal Spray** PA criteria to ensure appropriate utilization of etripamil nasal spray

ACTION: Modify proposed PA criteria to remove question #6
Motion to approve, 2nd, all in favor

E. Spinal Muscular Atrophy Class Update: Deanna Moretz, PharmD
Recommendations:
- No changes to the PDL are recommended based on the review of clinical evidence
- Revise the **Spinal Muscular Atrophy Drugs** PA criteria to include onasemnogene abeparvovec-brve
- Evaluate drug costs in the executive session

Public Comment: Robert Konop, Novartis; Lynda Finch, Biogen
ACTION: Motion to approve, 2nd, all in favor

DRAFT

F. Myasthenia Gravis DERP Report: Sara Fletcher, PharmD

Recommendations:

- No changes to the PDL or PA criteria are recommended based on the review of clinical evidence
- Update **Amifampridine** and **Efgartigimod** PA criteria as proposed
- Evaluate drug costs in the executive session

ACTION: Motion to approve, 2nd, all in favor

G. Loargys (pegzilarginase) Orphan Drug Evaluation: Deanna Moretz, PharmD

Recommendations:

- Implement proposed **Pegzilarginase-nbln (Loargys®) Injection** PA criteria to ensure use in appropriate FDA-approved populations

Public Comment: Abby Hata, Immedica North America

ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; Douglas Carr, MD; Patrick DeMartino, MD; Russ Huffman, PMHNP; Bruce Leewiwatanakul, DO; Eddie Saito, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Andrew Gibler, PharmD; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Lan Starkweather, PharmD; Brandon Wells; Lewis Backus

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Inhalers for Asthma/COPD

Recommendation:

- **SABA**: Make levalbuterol HFA, Xopenex HFA, and levalbuterol nebulizer preferred
- **LABA**: Make Striverdi Respimat and arformoterol nebulizer preferred and Serevent Diskus non-preferred
- **ICS/LABA**: Make Dulera and Airduo Respiclick non-preferred
- **LABA/LAMA**: Make Bevespi Aerosphere preferred
- **ICS**: Make budesonide nebulizer and fluticasone HFA preferred; beclomethasone dipropionate AER w/ADAP non-preferred; Pulmicort Flexhaler, Arnuity Ellipta, and Qvar Redihaler non-preferred

ACTION: Motion to approve, 2nd, all in favor

B. Healthier Oregon Policy Update

Recommendation:

- **Topical antifungals**: Make generic tolnafate cream and powder, ciclopirox shampoo, nystatin powder, nystatin/triamcinolone ointment, econazole nitrate cream, terbinafine cream, butenafine cream, clotrimazole solution preferred

DRAFT

- Antidiarrheals: Make generic diphenoxylate/atropine tablets and bismuth subsalicylate tablets, chew tabs, and oral suspension preferred
- PPIs: Make omeprazole magnesium DR capsules, omeprazole and omeprazole magnesium DR tablets, and omeprazole DR rapid tabs, esomeprazole magnesium DR tablet, omeprazole-sodium bicarbonate capsule preferred
- Laxatives: Make lubiprostone capsule, prucalopride succinate tablets, polyethylene glycol 3350 powder packs, methylcellulose powder (Citrucel), and senna leaf extract chew tabs preferred
- Nasal allergy inhalers: Make ipratropium bromide spray, triamcinolone acetonide spray, fluticasone propionate spray susp, and budesonide spray/pump preferred
- Ophthalmics for allergy: Make ketotifen fumarate drops preferred
ACTION: Motion to approve, 2nd, all in favor

C. Topoisomerase II Inhibitors Class
Recommendations:
- Make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

D. Benzodiazepines
Recommendations:
- Make alprazolam rapid tabs, alprazolam intensol (oral concentrate), and Loreev XR voluntary non-preferred
- Make all other benzodiazepines preferred
ACTION: Motion to approve, 2nd, all in favor

E. Spinal Muscular Atrophy
Recommendations:
- Make Zolgensma and high-dose nusinersen (28 mg and 50 mg) vials non-preferred
ACTION: Motion to approve, 2nd, all in favor

F. Myasthenia Gravis
Recommendations:
- Remove PDL status for myasthenia gravis drugs in orphan class (eculizumab [all versions], zilucoplan)
- Make efgartigimod alfa-hyaluronidase qvfc nonpreferred
ACTION: Motion to approve, 2nd, all in favor

VIII. ADJOURN

DRAFT

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: January 2025 - December 2025

Eligibility	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Total Members (FFS & Encounter)	1,241,274	1,243,854	1,234,473	1,242,572	1,246,331	1,249,863	1,242,513	1,233,644	1,231,323	1,230,074	1,225,045	1,223,371	1,237,028
FFS Members	99,039	93,047	91,577	91,602	90,100	89,262	90,257	88,300	87,978	90,439	89,058	89,968	90,886
OHP Basic with Medicare	7,659	7,451	7,022	6,746	6,382	6,097	6,372	6,183	6,002	6,282	6,108	6,305	6,551
OHP Basic without Medicare	8,472	8,170	8,072	8,028	8,016	7,876	7,937	7,856	7,841	7,922	7,892	7,892	7,998
ACA	82,908	77,426	76,483	76,828	75,702	75,289	75,948	74,261	74,135	76,235	75,058	75,771	76,337
Encounter Members	1,142,235	1,150,807	1,142,896	1,150,970	1,156,231	1,160,601	1,152,256	1,145,344	1,143,345	1,139,635	1,135,987	1,133,403	1,146,143
OHP Basic with Medicare	82,625	80,472	75,440	76,700	77,380	77,913	77,511	77,694	77,785	77,493	77,522	77,679	78,018
OHP Basic without Medicare	64,002	63,793	62,866	62,847	62,790	62,724	62,691	62,765	62,703	62,691	62,808	62,772	62,954
ACA	995,608	1,006,542	1,004,590	1,011,423	1,016,061	1,019,964	1,012,054	1,004,885	1,002,857	999,451	995,657	992,952	1,005,170

Gross Cost Figures for Drugs	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	YTD Sum
Total Amount Paid (FFS & Encounter)	$147,069,205	$133,458,549	$149,173,460	$151,547,617	$148,165,761	$148,455,155	$154,639,364	$145,102,232	$151,383,475	$158,711,370	$138,010,644	$161,079,978	$1,786,796,809
Mental Health Carve-Out Drugs	$14,619,079	$13,503,540	$14,845,426	$15,636,427	$15,273,342	$15,644,776	$15,970,250	$16,005,096	$16,149,979	$16,780,124	$15,446,498	$17,730,858	$187,605,394
OHP Basic with Medicare	$6,525	$5,748	$2,268	$5,567	$8,358	$10,675	$8,753	$10,307	$9,941	$19,531	$4,211	$5,551	$97,436
OHP Basic without Medicare	$4,549,707	$4,595,534	$5,042,973	$4,923,294	$4,720,030	$4,594,550	$4,688,172	$4,901,068	$4,663,165	$4,924,418	$4,257,286	$5,408,236	$57,268,431
ACA	$8,560,562	$7,554,853	$8,510,744	$9,056,320	$8,754,890	$8,794,514	$9,092,422	$8,994,010	$9,228,700	$9,783,155	$8,635,124	$9,874,075	$106,839,370
FFS Physical Health Drugs	$2,388,406	$2,251,048	$2,215,126	$2,259,784	$2,258,310	$2,124,672	$2,178,576	$1,975,332	$1,956,453	$2,133,231	$1,890,967	$2,104,153	$25,736,058
OHP Basic with Medicare	$29,730	$28,798	$27,238	$26,075	$24,680	$23,216	$24,981	$23,738	$22,336	$23,634	$21,268	$22,211	$297,904
OHP Basic without Medicare	$678,897	$705,078	$664,971	$718,207	$654,319	$596,726	$608,494	$476,549	$507,274	$623,203	$555,697	$567,495	$7,356,909
ACA	$1,372,569	$1,218,184	$1,281,340	$1,245,308	$1,306,048	$1,193,995	$1,240,745	$1,139,089	$1,160,733	$1,222,980	$1,053,058	$1,218,579	$14,652,629
FFS Physician Administered Drugs	$1,817,399	$1,688,126	$1,542,654	$1,750,105	$1,144,954	$962,197	$1,752,669	$1,285,578	$1,274,873	$1,311,589	$1,472,325	$1,248,997	$17,251,464
OHP Basic with Medicare	$143,936	$85,996	$121,094	$113,354	$60,542	$73,183	$119,966	$99,057	$97,356	$112,048	$80,719	$94,288	$1,201,540
OHP Basic without Medicare	$236,232	$104,317	$346,878	$293,345	$167,275	$106,091	$188,091	$151,283	$72,150	$110,964	$222,050	$153,513	$2,152,189
ACA	$766,120	$592,780	$436,177	$626,748	$348,726	$337,108	$516,344	$621,512	$455,902	$496,637	$419,724	$489,479	$6,107,256
Encounter Physical Health Drugs	$93,008,839	$86,203,368	$95,478,746	$97,736,510	$96,169,753	$93,541,990	$98,110,731	$93,990,343	$98,784,557	$103,824,567	$89,285,244	$101,893,372	$1,148,028,019
OHP Basic with Medicare	$368,077	$337,593	$355,263	$382,574	$373,285	$346,645	$350,686	$361,317	$330,780	$395,086	$358,033	$375,450	$4,334,791
OHP Basic without Medicare	$19,324,380	$17,084,750	$18,639,235	$19,002,030	$18,041,542	$17,690,217	$18,190,675	$18,166,141	$18,740,873	$19,596,796	$17,129,752	$19,537,963	$221,144,353
ACA	$60,647,350	$56,578,259	$62,622,194	$64,424,806	$63,625,867	$61,206,614	$64,863,930	$61,279,265	$64,540,153	$67,721,021	$58,169,343	$66,222,371	$751,901,175
Encounter Physician Administered Drugs	$35,235,483	$29,812,467	$35,091,507	$34,164,791	$33,319,402	$36,181,521	$36,627,139	$31,845,883	$33,217,613	$34,661,859	$29,915,610	$38,102,598	$408,175,874
OHP Basic with Medicare	$1,178,608	$875,046	$797,451	$894,201	$826,563	$780,194	$828,021	$679,082	$756,821	$820,071	$633,488	$626,769	$9,696,314
OHP Basic without Medicare	$5,738,280	$5,968,709	$9,498,713	$6,084,282	$6,181,766	$5,977,686	$6,521,627	$5,634,800	$6,332,889	$6,239,383	$5,561,565	$9,803,275	$79,542,974
ACA	$23,672,579	$18,102,738	$19,752,875	$21,265,940	$20,506,903	$23,755,911	$22,410,686	$19,996,734	$20,352,584	$21,401,360	$18,250,077	$21,663,725	$251,132,113

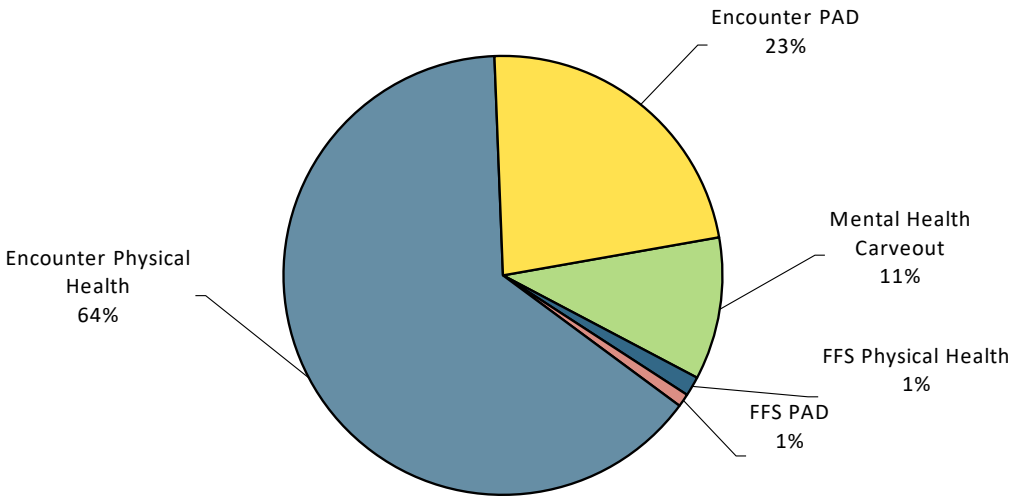
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

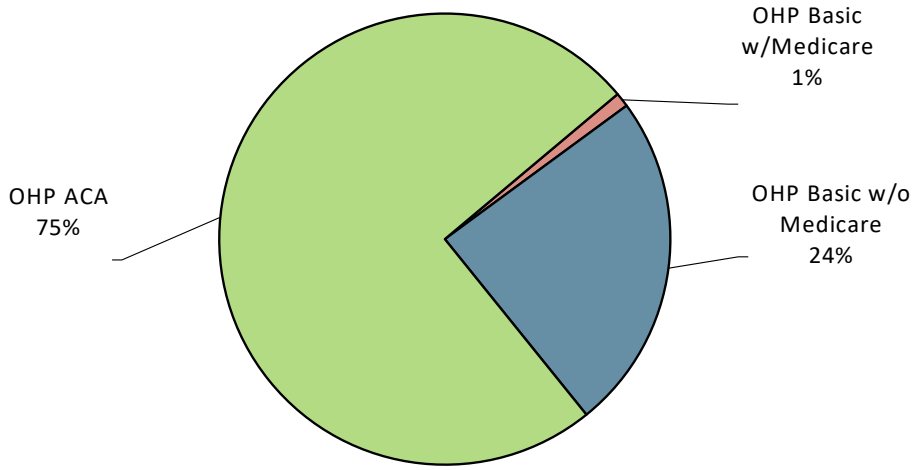
Last Updated: April 24, 2026

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: January 2025 - December 2025

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee.
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

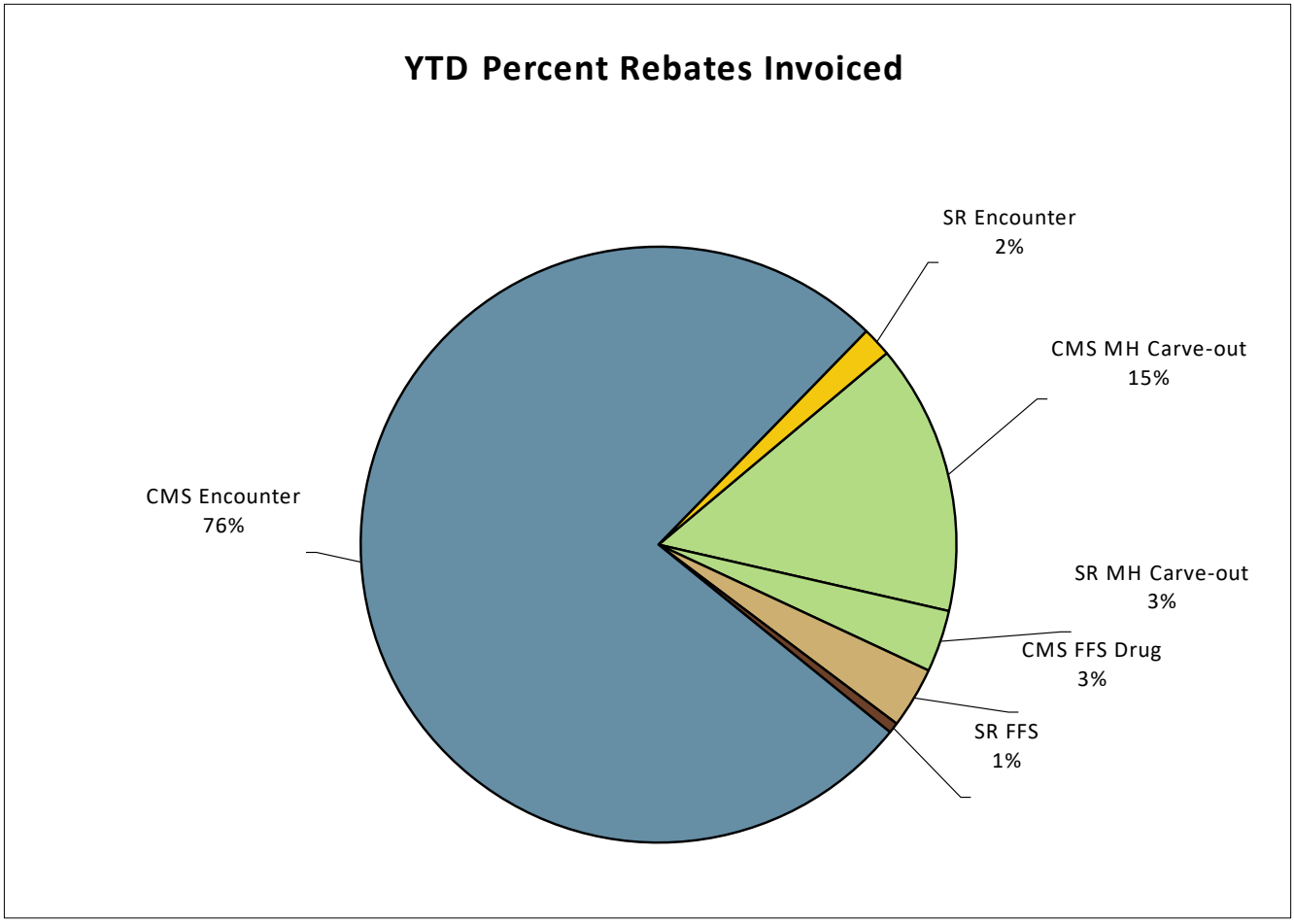
Last Updated: April 24, 2026

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Pharmacy Utilization Summary Report: January 2025 - December 2025

Quarterly Rebates Invoiced	2025-Q1	2025-Q2	2025-Q3	2025-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$63,503,670	$138,781,198	$121,855,581	$98,000,206	$422,140,655
CMS MH Carve-out	$15,437,788	$15,508,845	$15,634,284	$15,429,275	$62,010,192
SR MH Carve-out	$3,054,466	$3,496,840	$3,652,698	$3,996,794	$14,200,799
CMS FFS Drug	$4,222,380	$3,755,428	$3,134,987	$2,898,484	$14,011,280
SR FFS	$651,850	$737,025	$569,654	$473,527	$2,432,056
CMS Encounter	$38,602,257	$113,423,769	$97,144,925	$73,571,287	$322,742,237
SR Encounter	$1,534,929	$1,859,289	$1,719,033	$1,630,839	$6,744,090

Quaterly Net Drug Costs	2025-Q1	2025-Q2	2025-Q3	2025-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$366,197,544	$309,387,335	$329,269,490	$359,801,785	$1,364,656,154
Mental Health Carve-Out Drugs	$24,475,792	$27,548,859	$28,838,342	$30,531,410	$111,394,403
FFS Phys Health + PAD	$7,028,528	$6,007,566	$6,718,840	$6,789,251	$26,544,186
Encounter Phys Health + PAD	$334,693,224	$275,830,910	$293,712,307	$322,481,124	$1,226,717,565



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

Last Updated: April 24, 2026

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: January 2025 - December 2025

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$118.48	$107.29	$120.84	$121.96	$118.88	$118.78	$124.46	$117.62	$122.94	$129.03	$112.66	$131.67	$120.38
Mental Health Carve-Out Drugs	$11.78	$10.86	$12.03	$12.58	$12.25	$12.52	$12.85	$12.97	$13.12	$13.64	$12.61	$14.49	$12.64
FFS Physical Health Drugs	$24.12	$24.19	$24.19	$24.67	$25.06	$23.80	$24.14	$22.37	$22.24	$23.59	$21.23	$23.39	$23.58
FFS Physician Administered Drugs	$18.35	$18.14	$16.85	$19.11	$12.71	$10.78	$19.42	$14.56	$14.49	$14.50	$16.53	$13.88	$15.78
Encounter Physical Health Drugs	$81.43	$74.91	$83.54	$84.92	$83.18	$80.60	$85.15	$82.06	$86.40	$91.10	$78.60	$89.90	$83.48
Encounter Physician Administered Drugs	$30.85	$25.91	$30.70	$29.68	$28.82	$31.17	$31.79	$27.80	$29.05	$30.41	$26.33	$33.62	$29.68

Claim Counts	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Total Claim Count (FFS & Encounter)	1,372,984	1,245,826	1,358,392	1,384,468	1,370,079	1,325,158	1,357,432	1,297,286	1,330,225	1,395,713	1,248,832	1,353,098	1,336,624
Mental Health Carve-Out Drugs	229,233	209,570	228,400	230,361	227,804	224,446	232,525	224,310	227,462	236,908	211,673	230,222	226,076
FFS Physical Health Drugs	29,485	26,290	27,633	27,281	25,874	24,617	25,464	23,975	24,029	25,317	22,745	25,081	25,649
FFS Physician Administered Drugs	10,126	8,980	9,085	9,131	8,824	8,456	9,218	8,679	9,403	10,096	8,411	9,435	9,154
Encounter Physical Health Drugs	955,275	863,266	947,028	963,849	951,667	916,656	938,301	893,367	920,976	970,777	865,261	941,532	927,330
Encounter Physician Administered Drugs	148,865	137,720	146,246	153,846	155,910	150,983	151,924	146,955	148,355	152,615	140,742	146,828	148,416

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$107.12	$107.12	$109.82	$109.46	$108.14	$112.03	$113.92	$111.85	$113.80	$113.71	$110.51	$119.05	$111.38
Mental Health Carve-Out Drugs	$63.77	$64.43	$65.00	$67.88	$67.05	$69.70	$68.68	$71.35	$71.00	$70.83	$72.97	$77.02	$69.14
FFS Physical Health Drugs	$81.00	$85.62	$80.16	$82.83	$87.28	$86.31	$85.56	$82.39	$81.42	$84.26	$83.14	$83.89	$83.66
FFS Physician Administered Drugs	$179.48	$187.99	$169.80	$191.67	$129.75	$113.79	$190.14	$148.13	$135.58	$129.91	$175.05	$132.38	$156.97
Encounter Physical Health Drugs	$97.36	$99.86	$100.82	$101.40	$101.05	$102.05	$104.56	$105.21	$107.26	$106.95	$103.19	$108.22	$103.16
Encounter Physician Administered Drugs	$236.69	$216.47	$239.95	$222.07	$213.71	$239.64	$241.09	$216.70	$223.91	$227.12	$212.56	$259.50	$229.12

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$22.21	$22.29	$22.65	$22.89	$22.70	$23.12	$23.60	$24.22	$24.37	$25.02	$23.76	$24.28	$23.43
Mental Health Carve-Out Drugs	$15.76	$16.27	$15.73	$16.79	$15.54	$15.61	$15.65	$15.50	$15.38	$15.47	$15.67	$15.78	$15.76
FFS Physical Health Drugs	$22.43	$22.70	$23.23	$22.46	$23.82	$24.08	$25.17	$26.61	$24.58	$24.53	$24.42	$24.82	$24.07
Encounter Physical Health Drugs	$23.87	$23.85	$24.43	$24.46	$24.51	$25.07	$25.67	$26.51	$26.77	$27.58	$25.89	$26.50	$25.43

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$829.26	$868.23	$869.26	$874.25	$882.67	$882.08	$892.86	$893.29	$820.87	$783.32	$826.68	$900.17	$860.25
Mental Health Carve-Out Drugs	$1,733.06	$1,722.19	$1,725.93	$1,771.91	$1,750.69	$1,802.28	$1,743.95	$1,779.45	$1,737.20	$1,751.57	$1,823.23	$1,818.25	$1,763.31
FFS Physical Health Drugs	$476.58	$506.38	$473.23	$496.27	$507.61	$504.90	$487.65	$456.33	$454.20	$470.48	$476.09	$471.12	$481.74
Encounter Physical Health Drugs	$781.24	$821.83	$822.36	$823.55	$831.73	$824.83	$840.82	$836.45	$765.40	$726.59	$764.31	$839.36	$806.54

Generic Drug Use Percentage	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Generic Drug Use Percentage	91.5%	91.7%	91.6%	91.6%	91.7%	91.6%	91.5%	91.5%	90.5%	90.2%	90.9%	91.2%	91.3%
Mental Health Carve-Out Drugs	97.2%	97.2%	97.1%	97.1%	97.0%	97.0%	96.9%	96.8%	96.8%	96.8%	96.8%	96.6%	96.9%
FFS Physical Health Drugs	87.1%	87.0%	87.3%	87.3%	86.9%	87.1%	86.9%	87.0%	86.8%	86.6%	87.0%	86.8%	87.0%
Encounter Physical Health Drugs	90.3%	90.5%	90.4%	90.4%	90.5%	90.4%	90.3%	90.3%	89.1%	88.6%	89.5%	89.9%	90.0%

Preferred Drug Use Percentage	Jan-25	Feb-25	Mar-25	Apr-25	May-25	Jun-25	Jul-25	Aug-25	Sep-25	Oct-25	Nov-25	Dec-25	Avg Monthly
Preferred Drug Use Percentage	88.44%	88.42%	88.46%	88.49%	88.48%	88.51%	89.28%	89.34%	89.35%	89.30%	89.18%	89.08%	88.9%
Mental Health Carve-Out Drugs	86.28%	86.35%	86.27%	86.30%	86.29%	86.37%	86.24%	86.23%	86.20%	86.23%	85.93%	85.41%	86.2%
FFS Physical Health Drugs	94.41%	93.68%	94.21%	94.38%	93.95%	94.09%	94.85%	95.05%	95.01%	94.94%	94.96%	95.08%	94.6%
Encounter Physical Health Drugs	88.81%	88.80%	88.86%	88.88%	88.89%	88.92%	89.93%	90.02%	90.03%	89.96%	89.87%	89.88%	89.4%

Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last Updated: April 24, 2026

Drug Use Research & Management Program
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500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Mental Health Carve-out Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Antipsychotics, 2nd Gen	VRAYLAR *	$8,378,992	16.6%	5,455	$1,536	Y
2	Antipsychotics, Parenteral	INVEGA SUSTENNA	$6,454,948	12.8%	2,250	$2,869	Y
3	Antipsychotics, 2nd Gen	REXULTI *	$3,884,989	7.7%	2,716	$1,430	V
4	Antipsychotics, 2nd Gen	CAPLYTA *	$3,275,566	6.5%	2,013	$1,627	V
5	Antipsychotics, Parenteral	ABILIFY MAINTENA	$3,232,767	6.4%	1,281	$2,524	Y
6	Antidepressants	SPRAVATO *	$3,133,076	6.2%	1,920	$1,632	V
7	Antipsychotics, Parenteral	INVEGA TRINZA	$1,692,093	3.4%	203	$8,335	Y
8	Antidepressants	AUVELITY	$1,582,240	3.1%	1,516	$1,044	V
9	Antidepressants	TRINTELLIX	$1,277,106	2.5%	2,585	$494	V
10	Antipsychotics, Parenteral	ARISTADA	$1,202,639	2.4%	454	$2,649	Y
11	Antipsychotics, 2nd Gen	LYBALVI *	$1,124,413	2.2%	711	$1,581	V
12	Antipsychotics, Parenteral	ABILIFY ASIMTUFII	$979,497	1.9%	186	$5,266	Y
13	ADHD Drugs	QELBREE *	$876,140	1.7%	1,693	$518	Y
14	Antidepressants	BUPROPION XL	$836,516	1.7%	58,559	$14	Y
15	Antidepressants	SERTRALINE HCL	$790,255	1.6%	58,711	$13	Y
16	Antidepressants	TRAZODONE HCL	$736,284	1.5%	57,010	$13	V
17	Antidepressants	FLUOXETINE HCL	$634,215	1.3%	46,349	$14	Y
18	Antidepressants	DULOXETINE HCL	$622,105	1.2%	36,159	$17	Y
19	Antidepressants	ESCITALOPRAM OXALATE	$620,615	1.2%	46,726	$13	Y
20	Antipsychotics, Parenteral	INVEGA HAFYERA	$590,630	1.2%	32	$18,457	Y
21	Antiepileptics, Outpatient	LAMOTRIGINE	$465,645	0.9%	33,843	$14	Y
22	Antidepressants	BUSPIRONE HCL	$456,543	0.9%	32,514	$14	Y
23	Antipsychotics, 2nd Gen	ARIPIPRAZOLE *	$337,772	0.7%	23,385	$14	Y
24	Antipsychotics, Parenteral	UZEDY	$334,139	0.7%	121	$2,761	Y
25	Antidepressants	VENLAFAXINE HCL ER	$296,247	0.6%	18,835	$16	Y
26	Antipsychotics, 2nd Gen	QUETIAPINE FUMARATE *	$296,227	0.6%	21,840	$14	Y
27	Antipsychotics, 2nd Gen	COBENFY *	$262,212	0.5%	164	$1,599	V
28	Antidepressants	SERTRALINE HCL	$252,504	0.5%	1,757	$144	V
29	ADHD Drugs	ATOMOXETINE HCL *	$251,399	0.5%	10,853	$23	Y
30	ADHD Drugs	GUANFACINE HCL ER	$246,111	0.5%	15,961	$15	Y
31	Antidepressants	MIRTAZAPINE	$226,014	0.4%	14,642	$15	Y
32	Antidepressants	ZURZUVAE *	$222,611	0.4%	13	$17,124	V
33	Antipsychotics, 2nd Gen	OLANZAPINE *	$203,392	0.4%	14,241	$14	Y
34	Antiepileptics, Outpatient	LAMOTRIGINE ER	$179,929	0.4%	5,438	$33	V
35	Antidepressants	CITALOPRAM HBR	$167,298	0.3%	12,982	$13	Y
36	Antipsychotics, Parenteral	RISPERDAL CONSTA *	$167,097	0.3%	139	$1,202	Y
37	Antidepressants	DESVENLAFAXINE SUCCINATE ER	$165,744	0.3%	7,104	$23	Y
38	Antidepressants	AMITRIPTYLINE HCL *	$156,406	0.3%	11,848	$13	Y
39	ADHD Drugs	ONYDA XR	$155,358	0.3%	234	$664	V
40	Antipsychotics, 2nd Gen	RISPERIDONE *	$134,369	0.3%	9,700	$14	Y
		Top 40 Aggregate:	**$46,902,104**		**562,143**	**$83**	
		All Mental Health Carveout Drugs Totals:	**$50,409,137**		**670,579**	**$75**	
		All FFS Drug Totals:	**$71,922,317**		**783,358**	**$92**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: July 16, 2026

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500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Physical Health Carve-out Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Duchenne Muscular Dystrophy	VYONDYS-53 *	$1,785,710	16.2%	11	$162,337	N
2	Duchenne Muscular Dystrophy	AMONDYS-45 *	$1,075,280	9.8%	8	$134,410	N
3	Niemann-Pick Type C	MIPLYFFA *	$1,075,163	9.8%	12	$89,597	N
4	Duchenne Muscular Dystrophy	VILTEPSO *	$789,819	7.2%	13	$60,755	N
5	Epidermolysis Bullosa	VYJUVEK *	$728,184	6.6%	15	$48,546	N
6	STC 99 - Miscellaneous	DAYBUE STIX *	$715,448	6.5%	14	$51,103	N
7	Physican Administered Drug	Elosulfase Alfa, Injection *	$666,949	6.1%	33	$20,211	
8	Duchenne Muscular Dystrophy	DUVYZAT *	$637,379	5.8%	15	$42,492	N
9	Niemann-Pick Type C	AQNEURSA *	$575,833	5.2%	12	$47,986	N
10	Orphan Drug	LIVMARLI *	$373,154	3.4%	2	$186,577	
11	Orphan Drug	BYLVAY *	$364,926	3.3%	3	$121,642	
12	STC 99 - Miscellaneous	VYKAT XR *	$362,307	3.3%	11	$32,937	N
13	Lysosomal Storage Disorders	YARGESA *	$361,758	3.3%	9	$40,195	N
14	STC 99 - Miscellaneous	DAYBUE *	$342,959	3.1%	13	$26,381	N
15	Orphan Drug	STRENSIQ *	$279,425	2.5%	6	$46,571	
16	Orphan Drug	ELAPRASE *	$198,689	1.8%	5	$39,738	
17	Epidermolysis Bullosa	FILSUVEZ *	$185,133	1.7%	3	$61,711	N
18	STC 99 - Miscellaneous	SOHONOS *	$153,900	1.4%	4	$38,475	N
19	Orphan Drug	CTEXLI *	$117,280	1.1%	2	$58,640	
20	STC 87 - Electrolytes and Misc Nutr	ZYCUBO *	$112,040	1.0%	2	$56,020	
21	Orphan Drug	JOENJA *	$50,995	0.5%	1	$50,995	
22	Lysosomal Storage Disorders	MIGLUSTAT *	$47,944	0.4%	2	$23,972	N
23	Bile Therapy	CHOLBAM *	$21,495	0.2%	1	$21,495	N
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		Top 40 Aggregate:	**$11,021,770**		**197**	**$55,948**	
		All Physical Health Carveout Drugs Totals:	**$11,021,770**		**197**	**$55,948**	
		All FFS Drug Totals:	**$71,922,317**		**783,358**	**$92**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: July 16, 2026

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Phone 503-947-5220 | **Fax** 503-947-1119

Top 40 Physical Health Drugs Not Carved-out by Gross Amount Paid (FFS Only) - Second Quarter 2026

Rank	PDL Class	Drug	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	HIV	BIKTARVY	$398,469	3.8%	115	$3,465	Y
2	Substance Use Disorders, Opioid & Alcohol	SUBLOCADE	$252,658	2.4%	126	$2,005	Y
3	Physican Administered Drug	Injection, Ocrelizumab, 1 Mg *	$226,738	2.2%	16	$14,171	
4	Physican Administered Drug	Etonogestrel Implant System	$217,789	2.1%	358	$608	
5	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	OZEMPIC *	$205,951	2.0%	412	$500	N
6	Antiepileptics, Outpatient	FINTEPLA *	$192,074	1.8%	16	$12,005	N
7	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	MOUNJARO *	$177,528	1.7%	334	$532	N
8	Antiepileptics, Outpatient	EPIDIOLEX *	$174,615	1.7%	93	$1,878	N
9	Hepatitis C, Direct-Acting Antivirals	MAVYRET *	$171,947	1.6%	17	$10,115	Y
10	Targeted Immune Modulators	SKYRIZI ON-BODY *	$141,577	1.3%	10	$14,158	N
11	Spinal Muscular Atrophy	EVRYSDI *	$141,383	1.3%	12	$11,782	N
12	Targeted Immune Modulators for Asthma and Atopic D	DUPIXENT PEN *	$129,328	1.2%	48	$2,694	N
13	Physican Administered Drug	Inj Fam-Trastu Deru-Nxki 1mg *	$120,103	1.1%	11	$10,918	
14	Physican Administered Drug	Injection, Nivolumab *	$110,857	1.1%	29	$3,823	
15	Diabetes, GLP-1 Receptor Agonists and GIP Therapies	TRULICITY *	$106,133	1.0%	153	$694	Y
16	Physican Administered Drug	Mirena, 52 Mg	$100,178	1.0%	260	$385	
17	Anticoagulants, Oral and SQ	ELIQUIS	$96,803	0.9%	393	$246	Y
18	Physican Administered Drug	Inj Pembrolizumab *	$96,410	0.9%	44	$2,191	
19	Targeted Immune Modulators	SKYRIZI PEN *	$94,522	0.9%	8	$11,815	N
20	Diabetes, SGLT-2 Inhibitors	JARDIANCE	$94,336	0.9%	386	$244	Y
21	Contraceptives	SLYND	$92,439	0.9%	282	$328	
22	Physican Administered Drug	Contraceptive Pills For Bc *	$89,806	0.9%	2,099	$43	
23	Targeted Immune Modulators	HUMIRA(CF) PEN *	$87,642	0.8%	25	$3,506	Y
24	Growth Hormones	NORDITROPIN FLEXPRO *	$79,967	0.8%	53	$1,509	Y
25	Targeted Immune Modulators	COSENTYX SENSOREADY (2 PENS) *	$79,935	0.8%	16	$4,996	N
26	Substance Use Disorders, Opioid & Alcohol	BRIXADI	$78,868	0.8%	49	$1,610	Y
27	Physican Administered Drug	Iron Sucrose Injection	$77,430	0.7%	171	$453	
28	Antineoplastics, Newer	KISQALI *	$72,980	0.7%	5	$14,596	
29	Diabetic Supplies, CGM	DEXCOM G7 SENSOR *	$72,175	0.7%	301	$240	Y
30	Substance Use Disorders, Opioid & Alcohol	BUPRENORPHINE-NALOXONE *	$71,075	0.7%	1,021	$70	Y
31	Antineoplastics, Newer	EVEROLIMUS *	$70,980	0.7%	10	$7,098	
32	Cystic Fibrosis	KALYDECO *	$69,132	0.7%	3	$23,044	N
33	Cystic Fibrosis	TRIKAFTA *	$68,557	0.7%	25	$2,742	N
34	Weight Management Drugs	IMCIVREE *	$68,196	0.7%	5	$13,639	
35	Targeted Immune Modulators	RINVOQ *	$64,090	0.6%	23	$2,787	N
36	Diabetes, SGLT-2 Inhibitors	DAPAGLIFLOZIN	$62,854	0.6%	146	$431	Y
37	Antiepileptics, Outpatient	XCOPRI	$62,364	0.6%	85	$734	N
38	Pulmonary Arterial Hypertension Parenteral Drugs	WINREVAIR *	$61,305	0.6%	7	$8,758	N
39	Weight Management Drugs	ZEPBOUND *	$61,258	0.6%	70	$875	Y
40	Targeted Immune Modulators	TALTZ AUTOINJECTOR *	$59,692	0.6%	10	$5,969	Y
		Top 40 Aggregate:	**$4,700,145**		**7,247**	**$649**	
		All Physical Health Drugs Not Carved-out Totals:	**$10,491,410**		**112,582**	**$93**	
		All FFS Drug Totals:	**$71,922,317**		**783,358**	**$92**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: July 16, 2026

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Prior Authorization Criteria Update: Oncology

Purpose of the Update:
This update identifies antineoplastic drugs recently approved by the FDA to add to the oncology policy (see **Table 1**).

Table 1. New oncology drugs

Generic Name	Brand Name
Nilotinib	CAVHANZA
Pivekimab sunirine-pvzy	DECNUPAZ
Sonrotoclax	BEQALZI
Vepdegestrant	VEPPANU

Recommendation:

- Update prior authorization criteria to include new, recently approved antineoplastic drugs.

Oncology Agents

Goal(s):

- To ensure appropriate use for oncology medications based on FDA-approved and compendia-recommended (i.e., National Comprehensive Cancer Network® [NCCN]) indications.
- Incorporate 2-step review process for drugs on the high-cost drug carve-out list.

Length of Authorization:

- Up to 1 year

Requires PA:

- Initiation of therapy for drugs listed in **Table 1** (applies to both pharmacy and provider administered claims). This does not apply to oncologic emergencies administered in an emergency department or during inpatient admission to a hospital.

Covered Populations:

- Elzonris (tatagraxofusp-erzs): FFS and CCO populations beginning 1/1/26
- All others: FFS only

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: National Comprehensive Cancer Network (NCCN) Categories for Recommendations

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
For the 'Uniformed NCCN consensus' defined in Category 1 and 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Strong Panel disagreement regardless of the quality of evidence is a vote of at least 25%.	

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	**Yes:** Approve for length of therapy (if specified) or 12 months, (if duration is unspecified).	**No:** Go to #3
3. Is the request for any continuation of therapy?	**Yes:** Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	**No**: Go to #4

4. Is the diagnosis funded by OHP?	**Yes:** Go to #6	**No: If not eligible for EPSDT review:** Pass to RPh. Deny; not funded by the OHP **If eligible for EPSDT review:** Go to #5.
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity.
6. Is the indication FDA-approved for the requested drug? Note: This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes**: Go to #8	**No:** Go to #7
7. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug? Note: This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	**Yes:** Go to #8	**No:** Go to #9
8. Are there equally or higher recommended alternative agents based on NCCN categories of evidence (Table 1) for the requested indication and place in therapy? Note: When efficacy is similar, the choice of agent should be determined by safety, and then cost. In the absence of a safety concern, the prescriber is expected to use the least costly alternative.	**Yes:** HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).	**No:** HCDCO list: Pass to RPh. Pend; Refer to DMAP for secondary review. All other requests: Approve for length of therapy (if specified) or 12 months (if duration is unspecified).
9. Is there documentation based on chart notes that the patient is enrolled in a	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10

clinical trial to evaluate efficacy or safety of the requested drug?	Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.	
10. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. All other diagnoses must be evaluated for evidence of clinical benefit. The prescriber must provide the following documentation: • medical literature or guidelines supporting use for the condition, • clinical chart notes documenting medical necessity, and • documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Table 1. Oncology agents which apply to this policy (Updated 7/6/2026)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting.
Biosimilars for drugs on this list are included in the policy but may not be specifically listed.

Generic Name	Brand Name
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
abiraterone acetate/niraparib tosylate	AKEEGA
acalabrutinib	CALQUENCE
adagrasib	KRAZATI
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
afamitresgene autoleucel	TECELRA
alectinib HCl	ALECENSA
amivantamab-vmjw	RYBREVANT
amivantamab/ hyaluronidase-lpuj	RYBREVANT FASPRO
alpelisib	PIQRAY
asciminib	SCEMBLIX
apalutamide	ERLEADA
asparaginase (Erwinia chrysanthemi)	ERWINAZE
asparaginase Erwinia crysanthemi (recombinant)-rywn	RYLAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
avutometinib and defactinib	AVMAPKI FAKZYNJA CO-PACK
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
azacitidine	ONUREG
belantamab mafodotin-blmf	BLENREP
belinostat	BELEODAQ
belzutifan	WELIREG
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	TREANDA
bendamustine HCl	BENDEKA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capivasertib	TRUQAP
capmatinib	TABRECTA
carfilzomib	KYPROLIS, KITPROZY
cemiplimab-rwlc	LIBTAYO

Generic Name	Brand Name
ceritinib	ZYKADIA
ciltacabtagene autoleucel	CARVYKTI
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
cosibelimab-ipdl	UNLOXCYT
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
dasatinib anhydrous	PHYRAGO
datopotamab deruxtecan-dlnk	DATROWAY
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
denileukin diftitox-cxdl	LYMPHIR
dordaviprone	MODEYSO
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
eflornithine	IWILFIN
elacestrant	ORSERDU
elotuzumab	EMPLICITI
elranatamab-bcmm	ELREXFIO
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
ensartinib	ENSACOVE
entrectinib	ROZLYTREK
enzalutamide	XTANDI
epcoritamab-bysp	EPKINLY
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
fruquintinib	FRUZAQLA
futibatinib	LYTGOBI
gilteritinib	XOSPATA
glasdegib	DAURISMO
glofitamab-gxbm	COLUMVI
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA

Generic Name	Brand Name
idelalisib	ZYDELIG
imetelstat	RYTELO
Imlunestrant tosylate	INLURIYO
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lazertinib	LAZCLUZE
lenvatinib mesylate	LENVIMA
lifileucel	AMTAGVI
linvoseltamab-gcpt	LYNOZYFIC
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
lutetium Lu 177 vipivotide tetraxetan	PLUVICTO
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
melphalan hcl/hepatic delivery kit (HDS)	HEPZATO KIT
midostaurin	RYDAPT
mirvetuximab soravtansine-gynx	ELAHERE
mitomycin	ZUSDURI
mobecertinib	EXKIVITY
momelotinib	OJJAARA
mosunetuzumab-axgb	LUNSUMIO
motixafortide	APHEXDA
moxetumomab pasudotox-tdfk	LUMOXITI
nadofaragene firadenovec-vncg	ADSTILADRIN
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
nilotinib	CAVHANZA
niraparib and abiraterone acetate	AKEEGA
niraparib tosylate	ZEJULA
nirogacestat hydrobromide	OGSIVEO
nivolumab	OPDIVO
nivolumab and hyaluronidase-nvhy	OPDIVO QVANTIG
nivolumab; relatlimab-rmbw	OPDUALAG
nogapendekin alfa inbakicept-pmln	ANKTIVA
obecabtagene autoleucel	AUCATZYL
obinutuzumab	GAZYVA

Generic Name	Brand Name
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
omidubicel-onlv	OMISIRGE
osimertinib mesylate	TAGRISSO
olutasidenib	REZLIDHIA
pacritinib	VONJO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pembrolizumab;berahyaluronidase alfa-pmph	KEYTRUDA QLEX
pemigatinib	PEMAZYRE
penpulimab-kcqx	none
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
pirtobrutinib	JAYPIRCA
pivekimab sunirine-pvzy	DECNUPAZ
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
quizartinib	VANFLYTA
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relacorilant	LIFYORLI
relugolix	ORGOVYX
repotrectinib	AUGTYRO
retifanlimab-dlwr	ZYNYZ
revumenib	REVUFORJ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
ropeginterferon alfa-2b-njft	BESREMI
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO

Generic Name	Brand Name
selpercatinib	RETEVMO
selumetinib	KOSELUGO
sevabertinib	HYRNUO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sirolimus albumin-bound nanoparticles	FYARRO
sonidegib phosphate	ODOMZO
sonrotoclax	BEQALZI
sotorasib	LUMAKRAS
sunvozertinib	ZEGFROVY
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS
talazoparib	TALZENNA
taletrectinib	IBTROZI
talimogene laherparepvec	IMLYGIC
talquetamab-tgvs	TALVEY
tarlatamab-dlle	IMDELLTRA
tazemetostat	TAZVERIK
tebentafusp-tebn	KIMMTRAK
teclistamab-cqyv	TECVAYLI
telisotuzumab vedotin-tllv	EMRELIS
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tislelizumab-jsgr	TEVIMBRA
tisotumab vedotin-tftv	TIVDAK
tivozanib	FOTIVDA
toripalimab-tpzi	LOQTORZI
tovorafenib	OJEMDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trastuzumab-strf	HERCESSI
tremlimumab	IMJUDO
treosulfan	GRAFAPEX
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA

Generic Name	Brand Name
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vepdegestrant	VEPPANU
vimseltinib	ROMVIMZA
vismodegib	ERIVEDGE
vorasidenib	VORANIGO
zanidatamab-hrii	ZIIHERA
zanubrutinib	BRUKINSA
zenocutuzumab-Zbco	BIZENGRI
ziftomenib	KOMZIFTI
ziv-aflibercept	ZALTRAP
zongertinib	HERNEXEOS

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Non-Insulin Diabetes Drugs

Date of Review: August 2026

Literature Search: 07/01/18 – 05/15/26
Date of Last Review: GLP-1 Receptor Agonists and dual GLP-1 RA/GIP therapies (April 2024)
DPP-4 inhibitors (August 2020)
SGLT-2 Inhibitors (February 2025)
Sulfonylureas (July 2018)
Thiazolidinediones (July 2018)
Miscellaneous Antidiabetic Agents (July 2018)

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- New evidence for diabetic medicines is evaluated and included in this review.
- There are 7 classes of medicines, not including insulins, used for the treatment of diabetes, mostly type 2 diabetes (T2D),included in this review. The classes are glucagon-like peptide-1 receptor agonist (GLP-1 RAs), dual GLP-1 RA/glucagon-dependent insulinotropic polypeptide (GIP), dipeptidyl peptidase-4 inhibitors (DPP-4s), sodium-glucose cotransporter 2 (SGLT-2) inhibitors, sulfonylureas (SU), thiazolidinediones (TZD), and miscellaneous agents (such as metformin).
- Therapies initially approved to lower blood glucose for people with diabetes have been shown to have benefits in other diseases. Diabetes medicines have shown to improve kidney disease, heart failure, obstructive sleep apnea, polyendocrine metabolic ovary syndrome (PMOS), previously called polycystic ovary syndrome (PCOS), liver disease and cause weight loss.
- For people with chronic kidney disease the evidence found:
  - Older diabetes medicines called TZDs did not clearly lower the risk of dying from heart disease in people with T2D and kidney disease.
  - Metformin may slightly slow the loss of kidney function, but the benefit appears small.
  - GLP-1 medicines may lower the risk of death from any cause in people with diabetes and kidney disease.
  - DPP-4 medicines appear to provide little or no important benefit for people with diabetes and kidney disease.
- For heart disease (also called cardiovascular disease), GLP-1 medicines and SGLT2 inhibitors help lower the risk of death, heart problems, and hospitalization for heart failure in people with heart disease.
- For PMOS, metformin may improve the chances of pregnancy in women with PMOS undergoing fertility treatment, however; it has not clearly been shown to increase live birth rates. Guidelines recommend that metformin can be used to help manage PMOS, depending on a woman's symptoms and health goals.
- Evidence for the use of diabetic therapy for weight management has shown the following:

- Metformin may help reduce weight gain caused by antipsychotic medicines that are used to treat some mental health conditions, but the evidence is limited.
- Tirzepatide leads to greater weight loss than placebo and semaglutide.
- Semaglutide causes meaningful weight loss, considered to be 5% or more, compared with placebo and liraglutide, but usually less than tirzepatide.
- Liraglutide helps more people lose at least 5% of their body weight compared with placebo.
- Several weight-loss medicines can reduce body weight in children and teenagers with obesity, but the quality of evidence is low.
- The United States (US) Preventive Services Task Force found limited evidence supporting the use of weight-loss medicines in children and adolescents with obesity.
- Major obesity guidelines strongly recommend semaglutide and tirzepatide for treating overweight people with obesity.

- Some diabetes medicines, including metformin, TZDs, and alpha-glucosidase inhibitors, may help prevent or delay the development of T2D in high-risk people, such as those with prediabetes or have overweight or obesity.
- Several new diabetes treatment guidelines have been recently published. Recommendations include:
  - Metformin is the first treatment recommended for most adults with T2D.
  - Other diabetes medicines can be added if blood sugar goals are not reached.
  - Some newer guidelines recommend starting metformin together with an SGLT-2 inhibitor in certain patients, such as those with other health conditions, because this combination can improve blood sugar control, weight loss, and heart health.
- Recommendations from recent guidelines on the management of chronic kidney disease are the following:
  - For people with T2D and chronic kidney disease, SGLT-2 inhibitors and metformin are recommended as the main starting treatments.
  - SGLT2 inhibitors and GLP-1 medicines are strongly recommended because they reduce the risk of heart problems and death.
- Guidelines recommend that women who are pregnant with diabetes or develop gestational diabetes should be treated with insulin and/or metformin.
- There is limited evidence that suggest SGLT-2 inhibitors may help certain patients with lupus-related kidney disease, but the evidence is very weak and more research is needed.
- To summarize the new evidence:
  - Metformin remains the foundation of treatment for most people with type 2 diabetes.
  - SGLT-2 inhibitors and GLP-1 medications provide the strongest evidence for protecting the heart and kidneys from damage due to high blood sugar.
  - In people with obesity, tirzepatide produces the greatest weight loss, followed by semaglutide and liraglutide.
  - Many newer guidelines now emphasize not just lowering blood sugar, but also protecting the heart, kidneys, and reducing the risk of death.
- The Oregon Health Plan (OHP) pays for medications to treat T2D. Some of the diabetes medicines, especially when used for treatment of conditions other than diabetes, require that certain criteria are met through a process called prior authorization. After review of new evidence, the Drug Use Research and Management group recommends no changes to the current policy.

Conclusions:

- New evidence identified in this review includes: 13 high quality systematic reviews and meta-analyses, 14 high quality guidelines, 5 new formulations, 6 new indications, 4 safety warnings, and 8 randomized controlled trials (RCTs).

SYSTEMATIC REVIEWS

Chronic Kidney Disease

- A Cochrane review evaluating the use of thiazolidinediones (TZDs) in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) found that they had little to no effect on risk of cardiovascular (CV) death compared to placebo or standard of care based on low quality of evidence. There was insufficient evidence for other outcomes.[1]
- A 2024 Cochrane Review found metformin use in patients with and without diabetes, compared to placebo or other diabetes treatments, may slightly decrease the decline in kidney function (i.e. estimated glomerular filtration rate [eGFR]) based on low quality evidence from 3 studies (mean difference [MD] 1.92 mL/min; 95% confidence interval [CI], 0.33 to 3.51).[2]
- A Cochrane Review evaluated to evidence for the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in adult patients with CKD and T2D in a 2025 publication.[3] The use of GLP-1 RAs was found to decrease all-cause death (relative risk [RR] 0.85, 95% CI 0.74 to 0.98; moderate-quality of evidence) but had a minimal effect on CV death (RR 0.84, 95% CI 0.68 to 1.05; low-certainty evidence).
- The benefits and harms for the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in individuals with T2D and CKD was assessed in a 2025 Cochrane review.[4] DPP-4 inhibitors were found to offer little benefit over standard of care or placebo in patients with T2D and CKD based on very-low to low quality of evidence.

Cardiovascular Disease

- A Cochrane review evaluated the effects using DPP-4 inhibitors, GLP-1 RAs or sodium-glucose cotransporter 2 (SGLT-2) inhibitors in people with established cardiovascular disease (CVD), with or without diabetes.[5] There was moderate to high strength of evidence that the use of GLP-1 RAs and SGLT-2 inhibitors reduced the risk of CV mortality, all-cause mortality and hospitalizations for heart failure (HF).

Polycystic Ovary Syndrome

- A Cochrane review published in 2020 found that metformin, compared to placebo or no treatment, may increase pregnancy rates in women with polyendocrine metabolic ovary syndrome (PMOS) undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ISI). There were no clear increases in live birth rates with metformin.[6]

Weight Management

- A 2022 Cochrane review found low-quality evidence that metformin, compared to placebo or no treatment, may be effective in preventing antipsychotic associated weight gain in people with schizophrenia.[7]
- A Cochrane review evaluated the effects of tirzepatide in weight loss in adults with other comorbidities such as diabetes or hypertension. Tirzepatide was found to result in more weight loss compared to placebo and semaglutide based on moderate strength of evidence.[8]
- Semaglutide was studied in a 2025 Cochrane review and demonstrated meaningful weight loss compared to placebo and liraglutide but less than tirzepatide (moderate quality of evidence for placebo studies and low quality of evidence for active treatment comparisons).[9]
- A Cochrane review found that the use of liraglutide for weight loss resulted in more patients obtaining a 5% weight decrease compared to those receiving placebo based on moderate evidence. Evidence on long term health outcome such as major adverse cardiovascular events (MACE) and mortality did not demonstrate a benefit with the use of liraglutide over placebo.[10]
- Pharmacotherapy (e.g., GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate) was found to reduce body mass index (BMI) and decrease weight in children and adolescents with obesity based on low-quality evidence from a 2026 Cochrane Review.[11]
- Interventions for weight management in children and adolescents was published by the U.S. Preventive Services Task Force.[12] The use of liraglutide, semaglutide, orlistat and phentermine/topiramate were found to have limited evidence of BMI and weight reduction based on low strength of evidence.

Diabetes Screening

- The U.S. Preventive Services Task Force Screening for Prediabetes and Type 2 Diabetes Mellitus report was published in 2021.[13] There was no recommendation regarding preventative antidiabetic therapy; however, metformin, TZDs and alpha glucosidase inhibitors (AGIs) were found to reduce the incidence of diabetes.

GUIDELINES

Diabetes Prevention

- Guidance published in 2025 by the Scottish Intercollegiate Guideline Network (SIGN) recommends anti-diabetic and weight management pharmacotherapy to reduce the progression to T2D and to cause remission in certain people that are high risk due to comorbidities (e.g., CKD, CVD, overweight or obesity) and rising glucose levels.[14]

Glucose Management

- A guideline by SIGN on the pharmacological management of glycemia control in people with T2D was published in 2024.[15] Metformin is recommended first-line. Other treatments are recommended as second- or third-line therapies as needed for obtaining target glucose levels.
- The National Institute for Health and Care Excellence (NICE) updated guidance on the management of T2D in 2026.[16] One updated recommendation is for the use of metformin and an SGLT2 inhibitor in combination as initial management based on improved outcomes for glucose reduction, weight management and CV events.[16]
- The annual update to the Standards of Care in diabetes were published by the American Diabetes Association in 2026.[17] Recommendations for glucose management and pharmacotherapies to manage comorbidities are outlined below and align with fee-for-service (FFS) policy.
- Guidelines on the management of T2D were published in 2023 by the Veterans Administration/Department of Defense (VA/DoD).[18] Recommendations for pharmacotherapy are consistent with other guidelines.
- American College of Physicians (ACP) published guidance on the use of newer pharmacological treatment in patients with T2D. Recommendations support current FFS policy with metformin as the preferred first line therapy.[19]
- Guidelines for the management of type 1 diabetes (T1D) and T2D in children and young people was the focus of the 2023 guidance from NICE.[20] Metformin is recommended first line in children with T2D requiring pharmacotherapy.

Chronic Kidney Disease

- In 2022 Kidney Disease Improving Global Outcomes (KIDGO) published guidance on the management of T2D in patient with CKD.[21] The use of SGLT-2 inhibitors and metformin are recommended first line for most patients.
- The Department of Veterans Affairs (VA)/Department of Defense (DOD) published recommendations for the management CKD in the primary care setting. Both SGLT-2 inhibitors and GLP-1 RAs are strongly recommended in adults with CKD to reduce major adverse CV events and all-cause mortality.[22]

Weight Management

- Recommendations from The Obesity Society (TOS), the Obesity Medicine Association (OMA), and the Obesity Action Coalition (OAC) include strong recommendations for the use of semaglutide and tirzepatide for overweight and obesity based on moderate-quality evidence.[23]

Pregnancy

- A 2024 guideline from SIGN recommends the use of insulin and/or metformin for women who are pregnant and were diagnosed with diabetes before pregnancy or developed gestational diabetes.[24]
- A guideline by the Endocrine Society (ES) and European Society of Endocrinology (ESE) published guidance on the management of individuals who are pregnant with preexisting T1D or T2D.[25] Recommendations are consistent with other guideline recommendations for pharmacotherapy for pregnant women consisting of insulin and/or metformin.

Polycystic Ovary Syndrome

- An International evidence-based guideline for the assessment and management of PCOS was published in 2023.[26] The use of metformin is recommended for the management of PCOS dependent upon clinical variables.

Systemic Lupus Erythematosus

- Updated guidance from European Alliance of Associations for Rheumatology (EULAR) on the management of patients systemic lupus erythematosus (SLE) with kidney involvement recommends the use of SGLT-2 inhibitors in stable patients with SLE and lupus nephritis (LN) based on very low quality evidence.[27]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the evidence review.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy

- Most recently the SGLT-2 inhibitors were reviewed at the February 2025 Pharmacy and Therapeutics (P &T) Committee meeting. Canagliflozin was made non-preferred based on cost.
- The GLP-1 RAs were reviewed at the April 2024 P & T Committee meeting and no changes were made after review of the clinical evidence and costs.
- In August 2024, drugs were reviewed for the treatment of Non-alcoholic Steatohepatitis (NASH) and weight management drugs for NAS and CV disease. The criteria for GLP-1 RAs were updated to include coverage of GLP-1 RAs that had compendial-support for the treatment of NASH in adults with overweight and obesity. The PA criteria for the use of semaglutide was updated to remove the age requirement in people with established CV disease with overweight or obesity because this population is at increased risk independent of age.
- Newer diabetes drugs were reviewed at the August 2020 P & T Committee meeting. The Committee recommended removal of requirement for step therapy, except for metformin. After comparative cost consideration in executive session, the Committee recommended making ONGLYZA, Trulicity, FARXIGA, JARDIANCE and INVOKANA preferred.
- Other antidiabetic therapies, classified as miscellaneous drugs, were reviewed in July 2018. The P & T Committee recommended amending the SGLT-2 PA) criteria to remove the amylin analogs from question #6 from the PA criteria. After comparative cost consideration in executive session, the Committee recommended making no changes to the PDL.
- Antidiabetic therapies account for significant quarterly costs in the Fee-For-Service (FFS) population. The most expensive classes are GLP-1 RAs and SGLT-2 inhibitors accounting for approximately $488,000 for 658 claims. The other classes consist of 1,143 claims and cost approximately $8,400 per quarter.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Chronic Kidney Disease

Cochrane – Thiazolidinediones for People with Chronic Kidney Disease and Diabetes

A 2025 Cochrane review evaluated the effect of TZD use in patients with T2D. There were 3,044 participants in 85 studies included in the review.[1] The median age was 62 years, with one study enrolling children. Studies evaluated patients on dialysis (7 studies), CKD 1 and 2 (5 studies), CKD 3-5 (6 studies), and the remaining studies included people with CKD 1-5.[1] Main endpoints of interest were CV death, severe hypoglycemia, MACE, non-fata myocardial infarction (MI) and kidney failure requiring kidney replacement therapy (KRT). Risk of bias was considered high for all outcomes due to blinding issues.

In the meta-analysis the control group was either placebo or standard of care.[1] There was low-quality evidence that the risk of CV death was not different between TZDs and control (RR 2.0; 95% CI, 0.01 to 3.97; 4 studies).[1] There was insufficient evidence to determine hypoglycemia risk with TZDs. Other important outcomes were not studied. In a comparison between TZDs and sulfonylureas there was no difference in CV death (RR 2.78; 95% CI, 0.11 to 67.92; 4 studies) based on low-quality evidence in patients with CKD stage 1 or 2.[1] No other outcomes were evaluated.

Overall, there was no benefit found for the use of TZDs in people with T2D with existing kidney disease for a reduction in the risk of CV death.[1]

Cochrane – Metformin for Preventing the Progression of Chronic Kidney Disease

Metformin was studied for the prevention of CKD progression in a 2024 Cochrane review.[2] Eleven studies (n=8,449) met inclusion criteria. Participants had Autosomal Dominant Polycystic Kidney Disease (ADPKD) (4 studies) or diabetes (7 studies). Metformin was compared to placebo or no treatment in 6 studies, active control (i.e., rosiglitazone, glyburide, pioglitazone, or glipizide) in 4 studies and one study compared diet and lifestyle modifications or other antidiabetic therapies.[2] Most of the included trials were considered to have a low risk of bias across most domains.

Compared to placebo, metformin may slightly decrease the decline in kidney function (i.e., eGFR) based on low-quality evidence from 3 studies (MD 1.92 mL/min; 95% CI, 0.33 to 3.51).[2] There was no difference in the risk of death between groups based on very low quality of evidence (RR 1.00; 95% CI, 0.76 to 1.32).[2] Withdrawals due to intolerance were higher with metformin compared to placebo (RR 2.19; 95% CI,1.46 to 3.27) (moderate quality of evidence).[2] Evidence for the outcomes for kidney failure were uncertain.

Comparisons of metformin to active treatment controls found little or no difference between the groups for the following outcomes: kidney function decline, all-cause death, study withdrawals and incidence of serious AE. Metformin may increase the urine albumin-creatinine ratio, compared to other active treatments, based on low-quality evidence (MD 14.61; 95% CI, 8.17 to 21.05; two studies).[2]

Cochrane – Glucagon-like Peptide-1 Receptor Agonists for People with Chronic Kidney Disease and Diabetes

A Cochrane review evaluated the evidence for the use of GLP-1 RAs in people with CKD.[3] There were 42 studies included (n = 48,148). All participants were adults with T2D and a median duration of 26 weeks. Participants with CKD stages 1-5 and dialysis were included.

GLP-1 RAs were compared to placebo and found to reduce all-cause death (RR 0.85; 95% CI, 0.74 to 0.98) (moderate-quality evidence).[3] There was low-quality evidence that CV death was similar with GLP-1 RAs compared to placebo with an incidence of 47 per 100 patients treated with GLP-1 RAs compared to placebo 56 per 1000 patients treated (RR 0.84; 95% CI, 0.68 to 1.05).[3] For the outcome of 3-point MACE (e.g., CV death, nonfatal MI or nonfatal stroke), at 137 weeks follow up, GLP-1 RA decreased the incidence more than placebo (RR 0.84; 95% CI, 0.73 to 0.98) based on moderate-quality evidence.[3] GLP-1 RAs reduced the incidence of 4-point MACE (e.g., CV death, nonfatal MI, nonfatal stroke, and coronary revascularization or hospitalization for unstable angina or HF) more than placebo (RR 0.77; 95% CI, 0.67 to 0.89).[3] At 610 weeks follow up, the risk of kidney failure (e.g., starting dialysis or kidney transplant) was not significantly different between GLP-1 RAs and placebo (RR 0.86; 95% CI, 0.66 to 1.13) (moderate-quality evidence).[3] There was moderate-quality evidence of no effect of GLP-1 RAs compared to placebo on the composite kidney outcomes (RR 0.89; 95% CI, 0.78 to 1.02). There were no significant differences in hypoglycemia rates between the two groups (low quality of evidence).[3]

There was insufficient evidence to determine the effect of GLP-1 RAs to other antidiabetic drugs or standard of care.

The risk of bias was considered low in most studies for all the primary outcomes that were placebo comparisons. In comparisons of GLP-1 RAs to DPP-4 inhibitors, SGLT-2 inhibitors, insulin, other GLP-1 RAs or standard of care there was unclear or high risk of bias due to missing data for the outcomes of all cause and CV death.[3] Overall, GLP-1 RAs have a demonstrated benefit, over placebo, in reducing all-cause death in patients with T2D and CKD.

Cochrane - Dipeptidyl peptidase 4 Inhibitors for People with Chronic Kidney Disease and Diabetes

A 2025 Cochrane review assessed the benefits and harms of DPP-4 inhibitors in people with CKD and diabetes.[4] There were 59 studies, enrolling 27,893 adults, included in the review. The DPP-4 inhibitors that were studied included: alogliptin, gemigliptin (not available in the US), linagliptin, omarigliptin (not available in the US), saxagliptin, sitagliptin, trelagliptin (not available in the US) and vildagliptin (not available in the US). DPP-4s were compared to placebo, standard medical care, SGLT-2 inhibitors, GLP-1 RAs, sulfonylureas, other DPP-4 inhibitors, insulin, or alpha-glucosidase inhibitors.[4] The primary outcomes were CV death and hypoglycemia requiring third-party assistance.

The use of DPP-4s was not found to provide benefit, compared to placebo or standard medical care, for the outcomes studied. There was low quality of evidence that there was little to no effect of DPP-4 inhibitors, compared to placebo or standard medical care, for CV death (RR 0.96; 95% CI, 0.82 to 1.14) and hypoglycemia requiring third-party assistance (RR 0.97; 95% CI, 0.76 to 1.25).[4] For the outcomes of 3-point MACE and kidney failure there was moderate-quality evidence that there was little or no effect of DPP-4 inhibitors, RR 1.03 (95% CI, 0.91 to 1.17) and RR 1.09 (95% CI, 0.78 to 1.53), respectively.[4] There was very-low quality evidence for 4-point MACE, nonfatal stroke and nonfatal MI that demonstrated that there was little effect of DPP-4 inhibitors compared to placebo. The risk of bias was low for most domains.

The evidence was uncertain to determine the effects of DPP-4 inhibitors compared to other anti-diabetic treatments. Overall, DPP-4 inhibitors offer little benefit over standard of care or placebo in patients with T2D and CKD.

Polyendocrine Metabolic Ovary Syndrome

Cochrane -Metformin Treatment in Women with Polyendocrine Metabolic Ovary Sydrome

A 2020 review evaluated the use of metformin for women with PMOS undergoing IVF or ICSI.[6] Metformin was compared to placebo or no treatment in 13 studies (n=1132). Results were divided based on the protocol used for IVF treatment, long GnRH-agonist or short GnRH-antagonist. Important outcomes were live birth rate, clinical pregnancy rates and a reduction in ovarian hyperstimulation syndrome (OHSS).[6]

Live birth rates per women using the long GnRH agonist protocol found no difference between metformin and placebo or no treatment (RR 1.30; 95% CI, 0.94 to 1.79) (low-quality evidence).[6] Live birth rates for the short protocol using GnRH-antagonists found that metformin may reduce live birth rates (RR 0.48; 95% CI,0.29 to 0.79) based on low-quality evidence.[6] There was low quality of evidence that the risk for OHSS was reduced with metformin compared to placebo or no treatment (RR 0.46; 95% CI,0.29 to 0.72). Clinical pregnancy rates per women was increased with the use of metformin in women who used the long protocol GnRH-agonist (low-quality evidence); however, the evidence is uncertain in women who used the short protocol GnRH-antagonist (RR 1.38; 95% CI, 0.21 to 9.14)(very low quality of evidence).[6] The rate of miscarriage was not statistically significantly different between groups (RR 0.86; 95% CI, 0.56 to 1.32) based on low quality of evidence. Metformin was associated with a higher risk of adverse reactions with a RR of 3.35 (95% CI, 2.34 to 4.79) (low quality of evidence).[6]

Overall, there was not compelling evidence that metformin increases live birth rates; however, metformin may increase pregnancy rates in women who used a long GnRH-agonist long protocol. Metformin may also decrease the risk of OHSS.

Diabetes and Weight Management

Cochrane – Pharmacological Interventions for Prevention of Weight Gain in People with Schizophrenia

A 2022 Cochrane review evaluated medication used as preventative therapy for antipsychotic-induced weight gain in people with schizophrenia.[7] Seventeen trials were included, five of which evaluated metformin. The comparator in all trials was placebo or no treatment.

Small sample sizes, allocation concealment and blinding of investigators and participants reduced the certainty of evidence.[7] Metformin was found to decrease the average change in weight compared to no treatment by -4.03 kg (95% CI, -5.78 to -2.28; 4 RCT) based on low quality of evidence.[7] Average reduction in BMI was found to be higher in patients treated with metformin (MD -1.63; 95% CI, -2.96 to 0.29; 5 trials) (low quality of evidence).[7] Early study discontinuation and nausea were not statistically significantly different between groups.

Other therapies that were studied, that will be presented elsewhere, are topiramate, H2 antagonists, and monoamine modulators. Metformin had the most evidence for use but strong conclusions were limited by short study durations, small sample sizes and a limited number of studies.

Cochrane – Tirzepatide for Adults with Obesity

A 2025 review evaluated the use of tirzepatide in adults with obesity.[8] There were 9 RCTs (n=7111) that were identified. Tirzepatide, given once weekly at 5 mg to 15 mg, was compared to placebo and in one study compared to semaglutide. Patients were 36.1 years to 65.25 years old. All participants had a weight-related comorbidity, such as diabetes, prediabetes, HF, or obstructive sleep apnea (OSA).

In trials lasting 12 to 18 months, tirzepatide resulted in more weight loss compared to placebo (MD -16.03%; 95% CI, -18.91 to -13.14) and more people lost at least 5% of weight (RR 3.60; 95% CI, 2.44 to 5.30) (both based on moderate strength of evidence).[8] There was an increase in non-serious adverse events (AE) with tirzepatide compared to placebo (RR 1.33; 95% CI, 1.03 to 1.71). Tirzepatide increased quality of life scores, based on IWQoL-Lite-CT (Impact of Weight on Quality of Life-Lite Clinical Trials) by 2.35 points (0-100 scale) compared to baseline, which is unlikely to be clinically significant.[8] For the outcomes of serious AE, AE leading to withdrawal, MACE and mortality there was no statistical difference between groups.

For trials with a mean follow-up of 176 weeks, the percent weight loss was higher with tirzepatide compared to placebo from evidence from one study (MD -15.6%; 95% -19.14 to -12.18) (moderate quality of evidence).[8] There was moderate quality of evidence that the percent of people with at least a 5% weight

reduction was higher with tirzepatide (RR 2.81; 95% CI, 2.33 to 3.38). [8] Nonserious AE were higher with tirzepatide compared to placebo (RR 1.05; 95% CI, 0.98 to 1.11). There was no difference found between serious AE, AE leading to withdrawal, MACE, mortality and quality of life as measured by SF-36.[8]

In one trial comparing tirzepatide to semaglutide for up to 72 weeks found tirzepatide resulted in more weight loss than semaglutide (MD -6.5%; 95% CI, -8.13 to - 4.87) based on moderate quality of evidence.[8] There was no statistically significant difference in non-serious AE between tirzepatide and semaglutide, 766 per 1000 vs. 790 per 1000, respectively (RR 0.97; 95% CI, 0.90 to 1.05) (low quality of evidence). There was moderate quality of evidence that there was no statistically significant difference in the AE leading to withdrawal between tirzepatide and semaglutide, 61 per 1000 vs, 80 per 1000 (RR 0.77; 95% CI, 0.46 to 1.30).[8]

In summary, tirzepatide is effective in causing weight reductions more than placebo and semaglutide. The certainty of evidence for other important outcomes was low and the sustainability of weight loss for more than 176 weeks is unknown.

Cochrane – Semaglutide for Adults with Obesity

A systematic review and meta-analysis were assessed in adults living with obesity taking semaglutide.[9] Eighteen RCTs, including 27,949 participants, were evaluated. The mean age ranged from 41 to 70 years. Participants had a BMI of 31.9 kg/m2 to 40.3 kg/m2.[9] Comparisons were between placebo, tirzepatide and liraglutide. Main outcomes were weight loss, AE, MACE, quality of life and mortality.

In trials lasting 6 months to 17 months, semaglutide decreased percent body weight lost more than placebo by a MD of -10.73% (95% CI, -12.24 to -9.21) and more people taking semaglutide lost 5% of weight (RR 2.68; 95% CI, 2.30 to 3.12)(both high quality of evidence).[9] Semaglutide was associated with more nonserious AE compared to placebo (RR 1.11; 95% CI, 1.01 to 1.22) based on low quality of evidence. Adverse events leading to withdrawal was higher with semaglutide (RR 1.84; 95% CI, 1.53 to 2.21) (moderate strength of evidence).[9] Low quality of evidence found the difference in MACE between semaglutide and placebo was 58 per 1000 versus 92 per 1000, respectively (RR 0.63; 95% CI, 0.44 to 0.90). Mortality was 4 per 1000 for semaglutide and 5 per 1000 for placebo so unlikely to be clinically significant in the short term but was statistically significant (RR 0.69; 95% CI, 0.48 to 0.98).[9] There was moderate quality of evidence that there was not a difference in quality of life based on the SF-36.

Longer term studies up to 104 weeks found more weight loss with semaglutide compared to placebo MD of -11.11% (95% CI, -16.47 to -5.75) and more people taking semaglutide lost 5% of weight (RR 2.74; 95% CI, 1.95 to 3.84)(both moderate quality of evidence).[9] Adverse events leading to withdrawal were higher in patients treated with semaglutide compared to placebo (RR 2.03; 95% CI, 1.86 to 2.20) based on moderate evidence but no difference was found for nonserious AE (very low quality of evidence).[9] In follow up to 240 weeks the difference in MACE favored semaglutide compared to placebo, 64 per 1000 compared to 78 per 1000, respectively (RR 0.81; 95% CI, 0.73 to 0.90) based on moderate quality of evidence.[9] Quality of life was not statistically significantly different between groups. There was moderate quality of evidence that the difference in mortality was small and favored semaglutide more than placebo (RR 0.82; 95% CI, 0.72 to 0.94).

There were 2 trials that compared semaglutide to liraglutide and found the percent of weight change was higher with semaglutide compared to liraglutide (MD -6.75%; 95% CI, -13.03% to 0.-46%) and more people taking semaglutide lost at least 5% of weight (RR 1.30; 95% CI, 0.99 to 1.71) but it was not statistically significant (both low quality of evidence).[9] There were no statistically significant differences in the outcomes of nonserious AE, serious AE, withdrawals due to AE, mortality or quality of life based on SF-36 scores.

Semaglutide was compared to tirzepatide and was associated with less weight loss based in 1 trial (MD 6.5%; 95% CI, 4.87% to 8.13%) and more people obtained a 10% or more weight loss with tirzepatide compared to semaglutide, 813 per 1000 versus 601 per 1000, respectively (low quality of evidence for both).[9] There were no statistically significant differences in nonserious AE, serious AE, and AE leading to withdrawals.

There was clinically significant weight loss demonstrated by semaglutide in medium and long-term studies. All but one study was funded by the manufacturer which may present conflict of interest concerns.

Cochrane – Liraglutide for Adults with Obesity

Liraglutide was studied in adults with obesity in a 2025 Cochrane review.[10] There were 24 studies included which compared liraglutide to placebo and with an active comparator arm in 2 studies. Patients (n=9,937) ranged from 31 years to 65 years. All patients had weight related comorbidities, such as diabetes, non-alcoholic fatty liver disease, POS, and OSA.[10] All but 2 studies were funded by the manufacturer.

In studies lasting 26-68 weeks liraglutide was associated with a larger percent of weight loss compared to placebo (MD -4.72%; 95% CI, -5.32 to -4.12); 16 trials) but the evidence was considered very low.[10] The number of people achieving a 5% or more weight reduction was higher in those receiving liraglutide (RR 2.10; 95% CI, 1.80 to 2.45; 18 trials) (moderate level of evidence).[10] The risk of any AE was higher with liraglutide compared to placebo (RR 1.07; 95% CI, 1.04 to 1.11) added on low quality of evidence and serious AE was also higher RR 1.20 (95% CI, 1.00 to 1.43). The evidence was uncertain on the risk of nonserious AE and withdrawals due to AE based on very low quality of evidence. The risk of MACE was not statistically significantly different between liraglutide and placebo (RR 0.86; 95% CI, 0.66 to 1.10) based on moderate quality of evidence.[10] There was low quality evidence that quality of life scores, based on IWQoL-Lite-CT, was 2.9 points higher than placebo, which was not statistically or clinically significant. The evidence for mortality was very uncertain (RR 0.44; 95% CI, 0.08 to 2.25).[10]

Two trials studied long-term use of liraglutide, 104 to 160 weeks, and found liraglutide compared to placebo demonstrated a higher percent of weight loss from baseline with a MD of -4.34% (95% CI, -5.2% to -3.43%) (low quality of evidence).[10] Moderate quality of evidence found the number of people achieving a 5% or more weight loss was higher in patients treated with liraglutide compared to placebo (RR 1.78; 95% CI, 1.51 to 2.09). The risk of withdrawal due to AE was higher with liraglutide compared to placebo (RR 2.16; 96% CI, 1.59 to 2.93). The difference in quality of life scores, as measured by the IWQoL-Lite-CT, was statistically significantly different, but unlikely clinically significantly different from placebo (MD 3.81; 95% CI, 1.03 to 6.59) (moderate quality of evidence).[10] The evidence for any AE, nonserious AE, serious AE, MACE and mortality was of low to very low quality and was not statistically significantly different from placebo.

In summary, liraglutide use resulted in more weight loss than placebo in the short and long term with the most evidence for outcome for the number of patients achieving a 5% or more weight loss.

Cochrane - Pharmacological Interventions for the Treatment of Obesity in Children and Adolescents

A 2026 Cochrane review evaluated the evidence for the treatment obesity in children and adolescents with pharmacotherapy.[11] Trial participants that ranged from 0-19 years of age with essential obesity were included. Treatments were given for at least 3 months. Therapies studied were: GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate.[11] All treatments were in conjunction with a behavioral or lifestyle approaches. Thirty-seven RCTs were included (n=4,218). Eleven studies included both children and adolescents, 25 studies included adolescents only and one study evaluated only children. Median duration of follow-up was 11-13.5 months.[11]

For the comparison of pharmacological interventions (e.g., GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate) to placebo, there was a larger reduction in BMI with pharmacological therapy (MD -1.8 kg/m^2; 95% CI, -2.36 to -1.24) and weight change (MD -5.47 kg; 95% CI, -7.45 kg to -3.5 kg)(low quality of evidence).[11] There was moderate-quality evidence that there were more AEs with pharmacotherapy compared to placebo (RR 1.03; 95% CI, 1.00 to 1.07). There was low-quality evidence that discontinuations due to AEs were not statistically different between groups (RR 1.50; 95% CI, 0.82 to 2.75).[11] Quality of life scores were higher in patients treated with pharmacotherapy (e.g., GLP-1 RAs, phentermine plus topiramate) compared to placebo by a small amount that is unlikely to be clinically significant (MD 1.02 points [total score 0-100]; 95% CI, 1.94 to 3.98) (moderate quality of evidence).[11]

Comparisons of pharmacotherapy (e.g., metformin) to no intervention found very low-quality evidence for a reduction in BMI (MD -1.51 kg/m^2; 95% CI, -2.29 to -0.73) and weight change (MD -3.2 kg; 95% CI, -6.12 kg to -0.28 kg).[11] Other outcomes were not reported.

Overall, pharmacotherapy may result in small, but potentially clinically significant (i.e., 5% or more weight loss from baseline), weight reductions in adolescents with obesity.

U.S. Preventive Services Task Force - Interventions for Weight Management in Children and Adolescents

The U.S. Preventative Services Task Force evaluated weight management interventions for children and adolescents with high BMI.[12] Evidence was searched through January 2024. Behavioral interventions and medications were evaluated. Fifty-eight RCTs (n=10,143) were included.

Behavioral interventions were associated with small decreases in BMI compared to no intervention (MD -0.7; 95% CI, -1.0 to -0.3) (high strength of evidence).[12] Some medications had a more substantial reduction in weight, compared to placebo, as described in **Table 1**.

Table 1. Recommendations for Weight Management for Children and Adolescents[12]

Recommendation	Strength of Evidence	Results Summary	Notes
Health Outcomes			
Liraglutide	Insufficient	QoL: MD 1.3; 95% CI, -1.6 to 4.2; p>0.05	- Evidence from 1 RCT - No group differences in weight change
Semaglutide	Insufficient	QoL: MD 4.3; 95% CI, 0.2 to 8.3; P<0.05	- Evidence from only 1 RCT - Small improvement in weight-related quality of life
Orlistat	Insufficient	Not reported	- Evidence from 2 RCTs - No group differences in weight change
Phentermine/topiramate	Insufficient	Not reported	- Evidence from 1 RCT
Intermediate Outcomes			
Liraglutide	Low for BMI and weight reduction Low for lipid and blood pressure changes	BMI: MD -1.6; 95% CI, -2.5 to -0.7; p<0.05 Weight: MD -4.5 kg; 95% CI, -7.2 to -1.8; p<0.05	- Evidence from 1 RCT

Semaglutide	Low for BMI and weight reduction	BMI: MD -6.0; 95% CI, -7.3 to -4.6; p<0.05 Weight: MD -17.7 kg; 95% CI, -21.8 to -13.7; p<0.05	- Evidence from 1 RCT
Orlistat	Low for BMI and weight reduction	BMI: MD -0.9; 95% CI NR; p=0.001 Weight: MD -2.6 kg; 95% CI NR; p-value NR	- Evidence from 2 RCTs
Phentermine/topiramate (15/92 mg dose)	Low for BMI and weight reduction	BMI: MD -5.4; 95% CI, -6.4 to -4.3; p<0.05 Weight: MD -15.8 kg; 95% CI, -18.8 to -12.8; p<0.05	- Evidence from 1 RCT
Harms			
Liraglutide	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 3 RCTs
Semaglutide	Insufficient for serious adverse events High for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 1 RCT
Orlistat	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 2 RCTs
Phentermine/topiramate	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 2 RCTs
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; NR = not reported; QoL = quality of life; RCTs = randomized controlled trials.			

Screening and Prevention

U.S. Preventive Services Task Force Screening for Prediabetes and Type 2 Diabetes Mellitus: An Evidence Review

A 2021 review done by the Agency for Healthcare Research and Quality (AHRQ) evaluated the benefits and harms of screening for abnormal glucose levels in primary care to inform guidance by the U.S. Preventative Task Force.[28] Literature was searched through September 10, 2019 . No specific recommendation regarding preventative drug therapy were made; however, evidence suggested benefit of antidiabetic medications.

For recently diagnosed individuals with T2D, long-term health outcomes were improved with intensive glucose control with insulin and sulfonylureas. Over a period of 20 years, there was a decreased risk of all-cause mortality (RR 0.87; 95% CI, 0.79 to 0.96), diabetes-related mortality (RR 0.83; 95% CI, 0.73 to 0.96), and MI (RR 0.85; RR 0.85; 95% CI, 0.74 to 0.97) with insulin and sulfonylurea use.[28] Metformin decreased risk for all-cause mortality (RR 0.64; 95% CI, 0.45 to 0.91), diabetes-related mortality (RR 0.58; 95% CI, 0.37 to 0.91) and MI (RR 0.61; 95% CI, 0.41 to 0.89) for follow-up at 10 years.[28]

In patient with pre-diabetes, the incidence of diabetes was reduced with metformin (RR 0.73; 95% CI, 0.64 to 0.83), TZDs (RR 0.50; 95% CI, 0.28 to 0.92), and alpha glucosidase inhibitors (AGIs) (RR 0.64; 95% CI, 0.43 to 0.96).[28]

Cardiovascular

Cochrane - Dipeptidyl Peptidase-4 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Co-Transporter-2 Inhibitors for People with Cardiovascular Disease

A 2021 Cochrane review assessed the benefits and harms of using DPP-4 inhibitors, GLP-1 RAs and SGLT-2 inhibitors in people with CVD, with or without diabetes.[5] Thirty-one studies were included and considered to have an overall low risk of bias by the authors. All comparisons were to placebo. The DPP-4 inhibitors included the following medications: linagliptin, saxagliptin, alogliptin, sitagliptin, vildagliptin, and omarigliptin (not available in the US).[5] The GLP-1 RAs included trial of lixisenatide (discontinued), exenatide, albiglutide (discontinued) and semaglutide. SGLT-2 inhibitors included in the analysis were canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and sotaglifozin.[5] Outcomes studied were CVD mortality, fatal and non-fatal MI, fatal and non-fatal stroke, all-cause mortality, hospitalizations for HF and safety.

Overall evidence suggests that there was no benefit for the major outcomes studied with the DPP-4 inhibitors.[5] There was high strength of evidence that DPP-4 inhibitors did not reduce the risk of CVD mortality, MI, stroke, and all-cause mortality. There was moderate strength of evidence that hospitalizations for HF were not reduced. There was moderate strength of evidence that the risk of pancreatitis may be increased with DPP-4 inhibitors (OR 1.63; 95% CI, 1.12 to 2.37).[5]

The use of GLP-1 RAs was found to reduce several efficacy endpoints (**Table 2**). There was low quality strength of evidence that GLP-1 RAs may reduce worsening renal function (OR 0.61; 95% CI, 0.44 to 0.84).[5]

There was evidence of an efficacy benefit for the use of SGLT-2 inhibitors compared to placebo (**Table 2).** There was no evidence that SGLT-2 inhibitors reduced the risk of MI or stroke. There was evidence that SGLT-2 inhibitors reduced the risk of worsening renal function (OR 0.59; 95% CI, 0.43 to 0.82).[5]

Table 2. Cochrane Systematic Review of DDP-4s, GLP-1 RAs and SGLT-2 inhibitors with Evidence of Benefit in Patients with Established CVD[5]

Outcome	Result	Strength of Evidence
GLP-1 RAs		
CV mortality	OR 0.87; 95% CI, 0.79 to 0.95	High
Stroke	OR 0.87; 95% CI, 0.77 to 0.98	High
All-cause mortality	OR 0.88; 95% CI, 0.82 to 0.95	High
Hospitalization for HF	OR 0.95; 95% CI, 0.85 to 1.06	High
SGLT-2 inhibitors		
CV mortality	OR 0.82; 95% CI, 0.70 to 0.95	Moderate
All-cause mortality	OR 0.84; 95% CI, 0.74 to 0.96	Moderate
Hospitalization for HF	OR 0.65: 95% CI, 0.59 to 0.71	High
Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; GLP-1 RA = glucagon-like peptide-1 receptor agonists; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2.		

In patients with established CV disease there is moderate- to high-quality evidence that the use of GLP-1 RAs and SGLT-2 inhibitors reduce the risk of CVD mortality and all-cause mortality. There was no evidence of benefit in these patients for the use of DPP-4 inhibitors.

After review, 110 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

Diabetes Prevention

SIGN – Prevention and Remission of Diabetes

In 2025 SIGN published recommendations on preventing and remission of T2D. Recent advances in T2D demonstrate that clinically effective interventions are available to slow the progression to diabetes or even provide remission.[14] People at high risk of developing T2D, such as those with CVD, HTN, obesity, stroke, non-alcoholic fatty liver disease, PCOS, history of gestational diabetes, mental health conditions and those with learning disabilities, should be identified. Prediabetes is defined as a hemoglobin A1c (HbA1c) of 6.0-6.4% or a fasting plasma glucose (FPG) of 110 mg/dL to 125 m/dL and is associated with an increased risk of all-cause death.[14] Non-pharmacological interventions designed to improve diet, exercise and reduce body weight and ectopic fat should be employed to reduce T2D risk. Some patients may be candidates for treatment of prediabetes with medication (**Table 3**).[14] All patients considered for pharmacotherapy should be treated in a specialist weight management service. Non-pharmacological approaches may also be considered such as low-calorie diet and increased physical activity.

Table 3. Recommendations for Pharmacotherapy for People with Prediabetes[14]

Medication	Recommendation
Liraglutide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with a BMI ≥35 kg/m^2 with prediabetes (or lower for people from minority ethnic groups at increased risk of diabetes)
Semaglutide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with a BMI 30 kg/m^2 with prediabetes (or lower for people from minority ethnic groups at increased risk of diabetes)
Tirzepatide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with prediabetes or type 2 diabetes with a BMI ≥30 kg/m^2 (or lower for people from minority ethnic groups at increased risk of diabetes)
Metformin*	- Metformin may be offered to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated while participating in a lifestyle modification program or unable to participate in these types of programs and particularly if they have a BMI greater than 35 kg/m^2 - Start metformin with a low dose (for example, 500 mg once daily) and then increase gradually as tolerated, to 1,500 to 2,000 mg daily. If the person is intolerant of standard metformin consider using modified-release metformin - Metformin may cause vitamin B12 deficiency with long-term use; consider annual review of vitamin B12 levels, especially in those with anemia or peripheral neuropathy
Orlistat	- Can be considered if BMI is 28 kg/m^2 or more to manage obesity - Recommend that it be discontinued if at 3 months there has not been at least a 5% weight loss
Key: *Not indicated for weight management but has been shown to prevent progression from prediabetes to T2D Abbreviations: BMI = body mass index.	

Glucose Management

SIGN – Pharmacological Management of Glycemia Control in People with T2DM

A revised edition of the SIGN recommendations for glucose lowering treatments for people with T2DM were issued in 2024 and originally published in 2017.[15] Accreditation of the guideline process used by SIGN is endorsed by NICE. Recommendations pertaining to non-insulin therapies will be presented. All recommendations are in addition to lifestyle measures.

Key Recommendations for people with T2DM:[15]

- Metformin should be considered first-line oral treatment
- Patients with CV disease:
    - For patients with CV disease, a SGLT-2 inhibitor with proven CV benefit should be considered (empagliflozin and canagliflozin at GL publication)
    - GLP-1 RAs with proven CV benefit (liraglutide at GL publication), should be considered in people with established CV disease
- Sulfonylureas
    - For patients who are intolerant or have contraindications to metformin, a sulfonylurea should be considered as a first-line oral option
    - The use of sulfonylurea should be considered as an add-on second-line option to add to other oral therapies and may be useful in triple therapy
    - The use of sulfonylurea is associated with hypoglycemia and weigh gain
- Pioglitazone
    - For patients requiring dual and triple therapy, pioglitazone should be considered for lowering HbA1c
    - Pioglitazone should not be used in patients with heart failure
    - The long-term use of pioglitazone is associated with a risk of fracture
    - Pioglitazone is associated with the increased risk of peripheral edema, heart failure, weight gain, bladder cancer and fractures
- Dipeptidyl peptidase-4 inhibitors
    - The use of DPP-4s inhibitors should be considered, as dual or triple therapy, for lowering HbA1c
- Sodium glucose co-transporter 2 inhibitors
    - The use of SGLT-2 inhibitors should be considered as add-on therapy to metformin
    - See CV recommendation above
- Glucagon-like peptide-1 receptor agonists
    - GLP-1 RA therapy should be considered in individuals with a body mass index of $\geq$30 kg/m^2 (or ethnicity-adjusted equivalent) in combination with oral glucose lowering drugs or basil insulin (or both therapies) as a third or fourth option, when target glucose levels have not been achieved with other therapies.
    - In patients where combinations of oral glucose lowering therapies have been inadequate, GLP1 RAs should be considered as an alternative to insulin
    - See CV recommendations above
- Continuing oral therapies when adding basal insulin
    - Oral metformin should be continued with insulin therapy initiation to maintain or improve blood glucose control.
    - Consideration into stopping or reducing sulfonylureas when insulin is started while considering the benefits and risk of continuing other glucose-lowering therapies

NICE – Type 2 Diabetes Management

Guidelines for T2D management from NICE was updated February 2026.[16] Classes included in the update are: DPP-4 inhibitors, GLP-1 RAs (only liraglutide, dulaglutide and semaglutide were included), sulfonylureas, and SGLT-2 inhibitors. Pharmacotherapy recommendations are provided below. For initial therapy metformin and SGLT-2 inhibitor combination therapy is recommended based on evidence demonstrating that they were more effective at reducing HbA1c, weight and CV events compared to any other one therapy combination with metformin and metformin alone. There is also evidence that canagliflozin and dapagliflozin decreased the risk of end-stage renal failure.

Recommendations

Initial Therapy[16]:

- Metformin extended-release and an SGLT-2 inhibitor if there are no relevant comorbidities.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.

T2D and HF[16]:

- Metformin extended release and an SGLT-2 inhibitor.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- If additional therapy is needed to obtain glucose goals offer to add a DPP-4 inhibitor to current regimen.
- If a DPP-4 inhibitor is contraindicated, not tolerated, or not effective offer a SU or insulin.

T2D and ACVD[16]:

- Metformin extended-release, an SGLT-2 inhibitor and semaglutide subcutaneously up to 1 mg weekly for CV, glycemic and renal benefits.
- If metformin is contraindicated or not tolerated offer an SGLT-2 inhibitor and semaglutide subcutaneously up to 1 mg weekly for CV, glycemic and renal benefits.
- If a patient with T2D develops ACVD offer the addition of semaglutide subcutaneously for CV and renal benefits.
- If additional therapy is needed to obtain glucose goals offer to add a sulfonylurea, pioglitazone or insulin.

Early onset T2D[16]:

- Offer metformin extended release and SGLT2 inhibitor and consider adding a GLP-1 RA for CV, glycemic and renal benefits or tirzepatide for its glycemic benefits.
- If metformin is contraindicated or not tolerated offer an SGLT-2 inhibitor and a GLP-1 RA for CV, glycemic and renal benefits or tirzepatide for its glycemic benefits.
- If additional therapy is needed to obtain glucose goals offer to add a GLP-1 RA or tirzepatide. If these are contraindicated, not tolerated or not appropriate, offer a DPP-4 inhibitor. If a DPP-4 is not an option offer a sulfonylurea, pioglitazone or insulin.
- If the patient is taking a GLP-1 RA or tirzepatide and not at goal offer a sulfonylurea, pioglitazone or insulin.

T2D and obesity[16]:

- Metformin extended release and an SGLT-2 inhibitor should be offered.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- The addition of a GLP-1 RA or tirzepatide can be considered for patients with T2D living with obesity and they have been taking initial therapy for at least 3 months and additional medication is needed to reach glucose targets if they are not already taking a GLP-1 RA or tirzepatide.
- If these options are not tolerated, contraindicated or not appropriate offer a DPP-4 inhibitor to current regimen or sulfonylurea, pioglitazone or insulin if a DPP-4 inhibitor is not an option.
- If patients are not already taking a GLP-1 RA or tirzepatide and need additional glucose lowering, offer a sulfonylurea, pioglitazone or insulin.

T2D and CKD[16]:
- Metformin extended release and an SGLT-2 inhibitor is recommended if eGFR is above 30 ml/min/1.73 m^2.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- If the eGFR is 20 ml/min/1.73 m^2 to 30 ml/min/1.73 m^2 offer either dapagliflozin or empagliflozin and a DPP-4 inhibitor.
- If the eGFR is below 20 ml/min/1.73 m^2 consider a DPP-4 inhibitor.
- If a DPP-4 inhibitor is contraindicated, not tolerated or not effective consider pioglitazone or an insulin-based treatment.
- If additional glucose lowering is needed offer a DPP-4 inhibitor or if this is already being used or not an option, consider pioglitazone, a sulfonylurea or insulin.

T2D and frailty[16]:
- Metformin extended release is recommended.
- Offer an SGLT-2 inhibitor if the frailty of the person does not increase the risk for AE such as volume depletion or hypotension.
- If metformin is contraindicated or not tolerated and the patient is a candidate for an SGLT-2 inhibitor then offer SGLT-2 monotherapy if they are not a candidate then offer a DPP-4 inhibitor.
- If additional therapy is needed consider adding a DPP-4 inhibitor or a sulfonylurea, pioglitazone or insulin if a DPP-4 inhibitor is not an option.

T2D and no comorbidities requiring additional medication[16]:
- Offer the addition of a DPP-4 inhibitor to current regimen.
- If a DPP-4 inhibitor is contraindicated or not tolerated offer a sulfonylurea, pioglitazone or insulin therapy.

The use of a SGLT-2 inhibitor should be considered for their CV and renal benefits, even if they do not help the patient obtain glucose targets. The use of GLP-1 RAs should be discontinued if a person becomes underweight (BMI less than 18.5 kg/m^2).[16] The use of GLP-1 RAs and tirzepatide should be discontinued is the person is not obtaining their glucose goal and they are not being taken for CV benefit. The combined use of both a GLP-1 RA or tirzepatide and a DPP-4 inhibitor is not recommended. The risk of hypoglycemia and falls can be increased with SU or insulin therapy.

ADA – Standards of Care in Diabetes 2026

The ADA updates recommendations for standards of care for the management of diabetes on an annual basis.[17] Recommendations are graded from A to E, with A having the highest quality of evidence for support. Recommendations regarding non-insulin drug treatment will be presented.

Non-insulin pharmacologic recommendations for the treatment of T2D are included in **Table 4**.[17] Metformin is the most commonly prescribed first-line therapy for T2D. Medications should be evaluated at regular intervals, every 3-6 months and adjusted to meet glucose goals (Grade E).[17] Glucose lowering medications should be chosen based on glucose and weight goals, presence of comorbidities (e.g., CV, kidney disease, liver disease and other metabolic abnormalities) and hypoglycemia risk (Grade A).[17] The combination of DPP-4 inhibitors and GLP-1 RAs or GIP/GLP-1 RAs is not recommended due to lack of additional benefit (Grade B).[17]

Table 4. ADA Recommendations for Pharmacotherapy Management

Recommendation	Grade of Evidence
General Management[17]	
- Consider combination therapy as initial therapy to improve quicker attainment of glucose goals	A

- In individuals with T2D without severe hyperglycemia or hyperglycemic crisis, GLP-1–based therapy is preferred to insulin for initial or add-on glucose-lowering therapy	A
- If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended to improve glucose levels as well as beneficial effects on weight and hypoglycemia risk. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA.	A
Cardiovascular[29]	
- In individuals with established or at high risk of ACVD should receive medications with demonstrated benefit to reduce CV events, such as GLP-1 RAs and/or SGLT-2 inhibitors for glucose management and CV risk reduction (regardless of HbA1c)	A
- Individuals who have T2D and established ASCVD or CKD, a SGLT-2 inhibitor or GLP-1A RA with demonstrated CV benefit is recommended to reduce CV risk and lower glucose	A
- SGLT-2 inhibitors with demonstrated CV benefit are recommended for people with type 2 diabetes and established ASCVD or multiple ASCVD risk factors, or CKD	A
- In individuals with T2D with established ASCVD or multiple risk factors for ASCVD, or CKD, a GLP-1 RA with demonstrated cardiovascular benefit is recommended to reduce the risk of cardiovascular events	A
- Combination therapy with an SGLT-2 inhibitor with demonstrated CV benefit and a GLP-1 RA with demonstrated CV benefit may be considered In people with T2D and established ASCVD or multiple risk factors for ASCVD for additive reduction of the risk of adverse cardiovascular and kidney events	A
- A SGLT-2 inhibitor is recommended in individuals with HF (with reduced or preserved EF) for glucose management and prevention of HF hospitalization (regardless of HbA1c)	A
- In individuals with T2D, obesity and symptomatic HF with preserved ejection fraction should include a dual GIP and GLP-1 RA with demonstrated benefit for HF-related symptoms and reduction in HF events (regardless of HbA1c)	A
- In individuals with T2D, obesity and symptomatic HF with preserved ejection fraction should include a GLP-1 RA with demonstrated benefit for HF-related symptoms and/or reduction in HF events (regardless of HbA1c)	A
- In individuals with T2D and asymptomatic (stage B) HF or with high risk of or established CVD, treatment with an SGLT-2 inhibitor with evidence of HF prevention benefit or a GLP-1 RA with HF prevention benefit is recommended to reduce the risk of hospitalization for HF	A for SGLT-2 inhibitors B for GlP-1 RAs
- Guideline-directed medical therapy for MI and symptomatic stage CHF is recommended with ACE inhibitors or ARBs (including ARBs and neprilysin inhibitors), MRAs, β-blockers, and SGLT2 inhibitors	A
- In individuals with stable HF, metformin may be continued for glucose lowering if eGFR remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized individuals with HF	B
Chronic Kidney Disease[30]	
- In individuals with T2D who have CKD, with a confirmed eGFR of 20-60 mL/min/1.73 m^2 and/or albuminuria, an SGLT-2 inhibitor with demonstrated benefit should be use for glucose management and for slowing progression of CKD and reduction in CV events (regardless of HbA1c)	A
- In individuals with T2D and advanced CKD (eGFR <30 mL/min/1.73 m^2), a GLP-1 RA is preferred for glucose management due to lower risk of hypoglycemia and for CV event reduction	B

- In individuals with T2D and CKD a GLP-1 RA with demonstrated benefit is recommended to reduce kidney disease progression and cardiovascular risk	A
MASH and MASLD[17]	
- In individuals with T2D, MASLD, and over-weight or obesity, consider using a GLP-1 RA with demonstrated benefits in MASH	A
- In individuals with T2D, MASLD, and over-weight or obesity, consider using a dual GIP and GLP-1 RA with potential benefits in MASH	B
- A GLP-1 RA is preferred for glucose management for individuals with T2D and biopsy-proven MASH or those at high risk for liver fibrosis	A
- In individuals with T2D and biopsy-proven MASH or those at high risk for liver fibrosis pioglitazone or a dual GIP and GLP-1 RA can be considered for glucose management due to potential MASH benefits	B
- In individuals with T2D with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to potential beneficial effects on MASH combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia	B
Special Circumstances[17]	
- Metformin should be considered as first-line treatment of hyperglycemia due to mTOR inhibitors	E
- Consider metformin first-line for hyperglycemia due to PI3K inhibitors that affect the α isoform	E
- In individuals with post transplantation DM or preexisting T2D the use of a DPP-4 inhibitor can be considered for mild hyperglycemia if insulin is not an option	A
- In individuals with post transplantation DM or preexisting T2D a GLP-1 RA can be considered for long-term glucose management due to additional cardiometabolic benefits	C
Pregnancy[31]	
- Metformin and glyburide should not be used to manage glucose in individuals with DM and pregnancy	A
- If metformin is used for PCOS and ovulation induction, it should be discontinued by the end of the first trimester	A
- In individuals with a history of GDM is found to have prediabetes and have overweight or obesity should be provided intensive lifestyle interventions and/or metformin for diabetes prevention	A
Children and Adolescents[17]	
- For children and adolescents that are incidentally diagnosed with T2D, metformin is recommended as the initial choice unless contraindicated due to renal function	A
- If individualized glycemic goals are not achieved or maintained with metformin (with or without long-acting insulin), GLP-1 RA and/or SGLT-2 inhibitor should be considered in children and adolescents	A
Obesity[32]	
- Prioritize medications with a beneficial effect on weight when choosing a glucose-lowering medication for people with diabetes and overweight and obesity	B
- Lifestyle changes should be considered for people with diabetes and overweight or obesity considering benefits and risks	A
- GLP-1 RAs or dual GLP-1 RAs/GIPs (i.e., semaglutide or tirzepatide) are the preferred therapy for individuals with diabetes and overweight or obesity due to their added weight-independent benefits	A

- Pharmacotherapy for weight loss that is chronic should be continued beyond reaching weight loss goals to maintain health benefits due to discontinuation often leading to weight gain and worsening or reemergence of cardiometabolic risk factors	B
- Obesity pharmacotherapy should have the dose and dose titration individualized to balance effectiveness, health benefits and tolerability. Consideration that the optimal treatment dose may not be the maximum approved dose	B
- Treatment may be intensified with additional approaches, including lifestyle management programs, metabolic surgery and additional or alternative pharmacological agents in people with diabetes not reaching weight treatment goals	A for all except B for alternative pharmacological agents
- For individuals with T1D and obesity (BMI $\geq$ 30.0 kg/m^2 or $\geq$ 27.5 kg/m^2 in Asian American individuals) the same obesity management strategies used for the general adult population, including GLP-1 RA based therapy and metabolic surgery should be applied	B for GLP-1 RA and C for metabolic surgery
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular disease; CVD = cardiovascular disease; DM = diabetes; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide-1 receptor agonists; GDM = gestational diabetes; HbA1 = hemoglobin A1c; HF = heart failure; LVH = left ventricular hypertrophy; MASH = metabolic dysfunction–associated steatohepatitis; MASLD - metabolic dysfunction–associated steatotic liver disease; MI – myocardial infarction; MRA = mineralocorticoid receptor antagonist; mTOR = mechanistic target of rapamycin; PCOS = polycystic ovary syndrome; SGLT-2 = sodium-glucose cotransporter-2; T1D = type 1 diabetes; T2D = type 2 diabetes.	

VA/DoD – Guidelines for the Management of Type 2 Diabetes Mellitus

Recommendations were updated by the VA/DoD on managing patients with T2D.[18] Rigorous review of the evidence was performed and GRADE methodology was applied to the evidence, rating it from Strong (high or moderate strength of evidence) or Weak. Text representing the strength of the evidence is presented in **Table 5**.[18] Literature was searched through 2022. The use of dual GLP-1/GIP receptor agonists were not evaluated.

Table 5. Strength and Direction of Recommendations and General Corresponding Text[18]

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

The VA/DoD recommends the use of metformin as first line for patients with T2D when pharmacotherapy is indicated and there are no contraindications to its use.[18] If the patient has established ASCVD or high risk for ASCVD, diabetic nephropathy, or HF consider a GLP-1 RA or SGLT-2 inhibitor. An SGLT-2 inhibitor or GLP-1 RA should be considered for patients with diabetic nephropathy.[18] For specific pharmacotherapy recommendations see Table 6.

Table 6. Recommendations from the VA/DoD for Pharmacotherapy for the Management of T2D in Adults[18]

Recommendation	Strength of Evidence
Metformin or other select medications (not described) is suggested for those patients who have prediabetes and have participated in healthy lifestyle modification and remain at high risk of progression to T2D. Patients should be evaluated for specific patient characteristics (e.g., age, life expectancy, co-occurring conditions, BMI, other risk factors) when selecting a medication.	Weak
SGLT-2 inhibitors or GLP-1 RAs, with proven CV benefit to decrease the risk of major adverse CV events, are suggested therapy for patients with ASCVD (i.e., CKD, LVH, HF)	Strong
SGLT-2 inhibitors or GLP-1 RAs, with proven CV benefit to decrease the risk of major adverse CV events, are suggested therapy for patients at high risk of ASCVD (i.e., CKD, LVH, HF)	Weak
Patients with HF we recommend SGLT-2 inhibitors to prevent hospital admissions for HF	Strong
SGLT-2 inhibitors with proven renal protection to improve renal outcomes are recommended for patients with CKD	Strong
GLP-1 RAs with proven renal protection to improve macroalbuminuria for adults with T2DM who have CKD and are not able to take SGLT-2 inhibitors	Strong
Patients with CVD or renal disease we suggest that the addition of SGLT-2 or GLP-1 RA be considered even if the patient has obtained their target range for glycemic control	Weak
Classes of antidiabetic therapies besides insulin, sulfonylureas or meglitinides in adults, especially those 65 years and older, are suggested to reduce risk of hypoglycemia	Weak
Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; LVH = left ventricular hypertrophy; SGLT-2 = sodium-glucose cotransporter 2; T1D = type 1 diabetes; T2D = type 2 diabetes.	

ACP – Newer Pharmacological Treatment in Adults with Type 2 Diabetes

An update by ACP on the use of newer pharmacotherapies for T2D was published in 2024, updating a guideline published in 2017.[19] Newer pharmacotherapies included in the guideline are GLP-1 RAs (dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide), GLP-1RA/GIP (tirzepatide), SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin), and long-acting insulins (insulin glargine and insulin degludec).[19] Recommendations are based on a systematic review and network meta-analysis done by ACP. Recommendations are based on the certainty of evidence, ranging from low to high, and strength of recommendation: strong (ACP recommends) and conditional (ACP suggests). Most of the included studies were in addition to usual care in adults requiring additional glucose lowering. Studies including hospitalized adults with T2D and adults with T2D with acute comorbid conditions, such as acute stroke or MI, were excluded.[19] Main outcomes of interest were risk for all-cause mortality, CV morbidity, and progression of CKD. Weight loss was also an important outcome but data was insufficient to perform a network meta-analysis on weight loss.

The ACP recommends metformin and lifestyle modifications first line for patients with T2D.[19] The addition of an SGLT-2 inhibitor or GLP-1 RA to metformin is recommended for adults who have suboptimal glucose control (strong recommendation; high certainty of evidence). The use of SGLT2 inhibitors should be prioritized for those with CHF or CKD.[19] The ACP found both SGLT-2 inhibitors and GLP-1 RAs to reduce all-cause mortality compared to placebo or usual care based on high quality evidence. There was no evidence to suggest superiority of one class over another based on efficacy and harms outcomes. However, SGLT-2 inhibitors probably reduce the risk of hospitalizations due to CHF more than GLP-1 RAs and GLP1-RAs probably reduce the risk for stroke more than SGLT2s. The addition of a DPP-4 inhibitor to metformin is recommended against for the reduction in morbidity and all-cause mortality (strong recommendation; high-certainty of evidence).[19]

NICE – Management of Type 1 and Type 2 Diabetes Mellitus in Children and Young People

In 2023, NICE updated guidance on the treatment of young people with T1DM and T2DM.[20] Literature was searched through February 2023. Recommendations include:

- Maintenance of an HbA1c of 6.5% or less minimizes long-term complications.[20]
- Metformin is recommended as a first-line agent in children who require medication for T2D, in addition to dietary support.[20]
- Basal-bolus insulin is recommended in children who present with ketosis without diabetic ketoacidosis (DKA).[20]
- Review glucose monitoring 4 weeks after treatment is started.[20]
- If a change in treatment is required for individuals 10 years and older with T2D taking metformin monotherapy, offer liraglutide or dulaglutide if the following are met:[20]
    - HbA1c remains at 6.5% or greater,
    - Plasma glucose greater than126 mg/dL (4 or more days a week when fasting or before meals), or
    - Plasma glucose greater than 162 mg/dL (on 4 or more days a week, 2 hours after meals)
- Empagliflozin may be added to metformin children 10 years or older with T2D who are not able to tolerate liraglutide or dulaglutide or have a clear preference for empagliflozin.[20]
- Insulin can be considered in young people with T2D who are taking metformin, with or without liraglutide, dulaglutide, or empagliflozin, if an HbA1c of 6.5% cannot be obtained on current therapy.[20]
- In children on metformin and insulin, the addition of liraglutide or dulaglutide can be considered for those who are already on insulin therapy, instead of increasing insulin, if their HbA1c or glucose levels do not meet criteria (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals] or plasma glucose >162 mg/dL [on 4 or more days a week, 2 hours after meals]).[20]
- The addition of empagliflozin is recommended, instead of increasing insulin, in children already on insulin if their HbA1c or glucose levels do not meet recommendations for reducing or stopping insulin (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals]) and they are not able to tolerate liraglutide or dulaglutide or if they specifically request empagliflozin.[20]
- The lowest dose of medications should be used that achieves target HbA1c and blood glucose levels.[20]

Diabetes and Chronic Kidney Disease

KIDGO - Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

The KDIGO updated guidance in 2022 for management of individuals with diabetes mellitus with CKD.[21] The strength of the recommendation was either Level 1 (strong), which are recommendations, and Level 2 (weak) which are suggestions. The quality of evidence is graded from A (high) to D (low). The most important outcomes in the management of CKD are mortality, CV events (e.g., MI, stroke and HF) and kidney related outcomes (e.g., progression to kidney failure and acute kidney injury).[21] Recommendations which include antidiabetic therapies will be included:

- It is recommended to treat patients with T2D, CKD, and an eGFR ≥20 ml/min/1.73 m^2 with a SGLT-2 inhibitor (1A recommendation).[21] The choice of SGLT-2 inhibitor should prioritize therapies with documented kidney or CV benefit and consider eGFR.
- In patients with T2D, CKD and estimated glomerular filtration rate [EGFR] of >30 ml/min/1.73 m^2 metformin is recommended (1B recommendation).[21]
- In patients with T2D and CKD (without dialysis and estimated glomerular filtration rate [EGFR] of >30 ml/min/1.73 m^2), metformin with a SGLT-2 inhibitor is recommended (1A recommendation).[21]
- Long-acting GLP-1 RAs with CV benefit are recommended for patients requiring additional medications for glucose lowering or who cannot tolerate

metformin and/or SGLT-2 inhibitors (1B recommendation).[21]

- o GLP-1 RAs are also preferred for those patients desiring weight loss, have heart failure, high-risk of ASCVD and wish to avoid hypoglycemia.
- o The combined use of GLP-1 RAs and DDP-4 inhibitors should not be used.
- o If GLP-1 RAs are used with sulfonylureas or insulin, the dose of those products should be reduced to reduce the risk of hypoglycemia.

VA/DOD – Primary Care Chronic Kidney Disease Management

The VA/DOD updated guidance on the treatment of CKD in the primary care setting in adults who have, or are at risk for, CKD.[22] This comprehensive guideline provides recommendations for diagnosis, assessment, risk factors and treatment. Evidence is current through June 30, 2024.[22] For the purpose of this review, the role of antidiabetic therapies in CKD will be presented **(Table 7**).

Table 7. Antidiabetic Therapies in the Management of Chronic Kidney Disease[22]

Recommendation	Strength
Medications to decrease CV disease and kidney outcomes	
- To reduce the risk of major adverse CV events, HF, progression of kidney disease and mortality the addition of SGLT-2 inhibitors to maximally tolerated ACE inhibitor or ARB is recommended in patients with CKD disease who have one or more of the following: T2D, albuminuria (UACR >200 mg/g), HF (SGLT-2 inhibitor should be continued until dialysis)	Strong
- In patients with T2D and albuminuric CKD a GLP-1 RA is recommended to be added to an ACE or ARB to reduce the progression of CKD, major adverse CV events and all-cause mortality	Strong
Abbreviations: ACE = angiotensin converting enzyme Inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; SGLT-2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes; UACR = urine albumin-to-creatinine ratio.	

Diabetes and Weight Management

TOS/OMA/OAC – Pharmacological Management of Overweight or Obesity

A 2026 guideline on the management of adults with overweight or obesity was published by a multidisciplinary panel.[23] Methodology was well described and recommendations were graded using the Granding of Recommendations Assessment, Development and Evaluation (GRADE) approach. Medications included in the review are orlistat, bupropion-naltrexone, phentermine, phentermine-topiramate, liraglutide, semaglutide and tirzepatide. Obesity medications are FDA approved for adults with a BMI of $\geq$ 27 kg/m^2 with at least one complication or BMI $\geq$ 30 kg/m^2.[23] Pharmacotherapy recommendations are provided in **Table 8.** All treatments should be used in conjunction with lifestyle/behavioral interventions. Evidence for the use of GLP-1 RAs and GLP-1 RAs/GIPs in patients with T2D and overweight or obesity also demonstrate HbA1c lowering, MACE and mortality benefits.[23]

Table 8. Recommendation for Pharmacotherapy for Obesity[23]

Recommendation	Strength of Recommendation / Level of Evidence
Orlistat for adults aged 18 years or older with overweight or obesity	Conditional; low certainty of evidence
Bupropion- naltrexone in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty of evidence
Phentermine for 3 months or more in adults aged 18 years or older with overweight or obesity	Conditional; low certainty evidence
Phentermine- topiramate in adults aged 18 years or older with overweight or obesity	Conditional; low certainty of evidence

Liraglutide in adults aged 18 years or older with overweight or obesity	Conditional; low certainty evidence
Semaglutide in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty evidence
Tirzepatide in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty evidence
Setmelanotide in adults aged 18 years or older with monogenic obesity syndromes (e.g., risk alleles for LEPR, POMC, PCSK1, and BBS)	Strong; moderate certainty evidence
Continue obesity medications in adults undergoing medical obesity treatment during the weight maintenance phase, compared with not continuing obesity medications	Strong; moderate certainty evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older with OSA * Evidence examined included trials using liraglutide or tirzepatide; tirzepatide is FDA approved for moderate- to-severe OSA	Conditional; low certainty of evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older with HFpEF * Evidence examined included trials using semaglutide or tirzepatide, in which treatment of HFpEF is considered off-label use	Conditional; low certainty of evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older to reduce liver fat and treat MASH * Semaglutide is not FDA approved for treatment of MASLD without MASH	Conditional; low certainty of evidence
GLP- 1 receptor agonists compared to lifestyle interventions/placebo in adults aged 18 years or older with osteoarthritis	Conditional; low certainty of evidence
Semaglutide in adults aged 18 years or older with a history of myocardial infarction, stroke, or symptomatic peripheral vascular disease	Conditional; low certainty of evidence
FDA- approved obesity medications in adults aged 18 years or older with type 2 diabetes	Conditional; low certainty of evidence
Abbreviations: BBS = Bardet-Biedl syndrome; FDA = Food and Drug Administration; GIP = glucose-dependent insulinotropic polypeptide ; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HFpEF = heart failure with preserved ejection fraction; LEPR = leptin receptor; MASH = metabolic dysfunction–associated steatohepatitis; MASLD = - metabolic dysfunction–associated steatotic liver disease; OSA = obstructive sleep apnea; PCSK1 = Proprotein Convertase Subtilisin/Kexin Type 1; POMC = pro-opiomelanocortin (POMC).	

Diabetes and Pregnancy

SIGN – Management of Diabetes in Pregnancy

A 2024 guideline was published by SIGN outlined treatment and management of women with T1D and T2D during pregnancy.[24] Recommendations were considered 'strong' by being described as 'should' be used while 'conditional' recommendations are described as 'considered'. Recommendations for drug therapy will be included.

For gestational diabetes the avoidance of DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors and TZDs is recommended.[24] The use of sulfonylureas should be avoided due to risk of neonatal hypoglycemia. If the patient requires medication for glucose management the use of metformin or insulin should be used first line. In women who have diabetes before pregnancy the use of insulin and/or metformin are recommended.[24] The use of insulin and/or metformin during breastfeeding is also recommended.

Endocrine Society and European Society of Endocrinology – Preexisting Diabetes and Pregnancy

In 2025 a joint guideline was published by the ES and ESE for the management of patients with preexisting T1D and T2D.[25] Evidence was searched through and was graded using GRADE methodology, with certainty of evidence graded from very low to high. The strength of the recommendation was designated as a 1 (Strong recommendation) or 2 (Conditional recommendation).

Recommendations related to pharmacotherapy in individuals that are pregnant are:

- Discontinuation of GLP-1 RAs prior to conception, rather than between the start of pregnancy and end of the first trimester, is suggested in individuals who have T2D and are taking a GLP-1 RA (Grade 2 /very low-quality evidence).[25]
- In individuals with T2D taking insulin, the routine addition of metformin is recommended against (Grade 2 /very low-quality evidence).[25]
- The use of a hybrid closed-loop pump is suggested rather than an insulin pump with CGM (without an algorithm) or multiple daily insulin injections in individuals with T1D (Grade 2 /very low-quality evidence).[25]

Polyendocrine Metabolic Ovary Syndrome

International Evidence Based Guideline – Management of Polyendocrine Metabolic Ovary Syndrome

An International evidence-based guideline on the assessment and management of PMOS was published in 2023 as partnership with the American Society of Reproductive Medicine (ASRM), the ES, European Society of Endocrinology and the European Society of Human Reproduction and Embryology (ESHRE).[26] The guideline was developed via a process to align with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework. Recommendations were based on GRADE methodology and are comprised of the following 3 categories: EBR (evidence-based recommendations), CR (consensus recommendation) and PP (practice points). The evidence for the use of diabetes drugs in the management of PMOS will be presented.

Recommendations include the following:

- Women with PMOS are at an increased risk of impaired fasting glucose, impaired glucose tolerance and T2D, irrespective of age and BMI and glucose measurements should be assessed in adults and adolescents with PMOS (strong recommendation and low-quality evidence).[26]
- A conditional recommendation based on very low-quality evidence for the use of metformin as monotherapy for adults with PMOS and a BMI $\geq$25 kg/m^2 for anthropometric and metabolic outcomes (i.e., insulin resistance, glucose and lipid profiles).
- Metformin can be considered for adolescents at risk of or with PMOS for cycle regulation (Conditional recommendation based on very low-quality evidence).[26]
- In adults with PMOS and a BMI <25 kg/m^2 may consider metformin (Conditional recommendation with limited evidence).
- Women should be informed that metformin and lifestyle interventions have similar efficacy (Practice Point).[26] The use of combined oral contraceptive pills (COCP) could be recommended over the use of metformin for management of hirsutism in irregular menstrual cycles in PMOS (Conditional recommendation based on very-low quality evidence).[26]
- Metformin could be used over COCP for metabolic indications in PMOS (Conditional recommendation based on very-low quality evidence).
- A conditional recommendation based on very-low quality evidence for the combination of COCP and metformin could be considered to offer little additional clinical benefit over monotherapy in adults with PCOS with a BMI $\leq$30 kg/m^2.[26]
- Metformin, when used in combination with COCP, may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m^2, diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups according to a practice point recommendation.[26]
- Metformin may be considered for irregular menstrual cycles when COCP is contraindicated according to a practice point recommendation.

- Metformin should be considered over inositol for hirsutism and central adiposity; however, metformin has more gastrointestinal side-effects than inositol (Conditional recommendation based on very-low quality of evidence).[26]
- A conditional recommendation for the use of anti-obesity medications (e.g., liraglutide, semaglutide, and orlistat) could be considered, in addition to lifestyle interventions, could be considered in the management of higher weight adults with PCOS similar to recommendations for the general population.[26]
- A conditional recommendation against the use of anti-obesity agents for PCOS for reproductive outcomes.
- Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS (Conditional recommendation based on moderate quality of evidence).[26]
- A conditional recommendation based on low quality evidence for the use of metformin in women with PMOS and anovulatory infertility and no other fertility factors, could be used alone to improve clinical pregnancy and live birth rates; however, there are more effective ovulation agents.
- Clomiphene citrate in conjunction with metformin could be used rather than clomiphene citrate alone in women with PMOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates (Conditional recommendation based on low quality evidence).[26]
- Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PMOS with anovulatory infertility and no other infertility factors to improve live birth rates (Conditional recommendation based on low quality evidence).
- A conditional recommendation based on very low-quality evidence recommends adjunct metformin therapy as an option to be used before and/or during follicle stimulation hormone (FSH) ovarian stimulation in women with PMOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.[26]

<u>EULAR – Management of Systemic Lupus Erythematosus with Kidney Involvement</u>

In 2025 EULAR updated recommendations for patients with SLE and kidney involvement.[27] A literature search was performed from January 2019 to March 2024 to update the 2019 recommendations. The level of evidence was graded from 1-4 and the recommendations from highest (A) to lowest (D). Thirteen recommendations were included but for the purpose of this review only antidiabetic therapies will be discussed.

The guidance recommends the use of nonimmune treatments, which are considered second pillar treatment of lupus nephritis (LN).[27] SGLT-2 inhibitors are included for use in this population for stable patients with persistent proteinuria or eGFR ≤ 60 ml/min/1.73 m^2, or other risk factors for progressive CKD (Level 5/D). Studies of SGLT-2 inhibitors in patients with autoimmune disease-related CKD demonstrated delayed progression of GFR decline. Initiation of SGLT-2 inhibitors is recommended to be delayed 6-12 months after stabilization of LN with immunosuppressive therapy. There is insufficient evidence for use in pediatric patients.

After review, 6 guidelines were excluded due to poor quality.

New Formulations:

<u>RYBELSUS to OZEMPIC (semaglutide):</u> Oral semaglutide is available in two types of formulations, R1 and R2.[33] The R1 formulation is the original tablet available as 3 mg, 7 mg, and 14 mg. The R2 formulation (newer) is available as 1.5 mg, 4 mg and 9 mg. The doses are not interchangeable and it is recommended to not switch between the R1 and R2 formulations in during the first 30 days of use.[33] The R2 formulation has increased absorption with lower doses of semaglutide in an effort to reduce GI AE. The R2 formulation was changed from brand name Rybelsus to Ozempic tablets in January 2026.[33]

BRYNOVIN (sitagliptin): BRYNOVIN is an oral sitagliptin solution approved in January 2025 as an adjunct to diet and exercise to improve glucose control in adults with T2D.[34] BRYNOVIN is dosed at 100 mg daily (4 mL) with or without food. Renal adjustment is recommended for patients with an eGFR of less than 45 mL/min/1.73m^2.[34]

ZITUVIMET (sitagliptin/metformin): ZITUVIMET is sitagliptin, a DPP-4 inhibitor, and metformin, a biguanide combination tablet approved as an adjunct to diet and exercise to improve glucose control for adult patients with T2D.[35] The tablet is available as sitagliptin 50 mg/metformin 500 mg or sitagliptin 100 mg/metformin 1000 mg to be given twice daily with meals.[35]

ZITUVIMET XR (metformin/sitagliptin extended-release tablets): An extended-release tablet formulation of sitagliptin and metformin was approved in July of 2024. It is approved to improve glucose control in adult patients with T2D.[36] The extended-release tablets should be taken once daily, even if the patient is taking two tablets they should be taken together. ZITUVIMET XR is available as sitagliptin 100 mg/metformin 1,000 mg extended-release, sitagliptin 50 mg/ metformin 500 mg extended-release and sitagliptin 50 mg/metformin 1000 mg extended-release.[36]

ZITUVIO (sitagliptin): In October 2023 sitagliptin tablets were approved for use as an adjunct to diet and exercise to improve glucose levels in adults with T2D.[37] ZITUVIO is given as 100 mg daily with or without food. Patients with renal impairment should receive as reduced dose based on eGFR. ZITUVIMET is available 25 mg, 50 mg and 100 mg tablets.[37]

New Indications:

MOUNJARO (tirzepatide): In December of 2025 tirzepatide received the approval for an expanded indication for pediatric patients aged 10 years and older with T2D.[38] The expanded indication was approved based off a double-blind, placebo-controlled, open-label trial in pediatric patients 10 years of age and older with T2D and inadequate glucose control on metformin, basal insulin or both.[38] Tirzepatide 5 mg, tirzepatide 10 mg or placebo was given as a once-weekly subcutaneous injection. Tirzepatide 5 mg reduced HbA1c by -1.7% (95% CI, -2.4 to -1.0) and tirzepatide 10 mg by 2.0% (95% CI, -2.7 to -1.3) compared to placebo at 30 weeks.[38]

RYBELSUS (semaglutide): Semaglutide tablets were approved in October 2025 for a new indication for the reduction of the risk of major adverse CV events (CV death, non-fatal MI or non-fatal stroke) in adults with T2D who are at risk for these events.[33] Supportive evidence for this indication is based off a double-blind, placebo-controlled, randomized controlled trial in 9,650 patients with T2D and established CVD and/or CKD. Patients received semaglutide 14 mg or placebo. The primary outcome was time to first occurrence of a 3-point MACE (CV death, non-fatal MI and non-fatal stroke).[33] Semaglutide was more effective than placebo, 12.0% versus 13.8% (HR 0.86; 95% CI, 0.77 to 0.96).[33]

OZEMPIC (semaglutide): In January of 2025 semaglutide injection received a new indication to reduce the risk of sustained eGFR decline, end-stage kidney disease and CV death in adults with T2D.[39] Evidence for this approval was based on the FLOW trial described in Table 10.[40]

SYNJARDY (empagliflozin/metformin) and SYNJARDY XR (empagliflozin/metformin extended-release tablets): In March of 2025 SYNJARDY and SYNJARDY XR received the expanded indication to reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death and hospitalization in adults with CKD at risk of progression.[41] The expanded indication was supported by evidence from a study in patients (n=6,609) with CKD and with or without T2D in a double-blind,

placebo-controlled, randomized controlled trial. The primary composite endpoint was reduced with empagliflozin, and background metformin therapy, compared to placebo (HR 0.72; 95% CI, 0.48 to 1.09).[41]

XIGDUO XR (dapagliflozin/metformin extended-release tablets): The dapagliflozin component of the combination tablet received the expanded indication for approved use in adults with T2D to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in patients with HF.[42] Evidence for the indication was from two double-blind, placebo-controlled, randomized controlled trials (DAPA-HF and DELIVER). Trials included patients with and without diabetes. The primary composite outcome was CV death, hospitalization for HF or urgent HF visit. In both trials dapagliflozin reduced the primary endpoint more than placebo (DAPA-HF trial: HR 0.74; 95% CI, 0.65 to 0.85; p<0.0001) and (DELIVER trial: HR 0.82; 95% CI, 0.73 to 0.92; p=0.0008).[43,44]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Saxagliptin[45]	ONGLYZA	October 2024	Use in specific populations	Safety and effectiveness of saxagliptin have not been demonstrated in pediatric patients ages 10 to 17 years with T2D
Dulaglutide[39], liraglutide[46], semaglutide[39]	TRULICITY, VICTOZA, OZEMPIC	March 2026	Warnings and Precautions	Severe gastrointestinal adverse reactions have been reported in postmarketing reports including intestinal obstruction, severe constipation, including fecal impaction
Dulaglutide[38], exenatide[47], liraglutide[46], semaglutide[39], tirzepatide[38]	TRULICITY BYETTA VICTOZA OZEMPIC MOUNJARO	October 2024	Warnings and Precautions	Risk of pulmonary aspiration for patients undergoing elective surgeries or procedures requiring general anesthesia or deep sedation
Tirzepatide[38]	MOUNJARO	January 2026	Warnings and Precautions	Never share Kwikpens between patients, even if the needle is changed. There is a risk of transmission of blood-borne pathogens.

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40. Perkovic V, Tuttle K, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *NEJM*. 2024;391:109-121 DOI: 10.1056/NEJMoa240334.

41. SYNJARDY (empagliflozin and metformin) and SYNJARDY XR (empagliflozin and metformin extended-release) [prescribing information]. Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc. October 2025.

42. XIGDUO XR (dapagliflozin and metformin extended-release tablets)[prescribing information]. Wilmington, DE; AstraZeneca Pharmaceuticals LP. December 2024.

43. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *NEJM*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303

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45. Onglyza (saxagliptin)[prescribing information]. Wilmimgton, DE; AstraZeneca Pharmaceuticals LP.

46. Victoza (liraglutide) [prescribing information]. Plainsboro, NJ; Novo Nordisk Inc. October, 2025.

47. Byetta (exenatide) [prescribing information]. Wilimington, DE; AstraZeneca Pharmaceuticals LP. November 2024.

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51. Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *NEJM*. 2024;391(13):1193-1205.

52. McGuire D, Marx N, Mulvagh S, et al. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. *NEJM*. 2025 May 29;392(20):2001-2012.

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Appendix 1: Current Preferred Drug List

DPP-4 Inhibitors

Generic	Brand	Form	PDL
saxagliptin HCl	ONGLYZA	TABLET	Y
saxagliptin HCl	SAXAGLIPTIN HCL	TABLET	Y
sitagliptin phos/metformin HCl	JANUMET	TABLET	Y
sitagliptin phosphate	JANUVIA	TABLET	Y
alogliptin benz/metformin HCl	ALOGLIPTIN-METFORMIN	TABLET	N
alogliptin benz/metformin HCl	KAZANO	TABLET	N
alogliptin benz/pioglitazone	ALOGLIPTIN-PIOGLITAZONE	TABLET	N
alogliptin benz/pioglitazone	OSENI	TABLET	N
alogliptin benzoate	ALOGLIPTIN	TABLET	N
alogliptin benzoate	NESINA	TABLET	N
linagliptin	TRADJENTA	TABLET	N
linagliptin/metformin HCl	JENTADUETO XR	TAB BP 24H	N
linagliptin/metformin HCl	JENTADUETO	TABLET	N
linagliptin/metformin HCl	LINAGLIPTIN-METFORMIN	TABLET	N
saxagliptin HCl/metformin HCl	SAXAGLIPTIN-METFORMIN ER	TBMP 24HR	N
sitagliptin	SITAGLIPTIN	TABLET	N
sitagliptin	ZITUVIO	TABLET	N
sitagliptin HCl	BRYNOVIN	SOLUTION	N
sitagliptin phos/metformin HCl	JANUMET XR	TBMP 24HR	N
sitagliptin/metformin HCl	SITAGLIPTIN-METFORMIN	TABLET	N
sitagliptin/metformin HCl	ZITUVIMET	TABLET	N
sitagliptin/metformin HCl	SITAGLIPTIN-METFORMIN ER	TBMP 24HR	N
sitagliptin/metformin HCl	ZITUVIMET XR	TBMP 24HR	N

GLP-1 Receptor Agonists and GIP Therapies

Generic	Brand	Form	PDL
dulaglutide	TRULICITY	PEN INJCTR	Y
exenatide	BYETTA	PEN INJCTR	Y
exenatide	EXENATIDE	PEN INJCTR	Y
liraglutide	LIRAGLUTIDE	PEN INJCTR	Y
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N
semaglutide	OZEMPIC	PEN INJCTR	N
semaglutide	RYBELSUS	TABLET	N
tirzepatide	MOUNJARO	PEN INJCTR	N

SGLT-2 Inhibitors

Generic	Brand	Form	PDL
dapagliflozin propanediol	DAPAGLIFLOZIN	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin	INVOKANA	TABLET	N
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapaglifloz propaned/metformin	DAPAGLIFLOZIN-METFORMIN ER	TAB BP 24H	N
dapaglifloz propaned/metformin	XIGDUO XR	TAB BP 24H	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin phos	STEGLUJAN	TABLET	N
sotagliflozin	INPEFA	TABLET	N

Sulfonylureas

Generic	Brand	Form	PDL
glimepiride	GLIMEPIRIDE	TABLET	Y
glipizide	GLIPIZIDE	TABLET	Y
glyburide	GLYBURIDE	TABLET	Y
chlorpropamide	CHLORPROPAMIDE	TABLET	N
glimepiride	GLIMEPIRIDE	TABLET	N
glipizide	GLIPIZIDE ER	TAB ER 24	N
glipizide	GLUCOTROL XL	TAB ER 24	N
glipizide	GLIPIZIDE	TABLET	N
glyburide,micronized	GLYBURIDE MICRONIZED	TABLET	N

Thiazolidinediones

Generic	Brand	Form	PDL
pioglitazone HCl	ACTOS	TABLET	Y
pioglitazone HCl	PIOGLITAZONE HCL	TABLET	Y
pioglitazone HCl/glimepiride	DUETACT	TABLET	N
pioglitazone HCl/glimepiride	PIOGLITAZONE-GLIMEPIRIDE	TABLET	N
pioglitazone HCl/metformin HCl	ACTOPLUS MET	TABLET	N
pioglitazone HCl/metformin HCl	PIOGLITAZONE-METFORMIN	TABLET	N

Miscellaneous Antidiabetic Agents

Generic	Brand	Form	PDL
metformin HCl	METFORMIN HCL ER	TAB ER 24H	Y
metformin HCl	METFORMIN HCL	TABLET	Y
acarbose	ACARBOSE	TABLET	N
glipizide/metformin HCl	GLIPIZIDE-METFORMIN	TABLET	N
glyburide/metformin HCl	GLYBURIDE-METFORMIN HCL	TABLET	N
metformin HCl	METFORMIN HCL	SOLUTION	N
metformin HCl	METFORMIN ER OSMOTIC	TAB ER 24	N
metformin HCl	METFORMIN ER GASTRIC	TABERGR24H	N
metformin HCl	METFORMIN HCL	TABLET	N
miglitol	MIGLITOL	TABLET	N
nateglinide	NATEGLINIDE	TABLET	N
pramlintide acetate	SYMLINPEN 120	PEN INJCTR	N
pramlintide acetate	SYMLINPEN 60	PEN INJCTR	N
repaglinide	REPAGLINIDE	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 1601 citations were manually reviewed from the initial literature search. After further review, 1593 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 8 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Bliddal, et al[48] (STEP 9) DB, PC, RCT	Semaglutide 2.4 mg subcutaneously weekly Vs. Placebo Follow-up: 68 weeks	Participants with obesity (BMI ≥30 kg/m^2) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain (n=407)	Percent body weight change and change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score†	Change in body weight: Semaglutide: 13.7% Placebo: 3.2% (ED -10.5%; 95% CI, -12.3 to -8.6; P<0.001) Change in WOMAC pain score: Semaglutide: -41.7 points Placebo: -27.5 points (ED -14.1 points; 95% CI, -20.0 to -8.3; P<0.001)	- Mean WOMAC score was 70.9 points and mean BMI was 40.3 kg/m^2 - The WOMAC pain score is subjective - Long-term safety for chronic use is unknown - Results most applicable to those with very high BMIs - Funded by the manufacturer

Fox, et al[49] (SCALE) Phase 3a, RCT	Liraglutide 3.0 mg subcutaneously daily Vs. Placebo Treatment: 56 weeks Follow-up: 26 weeks	Children ages 6 to < 12 years with obesity (n=82)	Percent change in BMI	Liraglutide: -5.8% Placebo: 1.6% (ED -7.4%; 95% CI, -11.6 to -3.1; P<0.001)	- Serious adverse events in 12% of liraglutide and 8% in placebo group - Small sample size - Funded by the manufacturer
Kosiborod, et al[50] DB, RCT	Semaglutide 2.4 mg subcutaneously weekly Vs. Placebo Follow-up: 52 weeks	Patients with HF with preserved ejection fraction, BMI of $\geq$30 kg/m^2, and T2D (n=616)	Change from baseline in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)* and change in body weight from baseline	Change in KCCQ-CSS: Semaglutide: 13.7 points Placebo: 6.4 points (ED 7.3 points; 95% CI, 4.1 to 10.4; P<0.001) Change in body weight: Semaglutide: -9.8% Placebo: -3.4% (ED -6.4%; 95% CI, -7.6 to -5.2; P<0.001)	- One of the primary outcomes is subjective and a surrogate endpoint - No important health outcomes such as CV or all-cause mortality were studied - Funded by the manufacturer
Malhotra, et al [51] DB, Phase 3, RCT	Tirzepatide (maximum tolerated dose subcutaneously 10 mg or 15 mg weekly) Vs. Placebo subcutaneously weekly (n=52 weeks)	Two studies in adults with moderate-to-severe obstructive sleep apnea and obesity. One group was not receiving treatment with positive airway pressure (PAP) (n=234) at baseline and the second trial enrolled those receiving PAP (n=235)	Change in the apnea-hypopnea index (AHI) from baseline	Study 1: Tirzepatide: -25.3 events/hr Placebo: -5.3 events/hr ETD -20.0 events/hr; 95% CI, -25.8 to -14.2; P<0.001) Study 2: Tirzepatide: -29.3 events/hr Placebo: -5.5 events/hr ETD -23.8 events/hr; 95% CI, -29.6 to -17.9; P<0.001)	- Mean BMI 39 kg/m^2 - Neither study had participants with T1D or T2M - Evidence on outcomes such as stroke, CV events and MI would be helpful - Funded by the manufacturer
McGuire, et al[52] (SOUL)	Semaglutide orally up to max dose of 14 mg	Patients 50 years and older, HbA1c of 6.5% to 10.0% and	Major adverse cardiovascular events (a composite of death from cardiovascular causes,	Semaglutide: 579 (12%) Placebo: 668 (13.8%) (HR 0.86; 95% CI, 0.77 to 0.96; P=0.006)	- Most applicable for secondary prevention in patients with ASCVD and/or CKD

DB, PC, RCT, time to first event analysis	Vs. Placebo Mean follow-up: 47.5 months	known ASCVD, CKD or both (n=9650)	nonfatal myocardial infarction, or nonfatal stroke)		- An active comparator would be more informative - Funded by the manufacturer
Nicholls, et al[53] (SURPASS-CVOT) DB, NI, Phase 3	Tirzepatide subcutaneously once weekly (up to 15 mg) Vs. Dulaglutide 1.5 mg	Patients with T2D and atherosclerotic cardiovascular disease (n=13,299)	Composite of death from CV causes, MI or stroke (NI margin upper limit of 1.05; <1.00 indicated superiority)	Tirzepatide: 12.2% Dulaglutide: 13.1% (HR 0.92; 95% CI, 0.83 to 1.01; P=0.003 for noninferiority and P=0.09 for superiority)	- Mean age 64.1 years, mean HbA1c 8.4 and mean BMI was 32 kg/m^2 - Most applicable to patients with CV disease and T2D - Funded by the manufacturer
Packer, et al[54] DB, PC, RCT	Tirzepatide up to 15 mg subcutaneously weekly Vs. Placebo subcutaneously weekly Duration: 52 weeks Follow-up: 104 weeks	Patients with HF, and EF of at least 50% and a BMI of 30 kg/m^2 (n=365)	Composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) (scores range from 0 to 100, with higher scores indicating better quality of life)	Death from CV causes or worsening HF Tirzepatide: 36 (9.9%) Placebo: 56 (15.3%) (HR 0.62; 95% CI, 041 to 0.95; P=0.026) Change in KCCQ-CSS: Tirzepatide: 19.5 points Placebo: 12.7 points (MD 6.9 95% CI, 3.3 to 10.6; P<0.001)	- Composite endpoint driven by decreased risk of worsening heart failure - Results most applicable to individuals who are also obese - Most patients had mild to moderate HFpEF - Funded by the manufacturer
Perkovic, et al[40] (FLOW) DB, PC, RCT	Semaglutide 1.0 mg subcutaneously weekly Vs Placebo Median follow-up: 3.4 years	Patients with T2D and CKD (n=3533)	Major kidney disease events (e.g., composite of the onset of kidney failure, at least 50% reduction in the eGFR from baseline or death from kidney-related or CV causes)	Semaglutide: 331 Placebo: 410 (HR 0.76; 95% CI, 0.66 to 0.88; P=0.0003)	- Most patients were receiving ARBs (60.2%) or ACE inhibitors (35.1%) and some were also taking SGLT-2 inhibitors (15.6%) - Mean eGFR was 47.0 ml/min/1.73 m^2 - Results are most applicable to patients with a significant amount of albuminuria

					- Trial was stopped early due to benefit but may exaggerate treatment effect - Funded by the manufacturer

Key: * The Kansas City Cardiomyopathy Questionnaire clinical summary score ranges from 0 to 100 with higher scores demonstrating fewer symptoms and physical limitations; † The Western Ontario and McMaster Universities Osteoarthritis Index is scored from 0 to 100 with higher scores indicative of worse outcomes
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; DB= double blind; ED = estimated difference; EF = ejection fraction; ETD = estimated treatment difference; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1C; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; MD = mean difference; MI = myocardial infarction; NI = noninferiority; PC = placebo controlled; RCT = randomized clinical trial; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

Appendix 3: Abstracts of Comparative Clinical Trials

Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

Bliddal, Harold Bays, Sébastien Czernichow, et al

Background: Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied.

Methods: We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).

Results: A total of 407 participants were enrolled. The mean age was 56 years, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. The mean change in body weight from baseline to week 68 was -13.7% with semaglutide and -3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was -41.7 points with semaglutide and -27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.

Conclusions: Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo. (Funded by Novo Nordisk; STEP 9 ClinicalTrials.gov number, NCT05064735.).

Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

Claudia K. Fox, M.D., Margarita Barrientos-Pérez, M.D., Eric M. Bomberg, M.D., et al

BACKGROUND

No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age. Although the use of liraglutide has been shown to induce weight loss in adults and adolescents with obesity, its safety and efficacy have not been established in children.

METHODS

In this phase 3a trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we randomly assigned children (6 to <12 years of age) with obesity, in a 2:1 ratio, to receive either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions. The primary end point was the percentage change in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%.

RESULTS

A total of 82 participants underwent randomization; 56 were assigned to the liraglutide group and 26 to the placebo group. At week 56, the mean percentage change from baseline in BMI was −5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of −7.4 percentage

points (95% confidence interval [CI], −11.6 to −3.2; P<0.001). The mean percentage change in body weight was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of −8.4 percentage points (95% CI, −13.4 to −3.3; P=0.001), and a reduction in BMI of at least 5% occurred in 46% of participants in the liraglutide group and in 9% of participants in the placebo group (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02). Adverse events occurred in 89% and 88% of participants in the liraglutide and placebo groups, respectively. Gastrointestinal adverse events were more common in the liraglutide group (80% vs. 54%); serious adverse events were reported in 12% and 8% of participants in the liraglutide and placebo groups, respectively.

CONCLUSIONS

Among children (6 to <12 years of age) with obesity, treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions. (Funded by Novo Nordisk; SCALE Kids ClinicalTrials.gov number, NCT04775082.)

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Mikhail N Kosiborod, Mark C Petrie, Barry A Borlaug, et al

Background: Obesity and type 2 diabetes are prevalent in patients with heart failure with preserved ejection fraction and are characterized by a high symptom burden. No approved therapies specifically target obesity-related heart failure with preserved ejection fraction in persons with type 2 diabetes.

Methods: We randomly assigned patients who had heart failure with preserved ejection fraction, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more, and type 2 diabetes to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

Results: A total of 616 participants underwent randomization. The mean change in the KCCQ-CSS was 13.7 points with semaglutide and 6.4 points with placebo (estimated difference, 7.3 points; 95% confidence interval [CI], 4.1 to 10.4; P<0.001), and the mean percentage change in body weight was -9.8% with semaglutide and -3.4% with placebo (estimated difference, -6.4 percentage points; 95% CI, -7.6 to -5.2; P<0.001). The results for the confirmatory secondary end points favored semaglutide over placebo (estimated between-group difference in change in 6-minute walk distance, 14.3 m [95% CI, 3.7 to 24.9; P = 0.008]; win ratio for hierarchical composite end point, 1.58 [95% CI, 1.29 to 1.94; P<0.001]; and estimated treatment ratio for change in CRP level, 0.67 [95% CI, 0.55 to 0.80; P<0.001]). Serious adverse events were reported in 55 participants (17.7%) in the semaglutide group and 88 (28.8%) in the placebo group.

Conclusions: Among patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, semaglutide led to larger reductions in heart failure-related symptoms and physical limitations and greater weight loss than placebo at 1 year. (Funded by Novo Nordisk; STEP-HFpEF DM ClinicalTrials.gov number, NCT04916470.).

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., et al

BACKGROUND

Obstructive sleep apnea is characterized by disordered breathing during sleep and is associated with major cardiovascular complications; excess adiposity is an etiologic risk factor. Tirzepatide may be a potential treatment.

METHODS

We conducted two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity. Participants who were not receiving treatment with positive airway pressure (PAP) at baseline were enrolled in trial 1, and those who were receiving PAP

therapy at baseline were enrolled in trial 2. The participants were assigned in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. The primary end point was the change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline. Key multiplicity-controlled secondary end points included the percent change in AHI and body weight and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure.

RESULTS

At baseline, the mean AHI was 51.5 events per hour in trial 1 and 49.5 events per hour in trial 2, and the mean body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 39.1 and 38.7, respectively. In trial 1, the mean change in AHI at week 52 was −25.3 events per hour (95% confidence interval [CI], −29.3 to −21.2) with tirzepatide and −5.3 events per hour (95% CI, −9.4 to −1.1) with placebo, for an estimated treatment difference of −20.0 events per hour (95% CI, −25.8 to −14.2) (P<0.001). In trial 2, the mean change in AHI at week 52 was −29.3 events per hour (95% CI, −33.2 to −25.4) with tirzepatide and −5.5 events per hour (95% CI, −9.9 to −1.2) with placebo, for an estimated treatment difference of −23.8 events per hour (95% CI, −29.6 to −17.9) (P<0.001). Significant improvements in the measurements for all prespecified key secondary end points were observed with tirzepatide as compared with placebo. The most frequently reported adverse events with tirzepatide were gastrointestinal in nature and mostly mild to moderate in severity.

CONCLUSIONS

Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes. (Funded by Eli Lilly; SURMOUNT-OSA ClinicalTrials.gov number, NCT05412004.)

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

Darren K. McGuire, M.D., M.H.Sc., Nikolaus Marx, M.D., Sharon L. Mulvagh,

BACKGROUND

The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed.

METHODS

In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).

RESULTS

Among the 9650 participants who had undergone randomization, the mean (±SD) follow-up was 47.5±10.9 months, and the median follow-up was 49.5 months. A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P=0.006). The results for the confirmatory secondary outcomes did not differ significantly between the two groups. The incidence of serious adverse events was 47.9% in the oral semaglutide group and 50.3% in the placebo group; the incidence of gastrointestinal disorders was 5.0% and 4.4%, respectively.

CONCLUSIONS
Among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, the use of oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, without an increase in the incidence of serious adverse events. (Funded by Novo Nordisk; SOUL ClinicalTrials.gov number, NCT03914326.)

Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes
Stephen J Nicholls, Imre Pavo, Deepak L Bhatt, et al
Background: Tirzepatide, a dual incretin agonist of the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors, has favorable effects on glycemic control and body weight. The effects on cardiovascular outcomes are uncertain.
Methods: We conducted an active-comparator-controlled, double-blind, noninferiority trial in which patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomly assigned in a 1:1 ratio to receive a weekly subcutaneous injection of tirzepatide (up to 15 mg) or dulaglutide (1.5 mg), an agent that has been shown to reduce the incidence of cardiovascular events. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke and was tested for noninferiority of tirzepatide to dulaglutide with a margin of 1.05 for the upper limit of the 95.3% confidence interval for the hazard ratio. An upper limit of less than 1.00 was considered to indicate superiority of tirzepatide to dulaglutide.
Results: A total of 13,299 patients underwent randomization; 134 were subsequently excluded because they did not meet inclusion criteria. The modified intention-to-treat population thus included 6586 patients in the tirzepatide group and 6579 in the dulaglutide group. The mean (±SD) age of the patients was 64.1±8.8 years, 29.0% were women, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 32.6±5.5, the mean glycated hemoglobin level was 8.4±0.9%, and the mean duration of diabetes was 14.7±8.8 years. A primary end-point event occurred in 801 patients (12.2%) in the tirzepatide group and 862 (13.1%) in the dulaglutide group (hazard ratio, 0.92; 95.3% confidence interval, 0.83 to 1.01; P = 0.003 for noninferiority; P = 0.09 for superiority). The incidence of adverse events appeared to be similar in the two groups, although more gastrointestinal adverse events were observed in the tirzepatide group.
Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke. (Funded by Eli Lilly; SURPASS-CVOT ClinicalTrials.gov number, NCT04255433.).

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity
Milton Packer, Michael R Zile, Christopher M Kramer, et al
Background: Obesity increases the risk of heart failure with preserved ejection fraction. Tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, causes considerable weight loss, but data are lacking with respect to its effects on cardiovascular outcomes.
Methods: In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better quality of life).
Results: A total of 364 patients were assigned to the tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P = 0.026). Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively (hazard ratio, 1.58; 95% CI, 0.52 to 4.83). At 52 weeks, the mean (±SD)

change in the KCCQ-CSS was 19.5±1.2 in the tirzepatide group as compared with 12.7±1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.
Conclusions: Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity. (Funded by Eli Lilly; SUMMIT ClinicalTrials.gov number, NCT04847557.).

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes
Vlado Perkovic, Katherine R Tuttle, Peter Rossing, et al
Background: Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.
Methods: We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.
Results: Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P = 0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P = 0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P = 0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).
Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease. (Funded by Novo Nordisk; FLOW ClinicalTrials.gov number, NCT03819153.).

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 15, 2026

Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	1231
2	exenatide.mp. or Exenatide/	4378
3	liraglutide.mp. or Liraglutide/	5624
4	semaglutide.mp.	4681
5	Tirzepatide/ or tirzepatide.mp.	2009
6	dapagliflozin.mp.	4397
7	empagliflozin.mp.	4397
8	canagliflozin.mp. or Canagliflozin/	2319
9	ertugliflozin.mp.	377
10	sotagliflozin.mp.	303
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	22669
12	limit 11 to (english language and humans and yr="2024 -Current")	3943
13	limit 12 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	557
14	saxagliptin.mp.	966
15	alogliptin.mp.	677
16	linagliptin.mp. or Linagliptin/	1265
17	sitagliptin.mp. or Sitagliptin Phosphate/	3561
18	glimepiride.mp.	1847
19	glipizide.mp. or Glipizide/	1328
20	glyburide.mp. or Glyburide/	7328
21	Chlorpropamide/ or chlorpropamide.mp.	2112
22	pioglitazone.mp. or Pioglitazone/	7339
23	Metformin/ or metformin.mp.	37026
24	Acarbose/ or acarbose.mp.	4810
25	miglitol.mp.	426
26	Nateglinide/ or nateglinide.mp.	621
27	pramlintide.mp.	492
28	repaglinide.mp.	1003
29	teplizumab.mp.	244
30	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	63000
31	limit 30 to (english language and humans)	34586
32	limit 31 to yr="2018 -Current"	14890
33	limit 32 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	1601

Appendix 5: Key Inclusion Criteria

Population	Individuals with T2D, overweight and obesity, CKD, CVD, PCOS, SLE, MASH, OSA
Intervention	Antidiabetic therapies
Comparator	Active comparators or placebo
Outcomes	HbA1c, mortality, CV mortality, HF, MI, worsening renal function, BMI, weight loss, fertility, liver function (e.g., MASH resolution, fibrosis regression)
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred DPP-4 Inhibitors. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code

Approval Criteria		
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin, or have contraindications to metformin? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *8/20 (KS), 7/18; 9/17; 9/16; 9/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1/20; 10/13/16; 10/15; 1/15; 9/14; 1/14; 2/13*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. For requests for non-alcoholic or metabolic dysfunction-associated steatohepatitis (NASH/MASH), cardiovascular risk reduction, or obstructive sleep apnea, see weight management PA criteria.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

Initiating Metformin

5.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
6.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
7.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *8/26 (KS),8/24, 10/22 (KS), 8/20, 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1//24; 1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred SGLT-2 inhibitors require a PA. Preferred products do not require PA.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications of SGLT2 Inhibitors*

Indication	Bexagliflozin	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Sotagliflozin
Adults with Type 2 Diabetes Mellitus						
Glucose lowering	X	X	X	X	X	
Heart failure		X	X	X		X
Kidney disease		X	X	X		X
Children with Type 2 Diabetes Mellitus						
Patients 10 years and older		X	X	X		
Adults without Diabetes Mellitus						
Heart failure			X	X		X
Kidney disease			X	X		
* FDA indications are current as of June 2026 ~~November 2024~~						

Approval Criteria	
1. What is the diagnosis being treated?	Record ICD10 code

Approval Criteria		
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have type 2 diabetes?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have heart failure and is requesting an SGLT-2 inhibitor with demonstrated cardiovascular benefit (see Table 1 above)?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Does the patient have chronic kidney disease and is requesting an SGLT-2 inhibitor with demonstrated renal and cardiovascular benefits (see Table 1 above)?	**Yes:** Approve for up to 12 months	**No: No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *8/26 (KS), 2/25 (KS), 10/23 (KS), 10/22 (KS), 8/21 (KS), 8/20 (KS), 6/20, 7/18, 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *11/1/23; 1/1/23; 9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Glaucoma Drugs

Date of Review: August 2026

Literature Search: 01/01/2023-05/01/2026
Date of Last Review: April 2023

Current Status of PDL Class:

See **Appendix 1**.

Plain Language Summary:

- Glaucoma is an eye disease that damages the optic nerve, often due to high eye pressure, and can lead to permanent vision loss or blindness.
- Glaucoma treatment lowers eye pressure most commonly with eye drops to prevent further damage.
- The Oregon Health Plan (OHP) has numerous treatments for glaucoma available on the Preferred Drug List (PDL). No meaningful differences in effectiveness have been identified with the eye drops used to treat glaucoma.

Conclusions:

- No new high-quality systematic reviews have been published since the last review of this drug class. Two high-quality guidelines have been published. Both guidelines support current OHP fee-for-service (FFS) policies for preferred ophthalmic medications.
- The FDA has issued safety warnings for several ophthalmic medications. These warnings are summarized in **Table 1**.

Recommendations:

- No changes to the PDL are recommended based on review of recent evidence.
- Review drugs costs in executive session.

Summary of Prior Reviews and Current Policy

- The glaucoma drug class was last reviewed by the Pharmacy and Therapeutics Committee at the April 2023 meeting. After reviewing evidence for a new prostaglandin analog, omidenepag, the Committee agreed to maintain the medication product as non-preferred on the PDL. No additional PDL changes were recommended based on a review of the evidence.
- No evidence of meaningful differences in efficacy or effectiveness was identified with the ophthalmic products used to treat glaucoma. Fixed-combination products have not shown to provide substantial clinical benefit over the individual drug products.
- The OHP provides broad coverage for glaucoma treatments for each class of therapies: miotics, alpha- adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs (**Appendix 1**). No clinical prior authorization criteria are implemented for these drugs.
- About 1,700 OHP members have a glaucoma diagnosis, and these products are commonly utilized in OHP FFS program.

Author: Deanna Moretz, PharmD, BCPS

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized, comparative, controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included studies (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcomes studied (e.g., non-clinical).[1-4]

No high-quality systematic reviews were identified.

New Guidelines:

European Glaucoma Society

Guidelines from the European Glaucoma Society (EGS) were updated in 2025. Two updated guidelines reinforce the current OHP PDL status for glaucoma medications. The EGS recommend:

- Initiate monotherapy to treat high intraocular pressure (IOP). Laser trabeculoplasty is also a recommended option as first-line treatment. Patients with high IOPs (e.g., high 20 mms Hg or above) or severe disease may need a combination of drugs, laser trabeculoplasty or surgery (trabeculectomy). (Strength of Recommendation: Strong; Level of Evidence: High).[5]
- Prostaglandin analogs are the most effective medications and are usually recommended as a first-line treatment option for open-angle glaucoma. (Strength of Recommendation: Strong; Level of Evidence: High).[5]

National Institute for Health and Care Excellence

NICE published guidance for latanoprost-netarsudil for previously treated primary open angle glaucoma or ocular hypertension in 2024. NICE recommends:

- Latanoprost–netarsudil is an option for reducing IOP in adults with primary open-angle glaucoma or ocular hypertension when a prostaglandin analogue alone did not sufficiently reduced IOP, and if:
    - A fixed-dose combination treatment has not sufficiently reduced IOP; OR
    - A fixed-dose combination treatment containing a beta-blocker is clinically inappropriate.[6]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts.[7]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tafluprost	ZIOPTAN	2/2026	Warnings and Precautions	**Contact Lens Use** Contact lenses should be removed prior to the administration of ZIOPTAN and may be reinserted 15 minutes after administration.
Brimonidine	ALPHAGAN ALPHAGAN P COMBIGAN	9/2025	Warnings and Precautions	**Contamination of Topical Ophthalmic Products After Use** Do not touch the tip of the dispensing container to the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.
Netarsudil	RHOPRESSA	9/2024	Warnings and Precautions	**Epithelial Corneal Edema** Epithelial corneal edema, described as honeycomb or bullous, has been reported in some patients with pre- existing corneal stromal edema or following ocular procedures that could affect corneal endothelial function. Epithelial corneal edema typically resolves upon discontinuation of RHOPRESSA. Advise patients to notify their physician if they experience eye pain or decreased vision while using RHOPRESSA.
Latanoprost/Netarsudil	ROCKLATAN	1/2025	Warnings and Precautions	**Epithelial Corneal Edema** ROCKLATAN contains netarsudil which has been associated with epithelial corneal edema, described as honeycomb or bullous, and has been reported in some patients with pre-existing corneal stromal edema or following ocular procedures that could affect corneal endothelial function. Epithelial corneal edema typically resolves upon discontinuation of ROCKLATAN. Advise patients to notify their physician if they experience eye pain or decreased vision while using ROCKLATAN.

References:

1. Zhang D, Ren C, Wang X, et al. Treatment of glaucoma with drug-loaded contact lenses: A systematic review and meta-analysis. *Eur J Pharmacol*. 995:177425.
2. Shaikh O, Kuziez L, Saeedi OJ, Abbasian J, Elhusseiny AM. Topical Netarsudil in Childhood Glaucoma: A Systematic Review. *Curr Eye Res*. 50(5):461-466.
3. Martinez-de-la-Casa J, Corsino P, Grzybowski A, Tatham A, Vignesh SO, Hassan T. Latanoprost/timolol fixed-dose combination: two decades of efficacy and safety in glaucoma management. *BMC ophthalmol*. 26(1):14.
4. Lin JB, Harris JM, Baldwin G, Goss D, Margeta MA. Ocular effects of Rho kinase (ROCK) inhibition: a systematic review. *Eye*. 38(18):3418-3428.
5. Pazos M, Traverso CE, Viswanathan A. European Glaucoma Society - Terminology and guidelines for glaucoma, 6th Edition. *Br J Ophthalmol*. Sep 8 2025;109(Suppl 1):1-212. doi:10.1136/bjophthalmol-2025-egsguidelines
6. National Institute for Health and Care Excellence. Latanoprost-netarsudil for previously treated primary open angle glaucoma or ocular hypertension. October 2024. https://www.nice.org.uk/guidance/ta1009 Accessed May 6, 2026.
7. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed May 6, 2026.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
betaxolol HCl	BETAXOLOL HCL	DROPS	Y
brinzolamide	AZOPT	DROPS SUSP	Y
brinzolamide	BRINZOLAMIDE	DROPS SUSP	Y
carteolol HCl	CARTEOLOL HCL	DROPS	Y
dorzolamide HCl/timolol maleat	COSOPT	DROPS	Y
dorzolamide HCl/timolol maleat	DORZOLAMIDE-TIMOLOL	DROPS	Y
dorzolamide/timolol/PF	COSOPT PF	DROPERETTE	Y
dorzolamide/timolol/PF	DORZOLAMIDE-TIMOLOL	DROPERETTE	Y
latanoprost	LATANOPROST	DROPS	Y
latanoprost	XALATAN	DROPS	Y
pilocarpine HCl	PILOCARPINE HCL	DROPS	Y
timolol maleate	TIMOLOL MALEATE	DROPS	Y
timolol maleate	TIMOPTIC	DROPS	Y
travoprost	TRAVATAN Z	DROPS	Y
travoprost	TRAVOPROST	DROPS	Y
acetylcholine chloride	MIOCHOL-E	KIT	N
apraclonidine HCl	IOPIDINE	DROPERETTE	N
apraclonidine HCl	APRACLONIDINE HCL	DROPS	N
betaxolol HCl	BETOPTIC S	DROPS SUSP	N
bimatoprost	BIMATOPROST	DROPS	N
bimatoprost	LUMIGAN	DROPS	N
brimonidine tartrate	ALPHAGAN P	DROPS	N
brimonidine tartrate	BRIMONIDINE TARTRATE	DROPS	N
brimonidine tartrate/timolol	BRIMONIDINE TARTRATE-TIMOLOL	DROPS	N
brimonidine tartrate/timolol	COMBIGAN	DROPS	N
brinzolamide/brimonidine tart	SIMBRINZA	DROPS SUSP	N
carbachol	MIOSTAT	VIAL	N
dorzolamide HCl	DORZOLAMIDE HCL	DROPS	N
dorzolamide HCl	TRUSOPT	DROPS	N
latanoprost/PF	IYUZEH	DROPERETTE	N
latanoprostene bunod	VYZULTA	DROPS	N
levobunolol HCl	LEVOBUNOLOL HCL	DROPS	N
netarsudil mesylat/latanoprost	ROCKLATAN	DROPS	N
netarsudil mesylate	RHOPRESSA	DROPS	N
tafluprost/PF	TAFLUPROST	DROPERETTE	N
tafluprost/PF	ZIOPTAN	DROPERETTE	N
timolol	BETIMOL	DROPS	N
timolol	TIMOLOL	DROPS	N

timolol maleate	ISTALOL	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	DROP DAILY	N
timolol maleate	TIMOLOL MALEATE	SOL-GEL	N
timolol maleate	TIMOPTIC-XE	SOL-GEL	N
timolol maleate/PF	TIMOLOL MALEATE	DROPERETTE	N
timolol maleate/PF	TIMOPTIC OCUDOSE	DROPERETTE	N
bimatoprost	DURYSTA	IMPLANT	
travoprost	IDOSE TR	IMPLANT	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to May 01, 2026>

1	Betaxolol/	687
2	Carbonic Anhydrase Inhibitors/ or brinzolamide.mp.	6270
3	Carteolol/	348
4	dorzolamide.mp.	1307
5	Latanoprost/	1671
6	Pilocarpine/	7593
7	Timolol/	3994
8	Travoprost/	503
9	Acetylcholine/	51228
10	Adrenergic alpha-2 Receptor Agonists/ or apraclonidine.mp. or Adrenergic alpha-Agonists/	13509
11	Bimatoprost/	634
12	Brimonidine Tartrate/	1647
13	Carbachol/	13936
14	Levobunolol/	246
15	netarsudil.mp. or Protein Kinase Inhibitors/	68083
16	tafluprost.mp. or Prostaglandins F/	7892
17	Timolol/ or Brimonidine Tartrate, Timolol Maleate Drug Combination/	3994
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	171272
19	Glaucoma/	44749
20	18 and 19	2976
21	limit 20 to (english language and humans and yr="2023 -Current")	120

Appendix 3: Key Inclusion Criteria

Population	People with Glaucoma
Intervention	Ophthalmic Preparations in Appendix 1
Comparator	Other ophthalmic preparations in Appendix 1
Outcomes	Reduction in intraocular pressure by 25-30%
Setting	Outpatient

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Antianginals

Date of Review: August 2026

Literature Search: 01/01/2021 – 05/12/2026
Date of Last Review: May 2017

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- New studies were searched to find new information for medicines used in the treatment of chest pain commonly known as angina.
- For people with continuing angina symptoms, treatment focuses on easing chest pain and lowering the risk of heart attack.
- There are many different medicines that can be used to treat angina:
    - Nitrates such as nitroglycerin help relax blood vessels and may be used for quick relief of chest pain episodes.
    - Longer-acting nitrates like isosorbide mononitrate or other medicines called calcium channel blockers can be added if chest pain symptoms continue.
    - Beta-blockers are medicines used to slow the heart and reduce its work.
    - Ranolazine is a medicine that is sometimes added when other medicines do not work well enough or if a person cannot tolerate other medicines.
- Current clinical practice guidelines do not strongly favor one type of drug (e.g. nitrates, calcium channel blockers, beta blockers, etc.) for all patients with chronic stable angina.
- Based on new studies found, no new changes to the Oregon Health Plan (OHP) preferred drug list are recommended.

Conclusions:

- Clinical practice guidelines do not recommend one drug in the antianginal drug class over another due to insufficient comparative evidence. Guidelines for chronic coronary disease from the 2024 European Society of Cardiology (ESC) and AHA/ACC/ACCP/ASPC/NLA/PCNA recommend individualized agent selection based on comorbidity and tolerability.[1,2]
- Ranolazine (ASPRUZYO) is a new extended-release drug formulation supplied in oral granule sachets indicated for the treatment of adult patients with chronic stable angina pectoris.[3]
- Three new comparative RCTs were identified. One trial compared long acting cilostazol versus isosorbide mononitrate for patients with vasospastic angina;[4] the second trial compared ranolazine versus allopurinol for eligible symptomatic patients with a history of angioplasty;[5] and the third trial compared combination therapy with nicardipine and isosorbide dinitrate to prevent spasm in transradial percutaneous coronary intervention.[6]
- Two new FDA safety updates pertaining to antianginal agents were identified.[7]
- No new evidence was identified that would strengthen evidence of these drugs in populations based on demographic characteristics such as race, ethnicity, age or socioeconomic status.

Author: Dave Engen, PharmD

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

Angina management includes a wide variety of classes depending upon the underlying cause. Current first-line treatments for angina include beta-blockers (e.g. , calcium channel blockers, or long-acting nitrates). If a patient is still symptomatic after treatment with one first-line agent, a second first-line agent from a different therapeutic class may be added. Ranolazine should be reserved for add-on therapy when a patient is symptomatic despite treatment with a beta blocker, CCB, or a long-acting nitrate. Short acting nitroglycerin should remain available for the immediate relief of angina in patients with stable ischemic heart disease.[8]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Angina management includes a wide variety of testing, procedures, and drugs from different classes depending upon the underlying cause. This review will focus on antianginal drug therapy with nitrates. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

No new high-quality systematic reviews were identified. Three systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcomes studied (e.g., non-clinical).[9-11]

New Guidelines:

2024 European Society of Cardiology (ESC) Guidelines for the Management of Chronic Coronary Syndromes:[1]

Angina Management: Key ESC Guideline Recommendations and Evidence Summary:

Category	Drug(s)	When to Use / Key Points	Class	Level
Core principle	All antianginal therapy	Tailor to HR, BP, comorbidities, tolerability, and angina mechanism	I	C
First line therapy	Beta blockers (metoprolol, atenolol, carvedilol)	Main initial therapy for symptom control	I	B
	Calcium channel blockers (amlodipine, diltiazem, verapamil)	Alternative or combined with BB depending on HR/BP	I	B
Rapid symptom relief	**Short acting nitrates (sublingual nitroglycerin)**	**Immediate relief of acute angina episodes**	**I**	**B**
Combination therapy	BB + DHP CCB (e.g., metoprolol + amlodipine)	If symptoms persist on single agent	IIa	B
Second line / add on	**Long-acting nitrates (isosorbide mono/dinitrate)**	**Add if symptoms persist on BB/CCB or use in selected patients**	**IIa**	**B**
	Ranolazine	**Add-on or alternative, especially if low HR/BP limits other drugs**	**IIa**	**B**
Nitrate strategy	**Long-acting nitrates**	**Use daily nitrate free interval to prevent tolerance**	**IIa**	**B**
Heart-rate–specific therapy	Ivabradine	For LVEF <40% with persistent symptoms despite therapy	IIa	B
Avoid misuse	Ivabradine	Not recommended if LVEF >40% without HF	III	B
Drug interaction caution	Ivabradine + verapamil/diltiazem	Avoid combination (↑ bradycardia risk)	III	B
Contraindication	**Nitrates + PDE 5 inhibitors (e.g., sildenafil)**	**Avoid due to severe hypotension risk**	**III**	**B**
	Nitrates in hypertrophic cardiomyopathy	**Avoid due to potential worsening obstruction**	**III**	**B**

Key: BB=beta blockers; BP=blood pressure; CCB=calcium channel blockers; DHP=dihydropyridine; LVEF=left ventricular ejection fraction; HF=heart failure

Class of recommendation (strength of recommendation)	**Level of evidence** (quality of evidence)
Class I*:* Strong evidence (beneficial) Class II: Weaker evidence or less agreement (reasonable) Class IIa: Weight of evidence favors benefit Class IIb: Benefit less well established Class III: Not useful or potentially harmful	Level A: High-quality evidence from multiple randomized trials or meta-analyses Level B: Moderate evidence from a single RCT or large non-randomized studies

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Disease:[2]

Pharmacologic Therapy for Angina: Evidence-Based Recommendations

Pharmacologic management of chronic angina is directed toward relief of ischemic symptoms and improvement in functional status and quality of life. Recommendations are graded according to strength (Class of Recommendation) and quality (Level of Evidence). Therapy should be implemented in a stepwise, individualized manner, with escalation based on symptom burden and treatment tolerance.

First-Line Antianginal Therapy	**Second Line and Adjunctive Therapy**
Beta-blockers, CCBs, or long-acting nitrates	**Ranolazine:**
Strength: Class I; Quality: Level B-R	Strength: Class I; Quality: Level B-R
• Recommended as initial antianginal therapy to reduce symptom frequency and improve exercise tolerance. • Selection should be individualized based on comorbid conditions (e.g., beta-blockers in prior myocardial infarction; CCBs in vasospastic angina).	• Recommended for relief of angina symptoms, particularly in patients: -With persistent symptoms despite first-line therapy; or -Who are unable to tolerate further titration of heart rate– or blood pressure–lowering agents.
Short-acting nitrates (e.g., sublingual nitroglycerin):	
Strength: Class I; Quality: Level B-NR	
• Indicated for rapid relief of acute anginal episodes. • Should be prescribed to all patients with angina for on-demand symptom control.	• Provides symptomatic benefit through metabolic modulation (late sodium current inhibition) without significant effects on heart rate or blood pressure.

Escalation of Therapy for Persistent Symptoms:

Combination antianginal therapy (agents from different classes)
Strength: Class I; Quality: Level B-R
-Recommended in patients with persistent angina despite monotherapy.
-Drug selection should consider hemodynamic effects and avoid contraindicated combinations (e.g., beta-blockers with non-dihydropyridine CCBs in patients with bradycardia or conduction disease).

Therapies Not Recommended:

Ivabradine (in patients with normal left ventricular systolic function):
Strength: Class III (Harm); Quality: Level B R
-Not recommended due to lack of benefit and increased risk of adverse outcomes.

Interpretation of Recommendation Grading

Strength of Recommendation (Class)	Quality of Evidence (Level)
Class I: Strong recommendation; benefit greatly outweighs risk; intervention should be performed	Level A: High-quality evidence from multiple randomized trials/meta-analyses
Class IIa: Moderate recommendation; benefit > risk; intervention is reasonable	Level B-R: Moderate-quality evidence from randomized trials
Class IIb: Weak recommendation; benefit ≥ risk; intervention may be considered	Level B-NR: Moderate-quality evidence from nonrandomized studies
Class III: No benefit or harm; intervention should not be performed	Level C: Limited evidence/expert opinion

New Formulations:

ASPRUZYO (ranolazine) is a new drug formulation indicated for the treatment of adult patients with chronic stable angina pectoris.[3] ASPRUZYO's unique attribute is its extended-release oral granule formulation, enabling controlled ranolazine delivery via aqueous dispersion, soft-food admixture, or enteral tube administration.[3] Ranolazine selectively inhibits the late inward sodium current (I_{aL}), reducing intracellular Na^+ and secondary Ca^{2+} overload to improve diastolic relaxation and limit ischemia.[3] Key safety considerations include dose-dependent QT-interval prolongation and significant CYP3A-mediated drug-interaction potential, with avoidance recommended in moderate–severe hepatic impairment.[3]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts.[7]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
isosorbide dinitrate/hydralazine	BIDIL	3/2019	Contraindications	-Do not use BiDil™ in patients who are taking PDE-5 inhibitors, such as avanafil, sildenafil, tadalafil, or vardenafil. Concomitant use can cause severe hypotension, syncope, or myocardial ischemia. -Do not use BiDil™ in patients who are taking the soluble guanylate cyclase (sGC) stimulator riociguat. Concomitant use can cause hypotension.
nitroglycerin	NITROMIST	6/2022	Contraindications Warnings	NitroMist™ is contraindicated in patients with acute circulatory failure or shock. Patients who may be volume-depleted or who are already hypotensive are at increased risk of symptomatic hypotension.

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Author: Dave Engen, PharmD

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11. Yu X-h, Yu X-w, Xu Z-m, Li H-x. Yangxin decoction for the treatment of angina pectoris of coronary heart disease: A systematic review of randomized controlled trial. *Medicine.* 2022;101(35):e30394.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
isosorbide dinitrate	ISOSORBIDE DINITRATE	TABLET	Y
isosorbide mononitrate	ISOSORBIDE MONONITRATE	TABLET	Y
nitroglycerin	NITRO-DUR	PATCH TD24	Y
nitroglycerin	NITROGLYCERIN PATCH	PATCH TD24	Y
nitroglycerin	NITROGLYCERIN	TAB SUBL	Y
nitroglycerin	NITROSTAT	TAB SUBL	Y
isosorbide dinit/hydralazine	BIDIL	TABLET	N
isosorbide dinit/hydralazine	ISOSORBIDE DINIT-HYDRALAZINE	TABLET	N
isosorbide dinitrate	ISOSORBIDE DINITRATE	TAB SUBL	N
isosorbide mononitrate	ISOSORBIDE MONONITRATE	TAB ER 24H	N
isosorbide mononitrate	ISOSORBIDE MONONITRATE ER	TAB ER 24H	N
nitroglycerin	NITRO-BID	OINT. (G)	N
nitroglycerin	NITROGLYCERIN	OINT. (G)	N
nitroglycerin	NITROGLYCERIN	SPRAY	N
nitroglycerin	NITROLINGUAL	SPRAY	N
ranolazine	RANOLAZINE ER	TAB ER 12H	N

Appendix 2: New Comparative Clinical Trials

A total of 58 citations were manually reviewed from the initial literature search. After further review, 56 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). Abstracts of the remaining trials are summarized below.

Long-acting cilostazol versus isosorbide mononitrate for patients with vasospastic angina: a randomized controlled trial.[4]
Background: Cilostazol has a vasodilatory function that may be beneficial for patients with vasospastic angina (VSA). We conducted a randomized, open-label, controlled trial to compare the efficacy and safety of long-acting cilostazol and isosorbide mononitrate (ISMN) for VSA.
Methods: The study included patients with confirmed VSA between September 2019 and May 2021. Participants were randomly assigned to receive long-acting cilostazol (test group, 200 mg once daily) or conventional ISMN therapy (control group, 20 mg twice daily) for 4 weeks. The clinical efficacy and safety were evaluated using weekly questionnaires.
Results: Forty patients were enrolled in the study (long-acting cilostazol, n = 20; ISMN, n = 20). Baseline characteristics were balanced between the two groups. Long acting cilostazol showed better angina symptom control within the first week compared to ISMN [reduction of pain intensity score, 6.0 (4.0-8.0) vs. 4.0 (1.0-5.0), P = 0.005; frequency of angina symptom, 0 (0-2.0) vs. 2.0 (0-3.0), P = 0.027, respectively]. The rate of neurological adverse reactions was lower in the cilostazol group than in the ISMN group (headache or dizziness, 40 vs. 85%, P = 0.009; headache, 30 vs. 70%, P = 0.027).
Conclusion: Long-acting cilostazol provided comparable control of angina and fewer adverse neurologic reactions within 4 weeks compared to ISMN. Long-acting cilostazol provides more intensive control of angina within 1 week, suggesting that it may be an initial choice for the treatment of VSA.

Ranolazine Versus Allopurinol for Eligible Symptomatic Patients With a History of Angioplasty: Comparative Efficacy Study[5]

Background: Recurrent angina, which is defined as a return of chest pain or chest discomfort, occurs in many patients undergoing coronary interventions.

Objective: This study aims to compare the antianginal efficacy of ranolazine versus allopurinol for eligible symptomatic patients with a history of angioplasty.

Methods: A total of 62 eligible symptomatic patients with a history of angioplasty were randomly allocated into two groups. For group A, 300 mg of allopurinol was administered twice daily, while for group B, 1000 mg of ranolazine daily was prescribed for a duration of 4 weeks. An initial screening visit was done for all participants where patients' medical history was recorded and a physical examination was given; electrocardiography, blood pressure, and heart rate measurements were done as well. The patients were also given a blood and exercise test. At the end of the medication period, participants were revisited, and the tests were done again. All the required data were collected via a researcher-made form, and data analysis was conducted using SPSS. The study was approved by a formal ethics committee.

Results: The mean age of participants in the two groups (A and B) was 57.36 (SD 8.36) and 60.27 (SD 9.17) years, respectively. Among the 62 patients, 34 (59%) were men, while 28 (41%) were women. Creatinine, fasting blood sugar, C-reactive protein, N-terminal prohormone of brain natriuretic protein, uric acid, white blood cell, and hemoglobin levels of participants were not significantly different between groups (P>.05). Both allopurinol and ranolazine increased the total exercise time and decreased the ST depression of the patients. Additionally, they both improved the chest pain severity and Duke Treadmill Score of patients. At the same time, ranolazine had a statistically greater effect on ST depression reduction (mean 2.64, SD 0.74 vs mean 1.57, SD 0.49), while allopurinol showed better efficacy in reducing chest pain severity (mean 1.86, SD 0.37 vs mean 0.59, SD 0.21) and the Duke Treadmill Score (mean –14.77, SD 3.65 vs mean –6.88, SD 1.93).

Conclusions: Based on the results, the antianginal efficacy of allopurinol and ranolazine was approved but with different effects on ST depression, chest pain severity, and the Duke Treadmill Score. Therefore, the precise differences in their effects need to be explored further.

Combination Therapy With Nicardipine and Isosorbide Dinitrate to Prevent Spasm in Transradial Percutaneous Coronary Intervention (from the NISTRA Multicenter Double-Blind Randomized Controlled Trial)[6]

Background: Verapamil and nitroglycerin are widely used to prevent radial artery spasm (RAS) during percutaneous cardiovascular procedures. However, these agents are not typically available in most African countries and consequently, isosorbide dinitrate is often the only spasmolytic treatment.

Objective: Our aim was to compare the efficacy of isosorbide dinitrate alone versus isosorbide dinitrate used together with nicardipine to prevent RAS during transradial coronary procedures.

Methods: This was a randomized controlled double-blind multicenter trial. Patients (n = 1,523) were randomized to receive either a sole therapy of isosorbide dinitrate (n = 760) or the combination of isosorbide dinitrate and nicardipine (n = 763). Our primary end point was the occurrence of RAS; defined as considerable perceived hindrance of catheter advancement. Our secondary end points were severe RAS; defined as (1) severe arm pain, (2) the need for either morphine or midazolam treatment, and (3) necessity for crossover to the contralateral radial or femoral artery.

Results: RAS incidence was reduced with the combination therapy versus isosorbide dinitrate alone (15% vs 25%, p <0.001), with a number needed to treat of 10 patients. There was also a significant reduction in the incidence of the secondary end points with combination therapy (3.6% vs 8.2%, p <0.001), with a number needed to treat of 22 patients. This result was driven by reductions in both femoral crossover (0.5% vs 2.4%, p = 0.003) and the use of morphine or midazolam injections (1.6% vs 3.5%, p = 0.02) with combination therapy.

Conclusion: In conclusion, we demonstrated the superiority of the combination therapy of isosorbide dinitrate and nicardipine over isosorbide dinitrate alone in reducing the incidence of RAS.

Appendix 1: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to May 12, 2026

1 exp Isosorbide Dinitrate/3598
2 isosorbide mononitrate.mp./458
3 exp Nitroglycerin/12892
4 isosorbide dinitrate hydralazine.mp./39
5 exp Ranolazine/827
6 antianginals.mp./52
7 exp Angina Pectoris/ or angina.mp./78807
8 1 or 2 or 3 or 4 or 5 or 6 /16845
9 7 and 8 /3695
10 limit 9 to (english language and humans and yr="2021 -Current")/58

Appendix 2: Key Inclusion Criteria

Population	People with angina
Intervention	Drugs from antianginal PDL class (nitrates, ranolazine)
Comparator	Placebo or active treatment
Outcomes	Mortality, cardiovascular morbidity (angina pectoris, acute myocardial infarction, etc.), adverse events from treatment
Timing	Not applicable
Setting	Outpatient

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Ophthalmic, Anti-inflammatory Drugs

Date of Review: August 2026

Literature Search: 1/1/1946 – 5/6/2026
Date of Last Review: May 2015

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This document scanned studies published since 2015 that looked at the safety and effectiveness of eye drops used to treat uveitis or conjunctivitis. Symptoms of these eye conditions include sensitivity to light, redness, pain, and swelling or irritation (inflammation) of the eye.
- Uveitis can be caused by an infection or trauma to the eye. Some types of uveitis are caused by a chronic disease such as rheumatoid arthritis, psoriatic arthritis, or inflammatory bowel disease. Treatment of uveitis involves using steroid eye drops such as prednisolone or dexamethasone to relieve the pain and swelling.
- Conjunctivitis is most commonly caused by a bacterial or viral infection but can also be caused by allergens (pollen, dust) or chemical irritants. A nonsteroidal anti-inflammatory drug (NSAID) eye drop such as ketorolac may be used to treat conjunctivitis caused by allergens.
- After cataract surgery, a steroid or NSAID eye drop (ketorolac, nepafenac, bromfenac) is often prescribed to manage post-operative inflammation and pain. These eye drops should be used for up to 2 weeks after surgery. If used for longer than that, corticosteroid eye drops can increase the intraocular pressure in the eye, which can impair vision.
- No differences in the safety or effectiveness have been found between the different steroid eye drops or NSAID eye drops when used to treat these conditions.
- Oregon Health Plan (OHP) provides coverage for steroid and NSAID eye drops on the Preferred Drug List.

Conclusions:

- Four new high-quality systematic reviews have been published evaluating the safety and efficacy ophthalmic corticosteroids and NSAID preparations after cataract surgery.[1-4] One new high-quality guideline was published which addressed the use of corticosteroid and NSAID ophthalmic drops in management of juvenile idiopathic arthritis associated-uveitis and idiopathic chronic anterior uveitis.[5]
- A 2024 systematic review assessed the efficacy and safety of standard (prednisolone acetate 1% or dexamethasone 0.1%) versus soft (fluorometholone 0.1% or loteprednol etabonate 0.5%) ophthalmic corticosteroid drops for postoperative management of cataract surgery-induced inflammation.[1] The review found moderate-quality evidence that both groups of ophthalmic steroids produce comparable efficacy on anterior chamber inflammation and intraocular pressure (IOP).[1]
- A 2024 systematic review evaluated the safety and efficacy of NSAIDs and corticosteroids for postoperative management of cataract surgery.[2] Pertinent endpoints included visual acuity, macular thickness, and macular edema.[2] Nineteen studies provided moderate-quality evidence that NSAIDs or a combination of NSAIDs and corticosteroids are more efficacious and safer than corticosteroids alone for post-operative management of cataract surgery.[2]

Author: Deanna Moretz, PharmD, BCPS

- A 2018 systematic review evaluated the comparative safety and efficacy of prednisolone acetate and difluprednate to control inflammation after cataract surgery.[3] No statistically significant difference in efficacy between the two agents was found at 1 month based on moderate-quality evidence.[3] Low-to-moderate quality evidence showed that both drugs are safe for controlling inflammation after cataract surgery.[3]
- A 2016 Cochrane review assessed whether prophylactic ophthalmic NSAIDs, either in addition to or instead of, ophthalmic corticosteroids reduce the incidence of macular edema and associated visual morbidity postoperatively.[4] Prophylactic ophthalmic NSAIDs may reduce the risk of developing macular edema after cataract surgery, but there is insufficient evidence prophylactic use improves visual acuity and quality of life.[4]
- The American College of Rheumatology updated recommendations for the treatment of juvenile idiopathic arthritis–associated uveitis and idiopathic chronic anterior uveitis in 2023. Two recommendations include guidance for the use of ophthalmic anti-inflammatory agents based on very-low quality evidence:
    - Ophthalmic corticosteroids like prednisolone acetate 1% or dexamethasone 0.1% are the first-line treatment for juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis, based on expert opinion and very low-quality of evidence.[5]
    - Ophthalmic and systemic NSAIDs have no demonstrable effect as monotherapy for juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis, based on descriptive studies providing very low-quality evidence.[5]
- Since 2015, FDA has approved 3 corticosteroid ophthalmic formulations for the treatment of post-operative inflammation and pain following ocular surgery:
    - 3/2024: BYQLOVI (clobetasol) 0.05% ophthalmic suspension;[6]
    - 2/2019: LOTEMAX SM (loteprednol) 0.38% ophthalmic gel;[7] and
    - 8/2018: INVELTY (loteprednol) 1% ophthalmic suspension.[8]
- A summary of FDA safety labeling updates for anti-inflammatory ophthalmic agents is presented in **Table 2**.

Recommendations:
- Maintain BYQLOVI (clobetasol) 0.05%, LOTEMAX SM (loteprednol) 0.38%, and INVELTY (loteprednol) 1% ophthalmic preparations as non-preferred on the Oregon Health Plan's fee-for-service Practitioner-Managed Prescription Drug Plan.
- Evaluate drug costs in executive session.

Summary of Prior Reviews and Current Policy
- The Pharmacy and Therapeutics Committee last reviewed the ophthalmic anti-inflammatory drugs at the May 2015 meeting.
- There is high quality evidence that there is no difference in efficacy or safety between ophthalmic corticosteroid agents or ophthalmic NSAIDs.
- The Committee agreed to make at least one medication from the corticosteroid and NSAID drug class preferred on the PDL (see **Appendix 1**).

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

The Efficacy and Safety of Standard versus Soft Topical Steroids after Cataract Surgery (2024)

A 2024 systematic review assessed the efficacy and safety of standard (prednisolone acetate 1% or dexamethasone 0.1%) versus soft (fluorometholone 0.1% or loteprednol etabonate 0.5%) topical steroidal drops in the postoperative management of cataract surgery-induced inflammation.[1]

A literature search was conducted reviewing all available published clinical studies up to May 8, 2023.[1] Seven eligible publications from 1997 through 2020 met inclusion criteria, describing treatment of 593 eyes in 593 patients who underwent uncomplicated cataract surgery.[1] Four studies (57%) used fluorometholone 0.1% as the soft steroid, and 4 studies used prednisolone acetate 1% as the standard steroid.[1] Treatment regimens were similar between the arms within each study, but varied between the different studies.[1] Only 3 studies (43%) had a low risk of bias.[1]

Except for a significantly lower grade of anterior chamber flare in the standard steroid group at day 7 (standardized mean difference, 0.26; 95% confidence interval [CI], 0.05 to 0.47; $I^2 = 0\%$), inflammatory activity measurements did not differ at days 1 and 28 after surgery.[1] Pooled analysis of IOP demonstrated a higher IOP at the 7-day visit in the standard steroid group, whereas IOP at other time points (Day 1 and 28) was comparable among the groups.[1] Qualitative analysis of ocular adverse events showed similarities among the groups.[1] These findings, based upon moderate-quality evidence, suggest that both groups of ophthalmic steroids produce comparable efficacy on anterior chamber inflammation and postoperative IOP.[1]

NSAIDs and Corticosteroids for the Postoperative Management of Age-Related Cataract Surgery (2024)

This systematic review evaluated the safety and efficacy of NSAIDs and corticosteroids in the postoperative management of cataract surgery for age-related cataracts in adults.[2] Pertinent endpoints included visual acuity, macular thickness, and macular edema.[2] A total of 19 studies were included, with 3473 patients (3638 eyes) treated following cataract surgery with NSAIDs (n = 1479), corticosteroids (n = 1307), or a combination of the two (n = 687).[2] All included studies were judged to be of moderate quality, with exposure and outcome adequately ascertained.[2] The lengths of follow-up were adequate to manifest a change in clinical outcomes.[2]

Combination treatment demonstrated favorable best-corrected visual acuity compared to corticosteroids 4 to 6 weeks postoperatively (mean difference [MD] = –0.01 logarithm of the minimum angle of resolution [logMAR], 95% CI: –0.02 to –0.01, $I^2 = 0\%$).[2] The pooled estimate of 1 day (MD = 0.01 logMAR, 95% CI = –0.04, 0.05, $I^2 = 0\%$), 7 days (MD = –0.01 logMAR, 95% CI = –0.04, 0.02, $I^2 = 4\%$), 14 days (MD = 0.02 logMAR, 95% CI = –0.01, 0.05, $I^2 = 0\%$), and 4 to 6 weeks (MD = –0.01 logMAR, 95% CI = –0.03, 0.00, $I^2 = 0\%$) postoperatively showed comparable visual acuity between corticosteroids and NSAIDs groups.[2] NSAIDs had more favorable flare values than corticosteroids on day 7 (MD = –9.17 photons/ms, 95% CI = –16.52 to –1.82, $I^2 = 94\%$), day 14 (MD = –5.23 photons/ms, 95% CI = –8.35 to –2.11, $I^2 = 94\%$), and 4 to 6 weeks (MD = –1.62 photons/ms, 95% CI = –3.03 to –0.20, $I^2 = 93\%$) postoperatively.[2] Furthermore, 4 to 8 weeks postoperatively, patients treated with NSAIDs showed lower central macular thickness (MD = –13.26 µm, 95% CI = –18.66 to –7.86, $I^2 = 81\%$) compared to those treated with corticosteroids.[2] NSAIDs and combination treatment were associated with a lower incidence of central macular edema (odds ratio [OR] = 0.16, 95% CI = 0.07 to 0.35, $I^2 = 61\%$; OR = 0.21, 95% CI = 0.10 to 0.45, $I^2 = 31\%$) than corticosteroids 4 to 8 weeks postoperatively.[2] The authors concluded that based upon moderate-quality evidence, NSAIDs and combination treatment could be more efficacious and safer alternatives to corticosteroids alone in the postoperative management of cataract surgery.[2]

Difluprednate versus Prednisolone Acetate after Cataract Surgery (2018)

For this 2018 systematic review, literature was searched through July 2019. Six RCTs met inclusion criteria with 883 patients: 441 received difluprednate and 442 received prednisolone acetate after cataract surgery.[3] The evidence quality was graded as moderate for corneal edema and intraocular pressure and low for anterior chamber clearance.[3]

After small incision cataract surgery, difluprednate was superior in clearing anterior chamber cells at 1 week (OR=2.5; p>0.00001) and at 2 weeks (OR=2.5; p=0.04), as well as clearing the anterior chamber flare at 2 weeks (OR=6.7; p=0.04).[3] After phacoemulsification, difluprednate was superior in terms of corneal clarity at 1 day (OR=2.6; p=0.02) and 1 week after surgery (OR=1.96; p=0.0007).[3] No statistically significant difference in efficacy was detected between both agents at 1 month.[3] Both agents were safe as evaluated by the ocular hypertension (OR=1.23; p=0.8).[3] With low-to-moderate certainty evidence, difluprednate and prednisolone acetate are safe agents for controlling the inflammation after cataract surgery.[3]

Prophylactic Non-Steroidal Anti-Inflammatory Drugs for the Prevention of Macular Edema After Cataract Surgery (2016)

A 2016 Cochrane review assessed whether prophylactic ophthalmic NSAIDs either in addition to or instead of, ophthalmic corticosteroids reduce the incidence of macular edema and associated visual morbidity postoperatively.[4] Literature was searched through September 2, 2016.[4]

Thirty-four studies met inclusion criteria.[4] Over 5000 people were randomized in these trials.[4] The majority of studies enrolled one eye per participant; a small subset (4 trials) enrolled a proportion of people with bilateral surgery.[4] Twenty-eight studies compared NSAIDs plus corticosteroids with corticosteroids alone, and 6 studies compared NSAIDs with corticosteroids.[4] A variety of NSAIDs were used, including ketorolac, diclofenac, nepafenac, indomethacin, bromfenac, flurbiprofen and pranopfen.[4] Follow-up ranged from one to 12 months.[4] None of the studies were judged to be at low risk of bias in all domains.[4] Six studies were funded by industry, seven studies were funded from non-industry sources, and the rest of the studies did not report the source of funding.[4]

There was low-certainty evidence that ophthalmic NSAIDs in combination with corticosteroid may lower risk of poor vision due to macular edema at 3 months after cataract surgery compared to corticosteroids alone (risk ratio (RR) 0.41, 95% CI 0.23 to 0.76; eyes = 1360; studies = 5; I^2 = 5%).[4] There was low-quality evidence of reduced risk of macular edema with NSAIDs alone at 3 months after surgery (RR 0.40, 95% CI 0.32 to 0.49; eyes = 3638; studies = 21).[4]

There was inconsistent evidence on central retinal thickness at 3 months (I^2 = 87%), as results ranged from -30.9 micron (µm) in favor of NSAIDs plus corticosteroids to +7.44 µm in favor of corticosteroids alone.[4] Data on best corrected visual acuity (BCVA) were inconsistent, but nine out of 10 trials reporting this outcome found between-group differences (NSAIDs plus steroids versus steroids alone) in visual acuity of less than 0.1 logMAR.[4]

None of the six studies comparing NSAIDs alone with corticosteroids reported on poor vision due to macular edema at 3 or 12 months.[4] There was low-certainty evidence that central retinal thickness was lower in the NSAIDs group at 3 months (MD -22.64 µm, 95% CI -38.86 to -6.43; eyes = 121; studies = 2) compared to corticosteroids.[4] Five studies reported on macular edema and showed a reduced risk with NSAIDs compared to corticosteroids, based on low-quality evidence (RR 0.27, 95% CI 0.18 to 0.41; eyes = 520).[4] Three studies reported BCVA at 3 months, but results were inconsistent, though all 3 studies found differences of less than 0.1 logMAR between NSAIDs and corticosteroids.[4]

The authors concluded that ophthalmic NSAIDs may reduce the risk of developing macular edema after cataract surgery, but the extent to which the reduction observed has an impact on the visual function and quality of life is uncertain.[4] The value of adding topical NSAIDs to steroids, or using them as an alternative to

topical steroids, with a view to reducing the risk of poor visual outcome after cataract surgery is therefore uncertain, as there is insufficient evidence to suggest any important effect on vision after surgery between the 2 groups studied.[4]

Eight systematic reviews were excluded due to poorer quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[9-16]

New Guidelines:

American College of Rheumatology: New and Updated Recommendations for the Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis and Idiopathic Chronic Anterior Uveitis (2023)

- Topical glucocorticoids (usually prednisolone acetate 1% or dexamethasone 0.1%) are recommended as first-line treatment for juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis, based on expert opinion and very low-quality evidence.[5]
- Topical and systemic NSAIDs are not recommended as monotherapy for juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis due to lack of demonstrable effect, based on descriptive studies and very low-quality evidence.[5]

Two identified guidelines were excluded due to poorer quality.[17,18]

New Formulations:

- 3/2024: BYQLOVI (clobetasol) 0.05% ophthalmic suspension received FDA approval for the treatment of post-operative inflammation and pain following ocular surgery.[6] The recommended dose is one drop instilled into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.[6] Due to the risk of increased IOP and possible damage to the optic nerve, IOP should be monitored if this product is used for 10 days or longer.[6] This is the first clobetasol ophthalmic preparation approved by the FDA.

  Clinical efficacy was evaluated in 2 RCTs in which patients with 10 or more white blood cells (an indicator of inflammation) in the anterior chamber after cataract surgery were assigned to clobetasol or placebo.[6] One drop of clobetasol or placebo was self-administered twice a day for 14 days, beginning on the day after surgery.[6] The co-primary endpoints were complete resolution of inflammation (an anterior chamber white blood cell count of 0 maintained through Day 15 without rescue medication) and complete resolution of pain (a patient-reported pain grade of 0 maintained through Day 15 without rescue medication) assessed at post-operative day 8 and 15.[6] In the intent-to-treat analysis, both co-primary efficacy endpoints were statistically significantly better in clobetasol-treated patients compared to placebo-treated patients.[6] Results from both trials are presented in **Table 1**.[6] Ocular adverse reactions observed with clobetasol 0.05% included eye inflammation (2%), corneal edema (2%), anterior chamber inflammation (2%), cystoid macular edema (2%), intraocular pressure elevation (1%), photophobia (1%) and vitreous detachment (1%).[6] Many of these reactions may have been a consequence of the surgical procedure.[6]

Table 1. Co-Primary Endpoints for Clobetasol 0.05% Ophthalmic Suspension Versus Placebo.[6]

Treatment Arm	Study 1: Day 8	Study 1: Day 15	Study 2: Day 8	Study 2: Day 15
Percent of Patients with Anterior Cell Count = 0				
Clobetasol 0.05%	32.6%	58.6%	29.7%	57.8%
Placebo	11.7%	15.7%	13.0%	18.9%

Percent of Patients with Complete Pain Resolution				
Clobetasol 0.05%	82.3%	90.6%	87.0%	86.5%
Placebo	42.6%	42.1%	46.5%	40.7%
Differences were significant (p<0.01) for all outcomes				

- 2/2019: LOTEMAX SM (loteprednol) 0.38% ophthalmic gel formulation received FDA approval for the treatment of post-operative inflammation and pain following ocular surgery.[7] The recommended dose is one drop into the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.[7] If this product is used for 10 days or longer, IOP should be monitored due to the risk of increased IOP and possible damage to the optic nerve.[7] Loteprednol is available as a brand-name product from 5 other manufacturers in strengths ranging from 0.2% to 0.5%, and generic formulations of loteprednol in a variety of strengths are also FDA-approved.

  In two RCTs in patients who underwent cataract extraction with intraocular lens implantation, loteprednol 0.38% gel was administered three times daily to the affected eye beginning the day after cataract surgery and compared to patients who received placebo three times a day post-operatively.[7] In these trials, loteprednol was more efficacious compared to placebo in resolving anterior chamber inflammation and pain following surgery.[7] Loteprednol-treated patients had statistically significantly higher rates of complete clearing of anterior chamber cells than placebo (Study 1: 29% vs. 9%; MD 11%; 95% CI, 11 to 27%; and Study 2: 31% vs. 20%, MD 10%; 95% CI, 2 to 19%).[7] In addition, more loteprednol-treated patients were pain-free at post-operative Day 8 compared to placebo (Study 1: 73% vs. 48%; MD 25%; 95% CI, 15 to 35%; and Study 2: 76% vs. 50%; MD 26%; 95% CI; 17 to 35%).[7] Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.[7] In these studies there were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.[7]

- 8/2018: INVELTY (loteprednol) 1% ophthalmic suspension received FDAL approval for the treatment of post-operative inflammation and pain following ocular surgery.[8] The recommended dose is 1-2 drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.[8]

  Clinical efficacy and safety of loteprednol 1% were evaluated in 2 RCTs in which patients with an anterior cell grade greater than or equal to "2" (a cell count of 6 or higher using a slit-lamp biomicroscope) after cataract surgery were assigned to loteprednol or placebo following surgery.[8] One to 2 drops of loteprednol or vehicle were self-administered twice a day for 14 days, beginning the day after surgery.[8] Complete resolution of inflammation (a cell count of 0 maintained through day 15 without rescue medication) and complete resolution of pain (a patient-reported pain grade of 0 maintained through day 15 without rescue medication) were assessed 8 and 15 days post-surgery.[8] In the intent-to-treat analysis of both studies, a statistically significant benefit was seen in the loteprednol-treated group compared to placebo for complete resolution of ocular inflammation at Day 8 (24% vs. 13%; p<0.01) and Day 15 (50% vs. 27%; p<0.01), and complete resolution of pain at Day 8 (56% vs. 36%; p<0.01) and Day 15 (69% vs. 48%; p<0.01).[8] The most common adverse drug reactions observed with loteprednol 1% ophthalmic suspension were eye pain and posterior capsular opacification, both reported in 1% of patients.[8] These reactions may have been the consequence of the surgical procedure.[8]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[19]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Difluprednate	DUREZOL	7/2025	Warnings and Precautions	**Corneal and Scleral Melting** Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation of the globe.
Dexamethasone/ Tobramycin	TOBRADEX	4/2020	Warnings and Precautions	**Warnings:** Sensitivity to topically applied aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such erythema, itching, urticaria, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If a sensitivity reaction does occur, discontinue use.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
dexamethasone	MAXIDEX	DROPS SUSP	Y
dexamethasone sodium phosphate	DEXAMETHASONE SODIUM PHOSPHATE	DROPS	Y
diclofenac sodium	DICLOFENAC SODIUM	DROPS	Y
fluorometholone	FLUOROMETHOLONE	DROPS SUSP	Y
fluorometholone	FML	DROPS SUSP	Y
flurbiprofen sodium	FLURBIPROFEN SODIUM	DROPS	Y
ketorolac tromethamine	ACULAR	DROPS	Y
ketorolac tromethamine	ACULAR LS	DROPS	Y
ketorolac tromethamine	KETOROLAC TROMETHAMINE	DROPS	Y
loteprednol etabonate	LOTEMAX	DROPS SUSP	Y
loteprednol etabonate	LOTEPREDNOL ETABONATE	DROPS SUSP	Y
prednisolone acetate	PRED FORTE	DROPS SUSP	Y
prednisolone acetate	PREDNISOLONE ACETATE	DROPS SUSP	Y
bromfenac sodium	BROMFENAC SODIUM	DROPS	N
bromfenac sodium	BROMSITE	DROPS	N
bromfenac sodium	PROLENSA	DROPS	N

clobetasol propionate	BYQLOVI	DROPS SUSP	N
difluprednate	DIFLUPREDNATE	DROPS	N
difluprednate	DUREZOL	DROPS	N
fluorometholone	FML FORTE	DROPS SUSP	N
fluorometholone acetate	FLAREX	DROPS SUSP	N
ketorolac tromethamine/PF	ACUVAIL	DROPERETTE	N
loteprednol etabonate	LOTEMAX	DROPS GEL	N
loteprednol etabonate	LOTEMAX SM	DROPS GEL	N
loteprednol etabonate	LOTEPREDNOL ETABONATE	DROPS GEL	N
loteprednol etabonate	ALREX	DROPS SUSP	N
loteprednol etabonate	INVELTYS	DROPS SUSP	N
loteprednol etabonate	LOTEPREDNOL ETABONATE	DROPS SUSP	N
loteprednol etabonate	LOTEMAX	OINT. (G)	N
nepafenac	ILEVRO	DROPS SUSP	N
nepafenac	NEVANAC	DROPS SUSP	N
prednisolone acetate	PRED MILD	DROPS SUSP	N
prednisolone sodium phosphate	PREDNISOLONE SODIUM PHOSPHATE	DROPS	N

Appendix 2: New Comparative Clinical Trials

A total of 98 citations were manually reviewed from the initial literature search. All citations were excluded because of inappropriate study design (e.g., observational), comparator control (e.g., no control or placebo-controlled), or endpoints studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy
Ovid MEDLINE(R) ALL <1946 to May 06, 2026>

1	Dexamethasone/	58656
2	Diclofenac/	9482
3	Fluorometholone/	364
4	Flurbiprofen/	2087
5	Ketorolac/	1873
6	Loteprednol Etabonate/	167
7	Prednisolone/	35195
8	Bromobenzenes/ or Benzophenones/ or Ophthalmic Solutions/ or bromfenac.mp. or Anti-Inflammatory Agents, Non-Steroidal/	98041
9	Clobetasol/	1610
10	difluprednate.mp. or Ophthalmic Solutions/ or Fluprednisolone/ or Glucocorticoids/	91935
11	Benzeneacetamides/ or Anti-Inflammatory Agents, Non-Steroidal/ or nepafenac.mp. or Phenylacetates/	83388

12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	259518
13	Uveitis/	14716
14	Conjunctivitis/	6750
15	Cataract Extraction/	27660
16	13 or 14 or 15	48448
17	12 and 16	2873
18	limit 17 to (english language and humans and yr="2015 -Current")	795
19	limit 18 to (comparative study or guideline or practice guideline or "systematic review")	98

Appendix 4: Key Inclusion Criteria

Population	People with uveitis or post-operative cataract extraction
Intervention	Ophthalmic drops in Appendix 1
Comparator	Another ophthalmic drop in Appendix 1
Outcomes	Anterior chamber flare, corneal edema, increased intraocular pressure
Timing	Up to 14 days post-operatively
Setting	Outpatient

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Topical Steroids

Date of Review: August 2026

Literature Search: 1/1/2017 – 6/10/2026
Date of Last Review: September 2017 (topical steroids)
December 2025 (topical products for inflammatory skin disease)

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This review looked for new evidence on the safety and effectiveness of steroid creams, ointments, and lotions applied to the skin (topical steroids).
- Topical steroids are used to manage symptoms associated with skin conditions such as eczema (also called atopic dermatitis), insect bites, allergic dermatitis from contact with poison ivy, psoriasis, and vitiligo. When applied to the skin, steroids decrease redness, itch, swelling, irritation, and rash.
- Steroids vary in potency from very strong (clobetasol, betamethasone, halobetasol) to mild (hydrocortisone, triamcinolone). It is best to start with low potency corticosteroids to avoid side effects such as thinning skin or acne, especially when treating areas of thin skin such as the face or eyelids. Thinning of skin can make it easier to break, bruise, or stretch. Higher potency corticosteroids are recommended for more severe skin conditions. All topical steroids should be used for a short time to limit side effects.
- No new evidence was identified that suggest changes to the preferred drug list (PDL) under the Oregon Health Plan (OHP) are recommended.

Conclusions:

- Since the last review of topical agents for inflammatory skin conditions, one new high-quality clinical guideline was identified; one new topical steroid formulation was approved by the Food and Drug Administration (FDA); and one topical steroid received an expanded indication in pediatric patients.
- The American Academy of Dermatology (AAD) updated their guideline to provide evidence-based recommendations for topical therapies phototherapy, and systemic therapies for children under 18 years of age with atopic dermatitis (AD) of any severity.[1] For pediatric patients up to age 18 with AD, topical corticosteroids are strongly recommended based upon moderate-quality evidence.[1] No specific agent is recommended over another.
- In November 2017, FDA approved IMPOYZ (clobetasol propionate 0.025% cream) for treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.[2]
- In August 2020, FDA expanded the indication for ULTRAVATE (halobetasol propionate lotion) for the treatment of plaque psoriasis in patients 12 years of age and older.[3] The previously approved indicated was for adults only.[3]
- Recent FDA safety labeling changes are presented in **Table 1.**

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- Current evidence does not warrant changes to the preferred drug list (PDL) **(Appendix 1**).
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P&T) Committee reviewed topical products for inflammatory skin diseases at the December 2025 meeting. Recently published evidence showed the most effective medicines to treat atopic dermatitis (AD) included topical corticosteroids among other classes of topical therapies (i.e., calcineurin inhibitors, Janus kinase inhibitors, and phosphodiesterase-4 inhibitors).[4] The 2023 American Academy of Dermatology (AAD) guidance for management of AD with topical therapies in adults strongly recommends topical steroids for management of mild to severe AD.[5] According to the 2021 American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) guidance, first-line topical agents to treat mild-to-moderate plaque psoriasis (PsO) includes topical steroids.[6] The 2021 British Association of Dermatologists (BAD) guidance recommends high potency or very high potency topical steroids as first-line treatment for vitiligo.[7] However, use of topical steroids to treat vitiligo is off-label.[8]
- The PDL status for topical steroids is provided in **Appendix 1.** Preferred topical steroids include lotion, cream, and ointment formulations of betamethasone, clobetasol, desonide, fluocinolone, hydrocortisone, and triamcinolone. All other topical steroids and formulations are subject to standard nonpreferred prior authorization (PA) criteria. The comparative potency of topical corticosteroids is presented in **Appendix 2.**

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high-quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

No new high-quality systematic reviews have been published since the December 2025 P&T Committee review of topical inflammatory agents.

New Guidelines:

American Academy of Dermatology Guidance for Management of Atopic Dermatitis In Pediatric Patients (2026)

The AAD updated guidelines to provide evidence-based recommendations for topical therapies phototherapy, and systemic therapies for children under 18 years of age with AD of any severity.[1] Recommendations that specifically address use of topical corticosteroids for AD include:

- For pediatric patients up to age 18 with AD, topical corticosteroids are recommended (Strong Recommendation; Moderate-Quality Evidence).[1]
- For pediatric patients up to age 18 with AD, intermittent use of low to medium potency topical corticosteroids as maintenance therapy is recommended (up to 3 times per week) (Strong Recommendation; Moderate-Quality Evidence).[1]

One identified guideline was excluded due to poor quality.[9]

New Formulations and Indications:
11/2017: FDA approved IMPOYZ, a topical formulation of clobetasol propionate 0.025% cream, indicated for treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.[2] The safety and efficacy of clobetasol 0.025% cream was evaluated in 2 double-blind, vehicle-controlled RCTs which enrolled a total of 532 participants aged 18 years and older with moderate to severe plaque psoriasis.[2] Participants were treated twice daily with clobetasol 0.025% cream or vehicle cream for 14 days.[2] The primary endpoint was the proportion of subjects who achieved treatment success at 15 day, where treatment success was defined as an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from baseline.[2] In both RCTs, more participants achieved statistically significant treatment success at Day 15 with clobetasol compared to vehicle (30% vs. 9%; 95% confidence interval not reported; $p<0.001$).[2]

8/2020: ULTRAVATE (halobetasol propionate) lotion received an expanded indication for the treatment of plaque psoriasis in patients 12 years of age and older.[3] It had been previously approved for treatment of plaque psoriasis in patients aged 18 years and older.[3] The safety and of halobetasol lotion was evaluated in one open-label study in 16 adolescents with moderate to severe plaque psoriasis; evidence for efficacy was previously supported in trials conducted in adults.[3] Hypothalamic-pituitary adrenal (HPA) axis function (ACTH stimulation test) was evaluated in a subset of 14 patients.[3] After 2 weeks of treatment, 1 of 14 patients (7%) experienced laboratory evidence of adrenal suppression (i.e., cortisol serum level of ≤18 mcg/dL) that recovered upon retest. No other adverse reactions were reported in the study.[3]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[10]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Betamethasone Clobetasol Mometasone	DIPROLENE, LOTRISONE OLUX ELOCON	3/2018	Warnings and Precautions	Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported postmarketing with the use of topical corticosteroid products. Avoid contact of topical corticosteroids Ointment with eyes. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation.
Desoximetasone	TOPICORT	10/2021	Warnings and Precautions	Pediatric patients may be more susceptible to systemic toxicity from use of topical corticosteroids. Use in patients under 18 years of age is not recommended due to numerically high rates of HPA axis suppression (the safety and effectiveness of Topicort Topical Spray have not been established in pediatric patients).

References:

1. Davis DMR, Alikhan A, Bercovitch L, et al. Guidelines of care for the management of atopic dermatitis in pediatric patients. *Journal of the American Academy of Dermatology*. doi:10.1016/j.jaad.2026.02.113
2. IMPOYZ (clobetasol propionate) topical 0.025% cream. Prescribing Information. San Antonio, TX; Promius Pharma LLC. 11/2017.
3. ULTRAVATE (halobetasol propionate) 0.05% topical lotion. Prescribing Information. Ferndale, MI; Ferndale Laboratories, Inc. 8/2020.
4. Lax SJ, Van Vogt E, Candy B, et al. Topical Anti-Inflammatory Treatments for Eczema: A Cochrane Systematic Review and Network Meta-Analysis. *Clin Exp Allergy*. Dec 2024;54(12):960-972. doi:10.1111/cea.14556
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6. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. Feb 2021;84(2):432-470. doi:10.1016/j.jaad.2020.07.087
7. Eleftheriadou V, Atkar R, Batchelor J, et al. British Association of Dermatologists guidelines for the management of people with vitiligo 2021. *Br J Dermatol*. Jan 2022;186(1):18-29. doi:10.1111/bjd.20596
8. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed 12/12/2025.
9. Renert-Yuval Y, Ezzedine K, Grimes P, et al. Expert Recommendations on Use of Topical Therapeutics for Vitiligo in Pediatric, Adolescent, and Young Adult Patients. *JAMA Dermatol*. Apr 1 2024;160(4):453-461. doi:10.1001/jamadermatol.2024.0021
10. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed May 6, 2026.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
alclometasone dipropionate	ALCLOMETASONE DIPROPIONATE	CREAM (G)	Y
alclometasone dipropionate	ALCLOMETASONE DIPROPIONATE	OINT. (G)	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	CREAM (G)	Y
betamethasone dipropionate	ALPHATREX	LOTION	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	LOTION	Y
betamethasone dipropionate	ALPHATREX	OINT. (G)	Y
betamethasone dipropionate	BETAMETHASONE DIPROPIONATE	OINT. (G)	Y
betamethasone valerate	BETAMETHASONE VALERATE	CREAM (G)	Y
betamethasone valerate	BETATREX	CREAM (G)	Y
betamethasone valerate	BETAMETHASONE VALERATE	OINT. (G)	Y
betamethasone valerate	BETATREX	OINT. (G)	Y
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	CREAM (G)	Y
clobetasol propionate	CLOBETASOL PROPIONATE	CREAM (G)	Y
clobetasol propionate	CLOBETASOL PROPIONATE	OINT. (G)	Y
clobetasol propionate	CLOBETASOL PROPIONATE	SOLUTION	Y
desonide	DESONIDE	CREAM (G)	Y

desonide	DESOWEN	CREAM (G)	Y
desonide	TRIDESILON	CREAM (G)	Y
desonide	DESONIDE	OINT. (G)	Y
desonide	TRIDESILON	OINT. (G)	Y
desoximetasone	DESOXIMETASONE	CREAM (G)	Y
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	CREAM (G)	Y
fluocinolone acetonide	SYNALAR	CREAM (G)	Y
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	SOLUTION	Y
fluocinolone acetonide	SYNALAR	SOLUTION	Y
fluocinonide	FLUOCINONIDE	CREAM (G)	Y
fluocinonide	FLUOCINONIDE	SOLUTION	Y
fluocinonide/emollient base	FLUOCINONIDE-E	CREAM (G)	Y
hydrocortisone	ANTI-ITCH	CREAM (G)	Y
hydrocortisone	HYDROCORTISONE	CREAM (G)	Y
hydrocortisone	HYCORT	OINT. (G)	Y
hydrocortisone	HYDROCORTISONE	OINT. (G)	Y
hydrocortisone	ITCH RELIEF	OINT. (G)	Y
hydrocortisone acetate	HYDROCORTISONE ACETATE	CREAM (G)	Y
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	SOLUTION	Y
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	CREAM (G)	Y
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	OINT. (G)	Y
amcinonide	AMCINONIDE	CREAM (G)	N
betamethasone dipropionate	DIPROSONE	AEROSOL	N
betamethasone dipropionate	BETAMETHASONE DIPROP AUGMENTED	GEL (GRAM)	N
betamethasone valerate	BETAMETHASONE VALERATE	FOAM	N
betamethasone valerate	BETAMETHASONE VALERATE	LOTION	N
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	LOTION	N
betamethasone/propylene glyc	BETAMETHASONE DIPROP AUGMENTED	OINT. (G)	N
clobetasol propionate	CLOBETASOL PROPIONATE	FOAM	N
clobetasol propionate	CLOBETASOL PROPIONATE	GEL (GRAM)	N
clobetasol propionate	CLOBETASOL PROPIONATE	LOTION	N
clobetasol propionate	CLOBETASOL PROPIONATE	SHAMPOO	N
clobetasol propionate	CLOBEX	SHAMPOO	N
clobetasol propionate	CLODAN	SHAMPOO	N
clobetasol propionate	CLOBETASOL PROPIONATE	SPRAY	N
clobetasol propionate	CLOBEX	SPRAY	N
clobetasol propionate/emoll	CLOBETASOL EMOLLIENT	CREAM (G)	N
clobetasol propionate/emoll	CLOBETASOL EMOLLIENT	FOAM	N
clobetasol propionate/emoll	CLOBETASOL EMULSION	FOAM	N
clobetasol propionate/emoll	TOVET EMOLLIENT	FOAM	N

clobetasol/emollient no.65	TOVET KIT	COMBO. PKG	N
clobetasol/skin cleanser no.28	CLODAN	KT SHM CLN	N
clocortolone pivalate	CLOCORTOLONE PIVALATE	CREAM (G)	N
desonide	DESONIDE	LOTION	N
desoximetasone	DESOXIMETASONE	GEL (GRAM)	N
desoximetasone	DESOXIMETASONE	OINT. (G)	N
desoximetasone	DESOXIMETASONE	SPRAY	N
diflorasone diacetate	DIFLORASONE DIACETATE	CREAM (G)	N
diflorasone diacetate	DIFLORASONE DIACETATE	OINT. (G)	N
fluocinolone acetonide	DERMA-SMOOTHE-FS	OIL	N
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	OIL	N
fluocinolone acetonide	FLUOCINOLONE ACETONIDE	OINT. (G)	N
fluocinolone acetonide	SYNALAR	OINT. (G)	N
fluocinolone acetonide	CAPEX SHAMPOO	SHAMPOO	N
fluocinolone/emol comb no.65	SYNALAR	CMB ONT CR	N
fluocinolone/emol comb no.65	SYNALAR	CREAM (G)	N
fluocinolone/shower cap	DERMA-SMOOTHE-FS	OIL	N
fluocinolone/shower cap	FLUOCINOLONE ACETONIDE	OIL	N
fluocinolone/skin clnsr28	SYNALAR TS	KIT	N
fluocinonide	FLUOCINONIDE	GEL (GRAM)	N
fluocinonide	FLUOCINONIDE	OINT. (G)	N
flurandrenolide	FLURANDRENOLIDE	LOTION	N
fluticasone propionate	FLUTICASONE PROPIONATE	CREAM (G)	N
fluticasone propionate	BESER	LOTION	N
fluticasone propionate	FLUTICASONE PROPIONATE	LOTION	N
fluticasone propionate	FLUTICASONE PROPIONATE	OINT. (G)	N
fluticasone/emollient no.65	BESER KIT	KT LOTN CE	N
halcinonide	HALCINONIDE	CREAM (G)	N
halcinonide	HALOG	CREAM (G)	N
halcinonide	HALCINONIDE	SOLUTION	N
halcinonide	HALOG	SOLUTION	N
halobetasol propionate	HALOBETASOL PROPIONATE	CREAM (G)	N
halobetasol propionate	HALOBETASOL PROPIONATE	FOAM	N
halobetasol propionate	LEXETTE	FOAM	N
halobetasol propionate	HALOBETASOL PROPIONATE	LOTION	N
halobetasol propionate	ULTRAVATE	LOTION	N
halobetasol propionate	HALOBETASOL PROPIONATE	OINT. (G)	N
hydrocortisone	HYDROCORTISONE	CREAM PACK	N
hydrocortisone	CETACORT	LOTION	N
hydrocortisone	HYDROCORTISONE	LOTION	N

hydrocortisone	SCALP CORT	LOTION	N
hydrocortisone	HYDROCORTISONE	SOLUTION	N
hydrocortisone	SCALP	SOLUTION	N
hydrocortisone	TEXACORT	SOLUTION	N
hydrocortisone	HYDROCORTISONE	SPRAY	N
hydrocortisone acet/aloe vera	HYDROCORTISONE ACETATE W/ALOE	CREAM (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	CREAM (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE ACETATE W/ALOE	OINT. (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	OINT. (G)	N
hydrocortisone acet/aloe vera	HYDROCORTISONE W/ALOE	PACKET	N
hydrocortisone acetate	HYDROCORTISONE	OINT. (G)	N
hydrocortisone acetate	HYDROCORTISONE ACETATE	OINT. (G)	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	CREAM (G)	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	LOTION	N
hydrocortisone butyrate	HYDROCORTISONE BUTYRATE	OINT. (G)	N
hydrocortisone probutate	PANDEL	CREAM (G)	N
hydrocortisone valerate	HYDROCORTISONE VALERATE	CREAM (G)	N
hydrocortisone valerate	HYDROCORTISONE VALERATE	OINT. (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE W/ALOE	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE-ALOE	CREAM (G)	N
hydrocortisone/aloe vera	ITCH RELIEF WITH ALOE	CREAM (G)	N
hydrocortisone/aloe vera	HYDROCORTISONE W/ALOE	OINT. (G)	N
mometasone furoate	MOMETASONE FUROATE	CREAM (G)	N
mometasone furoate	MOMETASONE FUROATE	OINT. (G)	N
mometasone furoate	MOMETASONE FUROATE	SOLUTION	N
neomycin sulfate/fluocinolone	NEO-SYNALAR	CREAM (G)	N
neomycin/fluocinolone/emoll 65	NEO-SYNALAR	CREAM (G)	N
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	AEROSOL	N
triamcinolone acetonide	KENALOG	LOTION	N
triamcinolone acetonide	TRIAMCINOLONE ACETONIDE	LOTION	N
hydrocortisone	HYDROCORTISONE	CRM/PE APP	
hydrocortisone	PROCTO-MED HC	CRM/PE APP	
hydrocortisone	PROCTOSOL-HC	CRM/PE APP	
hydrocortisone	PROCTOZONE-HC	CRM/PE APP	
hydrocortisone	HYDRAVEX	GEL (GRAM)	
hydrocortisone	HYDROCORTISONE	GEL (GRAM)	
hydrocortisone	HYDROXYM	GEL (GRAM)	
hydrocortisone acetate	MICORT-HC	CRM/PE APP	
neomycin sulfate/hydrocort	NEOMYCIN W/HYDROCORTISONE	OINT. (G)	

Appendix 2: Comparative Potency of Topical Corticosteroids

Table 2. Potency Of Topical Corticosteroid Preparations Using United States Classification.[6]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency (Group 7)	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution
Low Potency (Group 6)	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency (Group 5)	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream
	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency (Group 4)	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency (Group 3)	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream
	Triamcinolone acetonide	0.1%	ointment

High Potency (Group 2)	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency (Group 1)	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment

Appendix 3: New Comparative Clinical Trials

A total of 113 citations were manually reviewed from the initial literature search. After further review, 113 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 09, 2026>

1	exp Psoriasis/th [Therapy]	5341
2	exp Dermatitis, Atopic/th [Therapy]	2953
3	exp Eczema/th [Therapy]	1170
4	exp Vitiligo/th [Therapy]	1203
5	Anti-Inflammatory Agents/ or Glucocorticoids/	178578
6	Administration, Topical/	42456
7	alclometasone.mp.	46
8	Betamethasone/	6553
9	Clobetasol/	1618
10	Desonide/	107

11	Desoximetasone/	84
12	Fluocinolone Acetonide/	1527
13	Hydrocortisone/	81040
14	Triamcinolone/	4177
15	amcinonide.mp.	56
16	clocortolone.mp.	27
17	flurandrenolide.mp.	22
18	Fluticasone/	3181
19	Halcinonide/	49
20	halobetasol.mp.	142
21	Mometasone Furoate/	968
22	1 or 2 or 3 or 4	10285
23	5 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	261150
24	6 and 23	7746
25	22 and 24	142
26	limit 25 to (english language and humans)	113

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Combination Antihypertensive Drugs, Calcium Channel Blockers and Oral Beta-Blockers

Date of Review: August 2026

Literature Search: 1/1/2015-5/15/2026
Date of Last Review: Combination Antihypertensives (July 2015)
Calcium Channel Blockers (July 2015)
Beta-Blockers, Oral (December 2022)

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This review looks at recent evidence for the effectiveness and safety of 2 classes of medicines used to treat hypertension.
- Hypertension, or high blood pressure, is often times a life-long medical condition where the force of blood pushing against the blood vessels is too high. This makes the heart work harder than normal to pump blood throughout the body. Over time, this extra strain can damage the blood vessels and increase the risk of having a heart attack, stroke, heart failure, or kidney disease.
- Most people with high blood pressure do not have symptoms. The risk of high blood pressure increases with advancing age, being overweight, family history of high blood pressure, a diet high in salt, not being physically active, smoking, and drinking too much alcohol.
- High blood pressure can be diagnosed when your provider checks it during a medical checkup. If the blood pressure reading is greater than 130/80 millimeters of mercury (mm Hg) on 2 or more readings taken on separate occasions, it is considered too high and should be treated with medicine. The top number (systolic) is the pressure inside the arteries when the heart is contracting. The bottom number (diastolic) is the pressure inside the arteries when the heart is relaxed.
- People with very high blood pressure (usually 180/120 mm Hg or higher) can have severe headaches, chest pain, dizziness, blurred vision, or an abnormal heart rhythm. If people have these symptoms, they should immediately seek medical care.
- There are many different medicines used to treat high blood pressure including calcium channel blockers and beta-blockers. Some people may need to take two or more blood pressure medicines to keep their blood pressure within normal range (less than 130/80 mm Hg).
- Calcium channel blockers include amlodipine, nifedipine, and diltiazem These medicines relax the muscles of the blood vessels and slow the heart rate. Calcium channel blockers are recommended as one of the first-line treatments for high blood pressure.
- Beta-blockers include atenolol, metoprolol, carvedilol, and propranolol. These medicines help the heart to beat slower and with less force. Beta-blockers also relax the blood vessels to decrease blood pressure. If people are using 3 medicines to manage their blood pressure and have not reached their target goal, a beta-blocker may be added to their other medicines. Beta-blockers are also used in people after they have had a heart attack or if they have heart failure.

Author: Deanna Moretz, PharmD, BCPS

- Calcium channel blockers and beta-blockers are preferred in pregnant women with high blood pressure because they have been proven to be safe to the baby and the mother.
- Oregon Health Plan (OHP) pays for these calcium channel blockers: amlodipine, nicardipine, nifedipine, diltiazem, and verapamil. Several beta-blockers are also paid for by OHP including acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol. Providers must submit documentation to OHP if other beta-blockers or calcium channel blockers are prescribed. This process is called prior authorization.

Conclusions:

- Since the last review of beta-blockers and CCBs, 3 high-quality systematic reviews[1-3] and 4 guidelines[4-7] have been published.
- The objective of a 2022 Cochrane review was to determine whether calcium channel blockers (CCBs) used as first-line therapy for hypertension are different from other classes of antihypertensive drugs in reducing the incidence of major adverse cardiovascular events (MACE).[1] For the treatment of hypertension, there is moderate certainty evidence that diuretics reduce the incidence of MACE and congestive heart failure (CHF) events more than CCBs.[1] There is low to moderate certainty evidence that CCBs probably reduce the incidence of MACE more than beta-blockers.[1] There is low to moderate certainty evidence that CCBs reduce the incidence of stroke when compared to angiotensin converting enzyme (ACE) inhibitors and reduce myocardial infarction (MI) events when compared to angiotensin II receptor blockers (ARBs) but increased CHF events when compared to ACE inhibitors and ARBs.[1]
- A 2018 Cochrane review evaluated the benefits and harms of first-line renin angiotensin system (RAS) inhibitors compared to other first-line antihypertensive drugs in people with hypertension.[2] All-cause death is similar for first-line RAS inhibitors and first-line CCBs, thiazides and beta-blockers (moderate certainty evidence).[2] First-line thiazides reduced the risk heart failure and stroke more than first-line RAS inhibitors (moderate certainty evidence).[2] First-line CCBs increased heart failure but decreased stroke compared to first-line RAS inhibitors (moderate certainty evidence).[2] Low certainty evidence suggests that first-line RAS inhibitors reduced stroke and total cardiovascular (CV) events compared to first-line beta-blockers.[2]
- A 2018 Cochrane review assessed the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.[3] Moderate certainty evidence shows that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension.[3] Based on low to moderate certainty evidence, the effect on other clinically important outcomes (i.e., proteinuria, preeclampsia, maternal death, impaired fetal growth, fetal death) remains unclear.[3] Moderate certainty evidence shows that If antihypertensive drugs are used, beta-blockers and CCBs appear to be more effective than the alternatives (i.e., methyldopa) for preventing severe hypertension.[3]
- The 2025 report of the American College of Cardiology/American Heart Association (ACC/AHA) joint committee on clinical practice guidelines for management of hypertension replaced 2017 guidance.[4] The blood pressure (BP) treatment goal is less than 130/80 mm Hg for all adults, with additional considerations for those who require institutional care, have a limited predicted lifespan, or are pregnant.[4] Initiation of medication therapy to lower BP in addition to lifestyle interventions is recommended for all adults with average BP greater than or equal to 140/90 mm Hg and/or for selected adults with average BP greater than or equal to 130/80 mm Hg who have clinical cardiovascular disease (CVD), previous stroke, diabetes, chronic kidney disease (CKD), or increased 10-year predicted CV risk greater than 7.5%.[4] Strong evidence from clinical trials supports 4 classes of first-line agents compared with placebo (thiazide-type diuretics, long-acting dihydropyridine CCBs, ACE inhibitors, and ARBs) due to their favorable profiles for BP lowering, CVD prevention, and tolerability.[4] Beta-blockers were less effective than first-line antihypertensive classes in preventing stroke and had a less favorable side effect profile; therefore, they should be reserved for adults with compelling indications (i.e., post-MI, heart failure).[4] Descriptions of the ACC/AHA classes of recommendations (COR) and level of evidence (LOE) are summarized in **Table 1.** Specific recommendations for the use of CCBs and beta-blockers in treating hypertension include:
    - For adults initiating antihypertensive drug therapy, thiazide-type diuretics, long acting dihydropyridine CCB, and ACE inhibitor or ARB are recommended as first-line therapy to prevent CVD. (COR: 1; LOE: A).[4]

- In adults with Stage 2 hypertension (systolic blood pressure [SBP] ≥ 140 mm Hg and diastolic blood pressure [DBP] ≥ 90 mm Hg) initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination, is recommended to improve BP control and adherence (COR: 1; LOE: B-R).[4]
- In adults with Stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control (COR: 2a; LOE: C-EO).[4]
- In adults with uncontrolled hypertension who cannot tolerate or have contraindications to a mineralocorticoid receptor antagonist (MRA), the addition of one of the following agents or classes – amiloride, beta-blockers, alpha-blockers, central sympatholytic drugs, dual endothelin receptor antagonist, or direct vasodilator – is reasonable to control BP. (COR: 2a; LOE: B-NR)[4]

- One of the most important changes in the European Society of Cardiology (ESC) 2024 hypertension guidance is the focus on evidence related to CVD outcomes of BP-lowering interventions rather than BP lowering alone.[5] The major drug classes with robust evidence for BP-mediated reduction in CVD events are ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics (thiazides and thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide), and beta-blockers.[5] The first 4 are recommended as first-line options for starting hypertension treatment in the general population.[5] Beta-blockers can be added preferentially in circumstances such as in the presence of angina or heart failure, after MI, or for controlling heart rate, where they are the cornerstone of therapy.[5] However, beta-blockers are less effective than ACE inhibitors, ARBs, CCBs, or diuretics at preventing stroke, and have a higher discontinuation rate due to side effects.[5] The ESC pharmacologic recommendations for treating hypertension are presented in **Table 2**.
- The Veterans Affairs/Department of Defense (VA/DoD) recommendations for management of hypertension were updated in 2020.[6] This guideline working group, on the basis of their review of the literature, defined hypertension as an SBP of 130 mm Hg or greater or a DBP of 90 mm Hg or greater.[6] Evidence supports the use of a thiazide-type diuretic, a CCB, or either an ACE inhibitor or an ARB as primary pharmacologic therapy for hypertension.[6] The effects of the various antihypertensive drug classes on reducing composite CV outcomes, and not just differences in BP–lowering effect, were the focus of the recommendation.[6] The VA/DoD guidance is similar to the ACC/AHA and ESC guidance. Specific goals of therapy and pharmacologic treatment recommendations are summarized in **Table 3**.
- The National Institute for Health and Care Excellence (NICE) published guidance for hypertension management in adults in 2019.[7] The recommendations align with other organizations and are summarized below. Calcium channel blockers are recommended as first line agents for treatment of hypertension and beta-blockers are reserved for people with resistant hypertension.[7]
- Recent Food and Drug Administration (FDA)-approved formulations and indications:
  - 12/2025: A 10 mg/mL oral solution of LOPRESSOR (metoprolol) received FDA approval, indicated for the treatment of adults with hypertension, in the long-term treatment of angina pectoris, and the in the treatment of hemodynamically stable patients with definite or suspected MI to reduce the risk of CV mortality when used in conjunction with intravenous metoprolol therapy.[8] The manufacturer did not conduct new studies for this new formulation and relied on the FDA's finding of safety and effectiveness of metoprolol tablets.
  - 7/2025: The FDA approved SDAMLO, new unit-dose oral powder formulation of amlodipine.[9] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[9] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
  - 6/2025: A new triple combination oral tablet, WIDAPLIK (telmisartan/amlodipine/indapamide) received FDA-approval, indicated for the treatment of hypertension in adults [10] The product is available in 3 strengths containing telmisartan, amlodipine, and indapamide in the following combinations: 10 mg/1.25 mg/0.625 mg; 20 mg/2.5 mg/1.25 mg; and 40 mg/5 mg/2.5 mg.[10] The efficacy of WIDAPLIK in lowering blood pressure was evaluated in a randomized study designed to evaluate the efficacy and safety of two doses of WIDAPLIK (10 mg/1.25 mg/0.625 mg and 20 mg/2.5 mg/1.25 mg)

compared to placebo (Study 1, NCT04518306) and in a randomized study designed to evaluate the efficacy and safety of WIDAPLIK (40 mg/5 mg/2.5 mg) as compared to each of its two-drug combinations at the same doses (Study 2, NCT04518293).[10] In both studies, triple therapy with telmisartan/amlodipine/indapamide showed statistically significant greater reductions in BP compared to placebo or dual therapy.[10] Study details are results are presented below.

- 2/2022: The FDA approved NORLIQVA, a 1 mg/mL oral solution formulation of amlodipine.[11] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[11] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 12/2019: A new medication, CONJPRI, levamlodipine oral tablet was FDA-approved to treat hypertension in adults and pediatric patients aged 6 years an older either alone or in combination with other antihypertensive agents.[12] Levamlodipine is an active isomer of amlodipine.[12] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 7/2019: The FDA approved KATERZIA, new 1 mg/mL oral solution formulation of amlodipine.[13] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[13] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications.
- 6/2106: The FDA approved an oral tablet combination product, BYVALSON (nebivolol/valsartan 5mg/80mg), indicated for the treatment of hypertension.[14] BYVALSON was studied in a Phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study in 4,161 patients with Stage 1 or 2 hypertension.[14] Treatment with BYVALSON 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in SBP and DBP of -8.3 and -7.2 mmHg, respectively.[14] Treatment with BYVALSON 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone ($p<0.0001$ for both SBP and DBP) or valsartan 80 mg, alone ($p=0.0007$ for SBP and $p<0.0001$ for DBP).[14] During the 4-week period, the overall incidence of adverse events on therapy with BYVALSON 5 mg/ 80 mg was similar to placebo and the individual components (nebivolol 5 mg and valsartan 80 mg).[14]

- Recent FDA safety revisions to manufacturers prescribing information are presented in **Table 6**.

Recommendations:

- Maintain LOPRESSOR (metoprolol) oral solution, SDAMLO (amlodipine) oral powder, WIDAPLIK (telmisartan/amlodipine/indapamide) tablets, NORLIQVA (amlodipine) oral solution, CONJPRI (levamlodipine) tablets, KATERZIA (amlodipine)oral solution, and BYVALSON (nebivolol/valsartan) tablets as non-preferred on the Preferred Drug List (PDL). Make nimodipine capsules preferred and the brand name NIMOTOP capsules and solution non-preferred.
- No other PDL changes are recommended based on review of recent evidence.
- Review drug costs in Executive Session.

Summary of Prior Reviews and Current Policy

- The beta blocker class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the August 2022 meeting. All of the beta blockers reviewed were effective in the treatment of hypertension, but there was no evidence of differences between beta blockers for BP control, survival, or quality of life. Three beta blockers, bisoprolol, carvedilol, and extended-release metoprolol succinate, have been shown to reduce mortality and morbidity in patients with heart failure with reduced ejection fraction (HFrEF).[15] A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI to manage atrial fibrillation.[16] Labetalol is the preferred oral beta-blocker

for managing gestational hypertension.[17] Finally, propranolol has demonstrated efficacy in migraine prophylaxis[18] and treatment of infantile hemangioma.[19,20] Topical timolol is also effective in treatment of thin (less than 1 mm), superficial infantile hemangioma.[20]

- After reviewing drug costs in the executive session, propranolol SA 24-hour capsules, generic oral propranolol solution, and nadolol tabs were designated as preferred on the PDL and open access for HEMANGEL (propranolol) oral solution for patients up to 6 months of age with infantile hemangioma was approved.
- **Appendix 1** summarizes the current preferred beta blocker status on the PDL which includes: acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol.
- Calcium channel blockers (CCBs) and fixed dose combinations of antihypertensives were last reviewed by the P & T Committee at the July 2015 meeting. There was insufficient evidence comparing relative efficacy and safety of CCBs with other CCBs. In 2015, guidelines recommended CCBs as a first-line treatment option for hypertension. There was insufficient evidence comparing a fixed-dose antihypertensive combination product containing a CCB with the respective drugs taken concomitantly as separate formulations for the treatment of hypertension. The committee agreed to maintain at least 2 preferred dihydropyridine CCBs, including amlodipine, and maintain at least 1 preferred extended-acting and immediate-release formulation of diltiazem and verapamil on the PDL.
- **Appendix 1** summarizes the current preferred CCB status on the PDL which includes: amlodipine, nicardipine, nifedipine, diltiazem, and verapamil. Preferred combination antihypertensives include amlodipine/olmesartan, benazepril/hydrochlorothiazide (HCTZ), enalapril/HCTZ, lisinopril/HCTZ, losartan/HCTZ, olmesartan/amlodipine/HCTZ, and telmisartan/HCTZ. Nonpreferred agents are subject to the standard non-preferred prior authorization criteria.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane Review: Calcium Channel Blockers Versus Other Classes Of Drugs For Hypertension (2022)
The objective of this review was to determine whether CCBs used as first-line therapy for hypertension are different from other classes of antihypertensive drugs in reducing the incidence of MACE.[1] Literature was searched through September 1, 2020 for RCTs comparing first-line CCBs with other antihypertensive classes, with at least 100 randomized hypertensive participants and a follow-up of at least 2 years.[1] This update included a total of 23 RCTs (18 dihydropyridines, 4 non-dihydropyridines, 1 not specified) with 153,849 participants with hypertension.[1]

As compared to diuretics, CCBs probably increased the incidence of MACE (risk ratio [RR] 1.05, 95% confidence interval [CI] 1.00 to 1.09, P = 0.03) and increased CHF events (RR 1.37, 95% CI 1.25 to 1.51, moderate-certainty evidence).[1] As compared to beta-blockers, CCBs reduced the incidence of the following outcomes:

MACE (RR 0.84, 95% CI 0.77 to 0.92), stroke (RR 0.77, 95% CI 0.67 to 0.88, moderate-certainty evidence), and CV mortality (RR 0.90, 95% CI 0.81 to 0.99, low-certainty evidence).[1] As compared to ACE inhibitors, CCBs reduced the incidence of stroke (RR 0.90, 95% CI 0.81 to 0.99, low-certainty evidence) and increased CHF events (RR 1.16, 95% CI 1.06 to 1.28, low-certainty evidence).[1] As compared to ARBs, CCBs reduced the incidence of MI (RR 0.82, 95% CI 0.72 to 0.94, moderate-certainty evidence) and increased CHF events (RR 1.20, 95% CI 1.06 to 1.36, low-certainty evidence).[1]

In summary, for the treatment of hypertension, there is moderate certainty evidence that diuretics reduce the incidence of MACE and CHF events more than CCBs.[1] There is low to moderate certainty evidence that CCBs probably reduce the incidence of MACE more than beta-blockers.[1] There is low to moderate certainty evidence that CCBs reduce the incidence of stroke when compared to ACE inhibitors and reduce MI events when compared to ARBs but increased CHF events when compared to ACE inhibitors and ARBs.[1] Many of the differences found in the current review are not robust, and further trials might change the conclusions.[1]

Cochrane Review: First-Line Drugs Inhibiting The Renin Angiotensin System Versus Other First-Line Antihypertensive Drug Classes For Hypertension (2018)

This review evaluated the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in people with hypertension.[2] Literature was searched through November 2017 for active-controlled, double-blinded RCTs with at least 6 months follow-up in people with elevated BP greater than or equal to 130/85 mmHg, which compared first-line RAS inhibitors with other first-line antihypertensive drug classes and reported morbidity and mortality or BP outcomes.[2] People with proven secondary hypertension were excluded.[2] This update includes 3 new RCTs, totaling 45 RCTs in all, involving 66,625 participants, with a mean age of 66 years.[2] Much of the evidence for the key outcomes is dominated by a small number of large RCTs at low risk for most sources of bias.[2] Imbalances in the added second-line antihypertensive drugs in some of the studies were important enough to downgrade the quality of the evidence.[2] Primary outcomes were all-cause death, fatal and non-fatal stroke, fatal and non-fatal MI, fatal and non-fatal CHF requiring hospitalizations, total CV events (fatal and non-fatal stroke, fatal and non-fatal MI and fatal and non-fatal CHF requiring hospitalization), and end-stage renal failure (ESRF).[2] Secondary outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR).[2]

Compared with first-line CCBs, moderate-certainty evidence showed that first-line RAS inhibitors decreased heart failure (35,143 participants in 5 RCTs, RR 0.83, 95% CI 0.77 to 0.90, absolute risk reduction [ARR] 1.2%), and that they increased stroke (34,673 participants in 4 RCTs, RR 1.19, 95% CI 1.08 to 1.32, absolute risk increase [ARI] 0.7%).[2] Moderate-certainty evidence showed that first-line RAS inhibitors and first-line CCBs did not differ for all-cause death (35,226 participants in 5 RCTs, RR 1.03, 95% CI 0.98 to 1.09); total CV events (35,223 participants in 6 RCTs, RR 0.98, 95% CI 0.93 to 1.02); and total MI events (35,043 participants in 5 RCTs, RR 1.01, 95% CI 0.93 to 1.09).[2] Low-certainty evidence suggests they did not differ for the incidence of ESRF (19,551 participants in 4 RCTs, RR 0.88, 95% CI 0.74 to 1.05).[2]

Compared with first-line thiazides, moderate-certainty evidence showed that first-line RAS inhibitors increased heart failure (24,309 participants in 1 RCT, RR 1.19, 95% CI 1.07 to 1.31, ARI 1.0%), and increased stroke (24,309 participants in 1 RCT, RR 1.14, 95% CI 1.02 to 1.28, ARI 0.6%).[2] Moderate-certainty evidence showed that first-line RAS inhibitors and first-line thiazides did not differ for all-cause death (24,309 participants in 1 RCT, RR 1.00, 95% CI 0.94 to 1.07); total CV events (24,379 participants in 2 RCTs, RR 1.05, 95% CI 1.00 to 1.11); and total MI events (24,379 participants in 2 RCTs, RR 0.93, 95% CI 0.86 to 1.01).[2] Low-certainty evidence suggests they did not differ for the incidence of ESRF (24,309 participants in 1 RCT, RR 1.10, 95% CI 0.88 to 1.37).[2]

Compared with first-line beta-blockers, low-certainty evidence suggests that first-line RAS inhibitors decreased total CV events (9239 participants in 2 RCTs, RR 0.88, 95% CI 0.80 to 0.98, ARR 1.7%), and decreased stroke (9193 participants in 1 RCT, RR 0.75, 95% CI 0.63 to 0.88, ARR 1.7%). Low-certainty evidence suggests that first-line RAS inhibitors and first-line beta-blockers did not differ for all-cause death (9193 participants in 1 RCT, RR 0.89, 95% CI 0.78 to 1.01); HF (9193

participants in 1 RCT, RR 0.95, 95% CI 0.76 to 1.18); and total MI events (9239 participants in 2 RCTs, RR 1.05, 95% CI 0.86 to 1.27).[2] There is no information about non-fatal serious adverse events, as none of the trials reported this outcome.[2]

In summary, all-cause death is similar for first-line RAS inhibitors, first-line CCBs, thiazides and beta-blockers (moderate certainty evidence).[2] First-line thiazides caused less heart failure and stroke than first-line RAS inhibitors (moderate certainty evidence).[2] First-line CCBs increased heart failure but decreased stroke compared to first-line RAS inhibitors (moderate certainty).[2] Low-quality evidence suggests that first-line RAS inhibitors reduced stroke and total CV events compared to first-line beta-blockers.[2]

Cochrane Review: Antihypertensive Drug Therapy For Mild To Moderate Hypertension During Pregnancy (2018)

This review assessed the effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.[3] Literature was searched through September 2017 for RCTs evaluating any antihypertensive drug treatment for mild to moderate hypertension during pregnancy, defined as SBP 140 to 169 mmHg and/or DBP 90 to 109 mmHg.[3] Comparisons were of one or more antihypertensive drug(s) with placebo, with no antihypertensive drug, or with another antihypertensive drug, and where treatment was planned to continue for at least 7 days.[3] Sixty-three trials met inclusion criteria (data from 58 trials, 5909 women), with moderate to high risk of bias overall.[3]

- Antihypertensive Drug Versus Placebo/No Antihypertensive Drug (31 Trials, 3485 Women)

Primary outcomes: moderate-certainty evidence suggests that use of antihypertensive drug(s) probably halves the risk of developing severe hypertension (RR 0.49; 95% confidence interval (CI) 0.40 to 0.60; 20 trials, 2558 women), but may have little or no effect on the risk of proteinuria/pre-eclampsia (average RR 0.92; 95% CI 0.75 to 1.14; 23 trials, 2851 women; low-certainty evidence).[3] Moderate-certainty evidence also shows that antihypertensive drug(s) probably have little or no effect in the risk of total reported fetal or neonatal death (including miscarriage) (average RR 0.72; 95% CI 0.50 to 1.04; 29 trials, 3365 women), small-for-gestational-age babies (RR 0.96; 95% CI 0.78 to 1.18; 21 trials, 2686 babies) or preterm birth less than 37 weeks (average RR 0.96; 95% CI 0.83 to 1.12; 15 trials, 2141 women).[3]

Secondary outcomes: the effect of antihypertensive drug(s) is uncertain on the risk of maternal death, severe pre-eclampsia , or eclampsia, or impaired long-term growth and development of the baby in infancy and childhood , because the certainty of this evidence is very low.[3] There may be little or no effect on the risk of changed/stopped drugs due to maternal side-effects, or admission to neonatal or intensive care nursery (low-certainty evidence). There is probably little or no difference in the risk of elective delivery (moderate-certainty evidence).[3]

- Antihypertensive Drug Versus Another Antihypertensive Drug (29 Trials, 2774 Women)

Primary outcomes: beta-blockers and CCBs together in the meta-analysis appear to be more effective than methyldopa in avoiding an episode of severe hypertension (RR 0.70; 95% CI 0.56 to 0.88; 11 trials, 638 women).[3] There was also an increase in this risk when other antihypertensive drugs were compared with CCBs (RR 1.86; 95% CI 1.09 to 3.15; 5 trials, 223 women), but no evidence of a difference when methyldopa and CCBs together were compared with beta-blockers (RR 1.18, 95% CI 0.95 to 1.48; 10 trials, 692 women).[3] No evidence of a difference in the risk of proteinuria/pre-eclampsia was found when alternative drugs were compared with methyldopa (average RR 0.78; 95% CI 0.58 to 1.06; 11 trials, 997 women), with CCBs (average RR: 1.24, 95% CI 0.70 to 2.19; 5 trials, 375 women), or with beta-blockers (average RR 1.21, 95% CI 0.88 to 1.67; 12 trials, 1107 women).[3]

For the babies, there was no evidence of a difference in the risk of total reported fetal or neonatal death (including miscarriage) when comparing other antihypertensive drugs with methyldopa (average RR 0.77, 95% CI 0.52 to 1.14; 22 trials, 1791 babies), with CCBs (average RR 0.90, 95% CI 0.52 to 1.57; 9 trials,

700 babies), or with beta-blockers (average RR: 1.23, 95% CI 0.81 to 1.88; 19 trials, 1652 babies); nor in the risk for small-for-gestational age in the comparison with methyldopa (average RR 0.79, 95% CI 0.52 to 1.20; 7 trials, 597 babies), with CCBs (average RR 1.05, 95% CI 0.64 to 1.73; 4 trials, 200 babies), or with beta-blockers (average RR 1.13, 95% CI 0.80 to 1.60; 7 trials, 680 babies).[3] No evidence of an overall difference among groups in the risk of preterm birth (less than 37 weeks) was found in the comparison with methyldopa (average RR: 0.91; 95% CI 0.68 to 1.22; 11 trials, 835 women), with CCBs (average RR 0.85, 95% CI 0.59 to 1.23; 6 trials, 330 women), or with beta-blockers (average RR 1.22, 95% CI 0.90 to 1.66; 9 trials, 806 women).[3]

In summary, moderate certainty evidence shows that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension.[3] Based on low to moderate certainty evidence, the effect on other clinically important outcomes (proteinuria, preeclampsia, maternal death, impaired fetal growth, fetal death) remains unclear.[3] Moderate certainty evidence shows that If antihypertensive drugs are used, beta-blockers and CCBs appear to be more effective than the alternatives (i.e. methyldopa) for preventing severe hypertension.[3]

After review, 42 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), network meta-analysis, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines (2025)

This 2025 update replaces the 2017 guidance. High BP is the most prevalent and modifiable risk factor for the development of CVD, including coronary artery disease, CHF, atrial fibrillation, stroke, dementia, CKD, and all-cause mortality.[4] The overarching BP treatment goal is less than 130/80 mm Hg for all adults, with additional considerations for those who require institutional care, have a limited predicted lifespan, or are pregnant.[4] For a given BP level, absolute risk for cardiovascular disease (CVD) varies according to age, sex, and presence of CVD or CVD risk factors.[4] Therefore, the decision to initiate antihypertensive treatment should be based on BP level and risk.[4] Based on BP level alone, all adults with hypertension benefit from antihypertensive therapy at a threshold greater than or equal to 140/90 mm Hg.[4] Adults with hypertension and clinical CVD (coronary heart disease, stroke, or CHF) are at increased risk for CVD events and benefit from antihypertensive therapy at a lower BP threshold of 130/80 mm Hg or greater to prevent recurrent events.[4] Among adults without clinical CVD, identification of patients at increased risk for CVD selects those who derive greatest benefit from antihypertensive therapy at a threshold of 130/80 mm Hg or greater.[4] Adults with hypertension are defined at increased risk if they have diabetes, CKD, or an estimated 10-year CVD risk of 7.5% and higher, according to PREVENT (Predicting Risk of CVD EVENTs).[4]

PREVENT was derived from contemporary data from 3.2 million individuals with baseline examinations from 1992 to 2022 and included a diverse sample of racial and ethnic groups.[4] PREVENT estimates risk for total CVD (MI, stroke, and heart failure), which is especially relevant as trials evaluating antihypertensive therapies and BP thresholds have focused on major adverse cardiovascular events (MACE) as the primary outcome.[4] PREVENT incorporates measures of kidney function, as CKD is an important end-organ manifestation of hypertension and is associated with higher CVD risk.[4] PREVENT includes the integration of place-based social risk using the social deprivation index (SDI), as the burden of hypertension is higher among those who reside in neighborhoods with higher deprivation.[4]

For all adults with stage 2 hypertension, the initiation of antihypertensive drug therapy with 2 first-line agents of different classes in a single-pill, fixed-dose combination is preferred over 2 separate pills to improve adherence and reduce time to achieve BP control.[4] Severe hypertension in nonpregnant individuals,

defined as BP greater than 180/120 mm Hg, without evidence of acute target organ damage, should be evaluated and treated in the outpatient setting with initiation, reinstitution, or intensification of oral antihypertensive medications in a timely manner.[4]

When initiating pharmacological therapy, primary consideration should be given to comorbidities (e.g., coronary artery disease, heart failure, stroke, diabetes, CKD) for which specific BP-lowering medication classes are indicated.[4] Strong RCT evidence supports 4 classes of first-line agents compared with placebo (thiazide-type diuretics, long-acting dihydropyridine CCBs, ACE inhibitors, and ARBs) due to their favorable profiles for BP lowering, CVD prevention, and tolerability.[4] Beta-blockers were less effective than first-line antihypertensive classes in preventing strokes and had a less favorable side effect profile; therefore, they should be reserved for adults with compelling indications (i.e., post-MI, heart failure).[4] American Heart Association guidance (2022) recommends that in patients with hypertension and HFrEF, even if asymptomatic, use 1 of the 3 beta-blockers proven to reduce mortality and hospitalizations (bisoprolol, carvedilol, metoprolol succinate) is preferred.[15] Throughout the ACC/AHA guideline, the term thiazide-type diuretic is used to collectively refer to HCTZ, chlorthalidone, and indapamide.[4] The interchangeability of thiazide-type and -like agents remains a debated topic.[4]

ACC/AHA pharmacologic recommendations that specifically cite beta-blockers and CCBs are summarized below. Descriptions of the recommendations and level of evidence are summarized afterward in **Table 1.**

- For adults initiating antihypertensive drug therapy, thiazide-type diuretics, long acting dihydropyridine CCB, and ACE inhibitor or ARB are recommended as first-line therapy to prevent CVD. (COR: 1; LOE: A).[4]
- In adults with Stage 2 hypertension (SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg) initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination, is recommended to improve BP control and adherence (COR: 1; LOE: B-R).[4]
- In adults with Stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control (COR: 2a; LOE: C-EO).[4]
- In adults with hypertension, simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor in combination is not recommended due to the potential for harm. (COR: Harm; LOE: A).[4]
- In adults with uncontrolled hypertension who cannot tolerate or have contraindications to a MRA, the addition of one of the following agents or classes – amiloride, beta-blockers, alpha-blockers, central sympatholytic drugs, dual endothelin receptor antagonist, or direct vasodilator – is reasonable to control BP. (COR: 2a; LOE: B-NR)[4]

Table 1. Descriptions for the Strength of Recommendations and Level of Evidence in ACC/AHA Guidance[4]

Class of Recommendation	**Class 1 (Strong)**	**Class 2a (Moderate)**	**Class 2b (Weak)**	**Class 3 - No Benefit (Moderate)**	**Class 3 - Harm (Strong)**
Benefit/Risk Ratio	Benefit >>> Risk	Benefit >> Risk	Benefit $\geq$ Risk	Benefit = Risk	Risk > Benefit
Level of Evidence	**A**	**B-R (Randomized)**	**Level B-NR (Non-randomized)**	**Level C-LD (Limited Data)**	**Level C-EO (Expert Opinion)**
Source	• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs	• Moderate-quality evidence from 1 or more RCTs	• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies,	• Randomized or nonrandomized observational or registry studies with limitations of design or execution	• Consensus of expert opinion based on clinical experience

	• One or more RCTs corroborated by high-quality registry studies	• Meta-analyses of moderate-quality RCTs	observational studies, or registry studies • Meta-analyses of such studies	• Meta-analyses of such studies; or physiological or mechanistic studies in human subjects	
Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; RCT = randomized controlled trial					

European Society Of Cardiology Guidelines for the Management Of Elevated Blood Pressure and Hypertension (2024)

One of the most important changes in the ESC 2024 Guidelines is the focus on evidence related to CVD outcomes of BP-lowering interventions rather than BP lowering alone.[5] The major drug classes with robust evidence for BP-mediated reduction in CVD events are ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics (thiazides and thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide), and beta-blockers.[5] The first 4 medications are recommended as first-line options for starting hypertension treatment in the general population.[5] Beta-blockers can be added preferentially in circumstances such as in the presence of angina or heart failure, after myocardial infarction, or for controlling heart rate, where they are the cornerstone of therapy.[5] In such settings, second-generation (cardioselective) and, specifically, third-generation (vasodilating) beta-blockers are preferred.[5] However, beta-blockers are less effective than ACE inhibitors, ARBs, CCBs, or diuretics at preventing stroke, and have a higher discontinuation rate due to side effects.[5] Beta-blockers and diuretics, especially when combined, are associated with an increased risk of new-onset diabetes in predisposed patients.[5] The effect of RAS blockers and CCBs on preventing progression of hypertension-mediated organ damage also appears to be superior to beta-blockers.[5] Beta-blockers should also be avoided in patients with isolated systolic hypertension or more generally with arterial stiffness, as they increase stroke volume (given the lower heart rate).[5]

To treat hypertension, many patients will require more than one BP-lowering medication. Combining drugs from different drug classes can have additive or synergistic effects and lead to greater BP reduction than increasing the dose of one drug.[5] The superior BP-lowering efficacy of combination therapy is mediated, at least in part, by the potential of combination therapy to target multiple pathophysiological pathways contributing to perturbed BP in each patient.[5] A further benefit of combination therapy is the potential to use lower doses of each individual BP-lowering agent, which may reduce side effects and improve adherence and persistence, though the evidence for this hypothesis has been questioned.[5] Another caveat is that the evidence for reduced CVD outcomes with BP-lowering drugs in combination therapy is based on observational studies.[5] There are no outcomes data from prospective trials that prove superiority of upfront combination therapy (either as single-pill combinations or as separate pills) over upfront monotherapy in the isolated treatment of hypertension.[5] If combination BP-lowering therapy is pursued, single-pill combinations are preferred.[5]

The magnitude of BP reduction achieved with the main classes of BP-lowering medications (ACE inhibitors, ARBs, dihydropyridine CCBs, diuretics, and beta-blockers) as monotherapy is similar overall.[5] Blood pressure reduction with standard doses of any of these 5 classes can be expected to be approximately 9/5 mmHg with office BP and 5/3 mmHg with ambulatory BP monitoring.[5] These BP-lowering effects may attenuate over time.[5] Combination therapy (e.g. with 3 drugs at half standard dose) over the short term can lower office BP by up to 20/11 mmHg.[5] The pharmacologic recommendations for treating hypertension are presented in **Table 2**. The definitions for the recommendations and level of evidence used to guide the recommendations are summarized below.

Classes of Recommendations[5]

Class I: Evidence and/or general agreement that a given treatment is beneficial, useful, effective.
Class II: Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a given treatment.
Class IIa: Weight of evidence is in favor of usefulness/efficacy
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Evidence or general agreement that the given treatment is not useful/effective, and in some cases may be harmful.

Levels of Evidence[5]
A: Data derived from multiple RCTs or meta-analyses
B: Data derived from a single RCT or large non-randomized studies
C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Table 2. ESC Guidance for Pharmacological Treatment of Hypertension[5]

Recommendation	Class of Recommendation	Level of Evidence
Among all BP-lowering drugs, ACE inhibitors, ARBs, dihydropyridine CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated the most effective reduction of BP and CVD events, and are therefore recommended as first-line treatments to lower BP.	I	A
It is recommended that beta-blockers are combined with any of the other major BP-lowering classes when there are other compelling indications for their use, e.g., angina, post myocardial infarction, heart failure with reduced ejection fraction, or for heart rate control.	I	A
Given trial evidence for more effective BP control versus monotherapy, combination BP-lowering treatment is recommended for most patients with confirmed hypertension (BP> 140/90 mm Hg) as initial therapy. Preferred combinations are RAS blockers (either an ACEI or ARB) with a dihydropyridine CCB or diuretic. Exceptions to consider included patients aged ≥ 85 years, those with symptomatic orthostatic hypotension, moderate-to-severe frailty, or elevated BP (systolic BP 120-129 mm Hg or diastolic BP 70-89 mm Hg) with a concomitant indication for treatment.	I	B
In patients receiving combination BP-lowering treatment, fixed-dose single-pill combination treatment is recommended.	I	B
If BP is not controlled with a two-drug combination, increasing to a three-drug combination is recommended, usually a RAS blocker with a dihydropyridine CCB and thiazide/thiazide-like diuretic, and preferably in a single-pill combination.	I	B
If BP is not controlled with a three-drug combination, adding spironolactone should be considered.	IIa	B
If BP is not controlled with a three-drug combination and in whom spironolactone is not effective or tolerated, treatment with eplerenone instead of spironolactone, or the addition of a beta-blocker if not already indicated and, net a centrally acting BP medications, an alpha-blocker, hydralazine or potassium-sparing diuretic should be considered.	IIa	B
Combining two RAS blockers (ACEI and ARB) is not recommended.	III	A
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; ESC = European Society of Cardiology; RAS = renin-angiotensin system		

Veterans Affairs/Department of Defense: Diagnosis and Management of Hypertension in Primary Care (2020)
This guideline updated hypertension recommendations that were published in 2014. The guideline working group, on the basis of their review of the literature, defined hypertension as an SBP of 130 mm Hg or greater or a DBP of 90 mm Hg or greater.[6] Evidence supports the use of a thiazide-type diuretic, a CCB, or either an ACE inhibitor or an ARB as primary pharmacologic therapy for hypertension.[6] The effects of the various antihypertensive drug classes on reducing composite CV outcomes, and not just differences in blood pressure–lowering effect, were the focus of the recommendation.[6] Although individual outcomes, such as heart failure or stroke, showed differences between classes, these individual differences were not significant when combined into the composite outcome, when age or ethnicity was not considered.[6] Therefore, for the overall reduction in CV outcomes, any of the antihypertensive drug therapies in the classes mentioned are reasonable first-, second-, or third-line therapy when data from all ages and ethnicities are considered together.[6]

Resistant hypertension (RHT) is defined as blood pressure not adequately controlled with a maximally tolerated dose of triple therapy (a thiazide-type diuretic, a CCB, and either an ACE inhibitor or an ARB).[6] Before adding a fourth drug to the treatment regimen, medication adherence should be assessed and the benefits of nonpharmacologic therapy should be reinforced in every patient who meets the criteria for RHT.[6] For patients with confirmed RHT, the addition of the MRA spironolactone is suggested for additional blood pressure reduction.[6] Drugs other than spironolactone may be more appropriate for patients with RHT who have a history of hyperkalemia, clinically significantly impaired kidney function, or sexual dysfunction or have developed either mastodynia or gynecomastia upon exposure to this drug in the past.[6] Specific goals of therapy and pharmacologic treatment recommendations are summarized in **Table 3**.

Table 3. Veterans Affairs/Department of Defense Recommendations for Hypertension Management[6]

Recommendation	Strength of the Recommendation
For all patients, including those with type 2 diabetes, we suggest treating them to a systolic blood pressure goal <130 mm Hg	Weak For
For patients 60 years and older, we recommend treating to a systolic blood pressure goal of < 150 mm Hg with added benefit to lowering systolic blood pressure further for those between 130 mm Hg and 150 mm Hg.	Strong For
For patients 60 years and older with type 2 diabetes, we recommend treating systolic blood pressure to a goal of < 140 mm Hg with added benefit to lowering systolic blood pressure further for those between 130 mm Hg and 140 mm Hg.	Strong For
For patients 30 years and over, we recommend treating to diastolic blood pressure goal of < 90 mm Hg.	Strong For
We recommend offering a thiazide-type diuretic, calcium channel blocker, or either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker as primary pharmacologic therapy for hypertension for reduction in composite cardiovascular outcomes.	Strong For
In African American patients with hypertension, we recommend against using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker as monotherapy.	Strong Against
In hypertensive patients 65 years and over, we suggest a thiazide type diuretic for reduction in composite cardiovascular outcomes.	Weak For
We recommend against more than one of the following 3 drug classes together in the same patient: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.	Strong Against
For the treatment of hypertension, there is insufficient evidence to recommend for or against initiating combination therapy over initiating monotherapy with the sequential addition of another medication	Neither For Nor Against
For patients with resistant hypertension (defined as those who are not adequately controlled with maximally tolerated dose of triple therapy [i.e., a thiazide-type diuretic, calcium channel blockers, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker]), we suggest adding spironolactone in those patients without contraindications.	Weak For

National Institute for Health and Care Excellence: Hypertension Management in Adults (2019)

NICE guidance for hypertension was updated in 2019, with additional updates in 2026.[7] All the guidance presented below is from 2019.

- Offer antihypertensive drug treatment in addition to lifestyle advice to adults of any age with persistent stage 2 hypertension (clinic BP of 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ambulatory BP monitoring daytime average or home BP monitoring average blood pressure of 150/95 mmHg or higher).[7]
- Discuss starting antihypertensive drug treatment, in addition to lifestyle advice, with adults aged under 80 years with persistent stage 1 hypertension

(clinic BP ranging from 140/90 mm Hg to 159/99 mm Hg and subsequent ambulatory BP monitoring daytime average or home BP monitoring average ranging from 135/85 mm Hg to 149/94 mm Hg) who have 1 or more of the following: target organ damage, established CVD, renal disease, diabetes, or an estimated 10-year risk of CVD of 10% or more.[7]

- Offer an ARB or ACE inhibitor (titrate to the highest licensed dose that the person can tolerate) to adults, children, and young people with CKD and hypertension.[7]
- Offer an ACE inhibitor or ARB to adults starting step 1 antihypertensive treatment who have type 2 diabetes and are of any age or family origin or are aged under 55 years but not of Black African or African-Caribbean family origin.[7]
- When choosing antihypertensive drug treatment for adults of Black African or African-Caribbean family origin, consider an ARB in preference to an ACE inhibitor.[7]
- Do not combine an ACE inhibitor with an ARB to treat hypertension.[7]
- Offer a CCB to adults starting step 1 antihypertensive treatment who are aged 55 years and over and do not have type 2 diabetes or are of Black African or African-Caribbean family origin and do not have type 2 diabetes (of any age).[7]
- If a CCB is not tolerated, for example because of edema, offer a thiazide-like diuretic to treat hypertension.[7]
- If starting or changing diuretic treatment for hypertension, offer a thiazide-like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as HCTZ.[7]
- If hypertension is not controlled in adults taking step 1 treatment of an ACE inhibitor or ARB, offer a choice of a CCB or thiazide-like diuretic in addition to step 1 treatment.[7]
- If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or ARB plus CCB and a thiazide-like diuretic, regard them as having resistant hypertension. Consider adding an alpha-blocker or beta-blocker for adults with resistant hypertension who have a blood potassium level greater than 4.5 mmol/L.[7]
- Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following: labetalol (oral or intravenous), oral nifedipine, or intravenous hydralazine.[7]
- For secondary prevention, offer people who have had an MI treatment with an ACE inhibitor, dual platelet therapy (unless they have a separate indication for anticoagulation), beta-blocker and statin.[7]
- For people with HFrEF offer an ACE inhibitor, beta-blocker, MRA, and sodium glucose transporter-2 (SGLT2) inhibitor.[7]
- Offer either a beta-blocker or CCB as first-line treatment for stable angina. If the person cannot tolerate the beta-blocker or CCB, consider switching to the other option (CCB or beta-blocker).[7]
- First line therapy for hypertension in adults with type 1 diabetes is a RAS blocking drug.[7]

Additional Guidelines for Clinical Context:
After review, 5 guidelines were excluded due to poor quality.[21-25]

New Formulations:
12/2025: A new 10 mg/mL oral solution of LOPRESSOR (metoprolol) received FDA approval, indicated for the treatment of adults with hypertension, in the long-term treatment of angina pectoris, and the in the treatment of hemodynamically stable patients with definite or suspected MI, to reduce the risk of CV mortality when used in conjunction with intravenous metoprolol therapy.[8] The manufacturer did not conduct non-clinical and clinical studies for this new formulation and relied on the FDA's finding of safety and effectiveness metoprolol tablets.

7/2025: The FDA approved SDAMLO, new unit-dose oral solution formulation of amlodipine.[9] This product is supplied in 2.5 mg, 5 mg, and 10 mg unit of use bottles that each contain amlodipine powder that must be reconstituted prior to administration.[9] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[9] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. The New Drug Application (NDA) was supported by a relative comparative bioavailability study of SDAMLO oral solution 5 mg and amlodipine 5 mg tablets.

6/2025: A new triple combination oral tablet, WIDAPLIK (telmisartan/amlodipine/indapamide) received FDA-approval, indicated for the treatment of hypertension in adults [10] The product is available in 3 strengths containing telmisartan/amlodipine, and indapamide in the following combinations: 10 mg/1.25 mg/0.625 mg; 20 mg/2.5 mg/1.25 mg; and 40 mg/5 mg/2.5 mg.[10] The efficacy of WIDAPLIK in lowering BP was evaluated in a randomized study designed to evaluate the efficacy and safety of two doses of WIDAPLIK (10 mg/1.25 mg/0.625 mg and 20 mg/2.5 mg/1.25 mg) compared to placebo (Study 1, NCT04518306) and in a randomized study designed to evaluate the efficacy and safety of WIDAPLIK (40 mg/5 mg/2.5 mg) as compared to each of its two-drug combinations at the same doses (Study 2, NCT04518293).[10]

In Study 1, the primary endpoint was the change from baseline to Week 4 in home SBP.[10] Both doses of WIDAPLIK showed statistically significant greater reductions in home SBP compared to placebo (see **Table 4).**

Table 4. Change From Baseline to Week 4 in Systolic Blood Pressure With Triple Therapy vs. Placebo in Study 1[10]

Systolic Blood Pressure (mm Hg)	**Placebo N=63**	**Telmisartan/Amlodipine/Indapamide 10 mg/1.25 mg/0.625 mg N=113**	**Telmisartan/Amlodipine/Indapamide 20 mg/2.25 mg/1.25 mg N=119**
Baseline, Mean	138.7	138.4	138.8
Week 4, Mean	136.4	129.2	128.0
LSM Change from Baseline	-2.2	-9.6	-10.4
LSM Difference Vs. Placebo		-7.3 (95% CI -10.2 to 0.45) P<0.001	-8.2 (95% CI -11.3 to -5.2) P<0.001
Abbreviations: CI = confidence interval; Hg = mercury; mg = milligrams; mm = millimeters; LSM = least-squares mean; N = number; NR = not reported			

In Study 2, the primary endpoint was the change in home seated mean SBP from baseline to Week 12.[10] WIDAPLIK (40 mg/5 mg/2.5 mg) showed statistically significant greater reductions in home SBP compared to each of the dual combinations (see **Table 5**).[10]

Table 5. Change From Baseline to Week 12 in Blood Pressure with Triple Therapy vs. Dual Therapy in Study 2[10]

Systolic Blood Pressure (mm Hg)	**Telmisartan/Amlodipine/Indapamide 10 mg/1.25 mg/0.625 mg N=551**	**Telmisartan/Indapamide 40 mg/2.5 mg N=276**	**Telmisartan/Amlodipine 40 mg/5 mg N=282**	**Amlodipine/Indapamide 5 mg/2.5 mg N=276**
Baseline, Mean	128.7	128.9	128.4	129.2

Week 4, Mean	124.0	126.5	129.4	128.8
LSM Change from Baseline	-4.0	-1.5	1.4	0.5
LSM Difference vs. Dual Comparator		-2.5 (95% CI -3.7 to -1.3) P<0.0001	-5.4 (95% CI -6.8 to -4.1) P<0.0001	-4.4 (-5.8 to -3.1) P<0.0001
Abbreviations: CI = confidence interval; Hg = mercury; mg = milligrams; mm = millimeters; LSM = least-squares mean; N = number				

There are no studies of WIDAPLIK demonstrating reductions in CV risk in patients with hypertension; however, previous studies with amlodipine, indapamide and several angiotensin II receptor blockers, which are in the same pharmacological class as the telmisartan component, have demonstrated such benefits.[10] Safety data were obtained from two placebo-controlled RCTS that included 1,680 patients with hypertension of whom 782 received WIDAPLIK.[10] Symptomatic hypotension, hyponatremia, and hypokalemia were more common with active treatment than placebo.[10] Most cases were mild to moderate in severity.[10]

2/2022: The FDA approved NORLIQVA, new 1 mg/mL oral solution formulation of amlodipine.[11] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[11] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA.

12/2019: A new medication, CONJPRI, levamlodipine oral tablets were FDA-approved to treat hypertension in adults and pediatric patients aged 6 years an older either alone or in combination with other antihypertensive agents.[12] Levamlodipine is an active isomer of amlodipine.[12] The recommended adult starting dose is 2.5 mg orally once daily with a maximum dose of 5 mg once daily.[12] The recommended pediatric dose is 1.25 mg to 2.5 mg once daily.[12] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA. Levamlodipine has been approved and marketed in China since 2003.[12] There is no evidence that levamlodipine is more effective than amlodipine.

7/2019: The FDA approved KATERZIA, new 1 mg/mL oral solution formulation of amlodipine.[13] This product is indicated for the treatment of hypertension in adults and children 6 years of age and older, for management of coronary artery disease in patients without heart failure or an ejection fraction < 40% and symptomatic treatment of vasospastic and chronic stable angina.[13] The approval of this product was based upon previous findings for the safety and effectiveness of amlodipine tablets for the approved indications. No new clinical efficacy data was submitted to the FDA in the NDA.

6/2016: The FDA approved an oral tablet combination product, BYVALSON (nebivolol/valsartan 5mg/80mg), indicated for the treatment of hypertension.[14] BYVALSON was studied in a Phase 3, double-blind, placebo-controlled, dose-escalating, 8-week study in 4,161 patients with Stage 1 or 2 hypertension.[14] Patients were initially randomized to 1 of 8 treatment groups including: 3 fixed-dose combinations of nebivolol and valsartan (5 mg/ 80 mg, 5 mg/ 160 mg, 10 mg/ 160 mg), nebivolol monotherapy (5 mg, 20 mg), valsartan monotherapy (80 mg, 160 mg), or placebo. After 4 weeks of treatment, all doses were doubled in the fixed-dose combination. groups (to 10 mg/ 160 mg, 10 mg/ 320 mg, and 20 mg/ 320 mg), nebivolol monotherapy groups (to 10 mg, 40 mg), and valsartan monotherapy groups (to 160 mg, 320 mg).[14] Treatment with BYVALSON 5 mg/ 80 mg for 4 weeks resulted in placebo-adjusted reductions from baseline in SBP and DBP of -8.3 and -7.2 mmHg, respectively.[14] Treatment with BYVALSON 5 mg/ 80 mg resulted in greater reductions in SBP and DBP than did treatment with nebivolol 5 mg alone (p<0.0001 for both SBP and DBP) or valsartan 80 mg, alone (p=0.0007 for SBP and p<0.0001 for DBP).[14]

The safety of the 5 mg/ 80 mg dose of nebivolol/valsartan was evaluated during the first 4 weeks of the 8-week placebo-controlled trial. During the 4-week period, the overall incidence of adverse events on therapy with BYVALSON 5 mg/ 80 mg was similar to placebo and the individual components (nebivolol 5 mg and valsartan 80 mg).[14] Discontinuation of therapy due to a clinical adverse event occurred in 2.0% of patients treated with BYVALSON 5 mg/ 80 mg versus 3.2% of patients given placebo and approximately 1% of patients given nebivolol 5 mg or valsartan 80 mg as monotherapy.[14]

New FDA Safety Alerts:

Table 6. Description of New FDA Safety Alerts[26]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Metoprolol	KAPSPARGO LOPRESSOR TOPROL XL	4/2023	Warnings and Precautions	**Anaphylactic Reaction** While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction. **Bradycardia** Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of metoprolol succinate. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff-Parkinson-White) or on concomitant drugs that cause bradycardia, may be at increased risk. Monitor heart rate in patients receiving metoprolol succinate. If severe bradycardia develops, reduce or stop metoprolol succinate. **Hypoglycemia** Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.
Esmolol	BREVIBLOC	5/2024	Warnings and Precautions	**Hypoglycemia** Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

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10. WIDAPLIK (telmisartan, amlodipine, and indapamide) oral tablets. Prescribing Information. Pradesh, India; Piramal Pharma Limited. 6/2025.
11. NORLIQVA (amlodipine) oral solution. Prescribing Information. Farmville, NC; CMP Pharma, Inc. 2/2022.
12. CONJUPRI (levamlodipine) oral tablets. Prescribing Information. Hebei Province, China; CSPC Ouyi Pharmaceutical Co., Ltd. 12/2019.
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Appendix 1: Current Preferred Drug List

Combination Antihypertensives

Generic	Brand	Form	PDL
amlodipine bes/olmesartan med	AMLODIPINE-OLMESARTAN	TABLET	Y
amlodipine bes/olmesartan med	AZOR	TABLET	Y
benazepril/hydrochlorothiazide	BENAZEPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
benazepril/hydrochlorothiazide	LOTENSIN HCT	TABLET	Y
enalapril/hydrochlorothiazide	ENALAPRIL MALEATE/HCTZ	TABLET	Y
enalapril/hydrochlorothiazide	ENALAPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
lisinopril/hydrochlorothiazide	LISINOPRIL-HYDROCHLOROTHIAZIDE	TABLET	Y
lisinopril/hydrochlorothiazide	ZESTORETIC	TABLET	Y
losartan/hydrochlorothiazide	HYZAAR	TABLET	Y
losartan/hydrochlorothiazide	LOSARTAN-HYDROCHLOROTHIAZIDE	TABLET	Y
olmesartan/amlodipin/hcthiazid	OLMESARTAN-AMLODIPINE-HCTZ	TABLET	Y
olmesartan/amlodipin/hcthiazid	TRIBENZOR	TABLET	Y
olmesartan/hydrochlorothiazide	BENICAR HCT	TABLET	Y
olmesartan/hydrochlorothiazide	OLMESARTAN-HYDROCHLOROTHIAZIDE	TABLET	Y
telmisartan/hydrochlorothiazid	MICARDIS HCT	TABLET	Y
telmisartan/hydrochlorothiazid	TELMISARTAN-HYDROCHLOROTHIAZID	TABLET	Y
amlodipine besylate/benazepril	AMLODIPINE BESYLATE-BENAZEPRIL	CAPSULE	N
amlodipine besylate/benazepril	LOTREL	CAPSULE	N
amlodipine besylate/valsartan	AMLODIPINE-VALSARTAN	TABLET	N
amlodipine besylate/valsartan	EXFORGE	TABLET	N
amlodipine/atorvastatin	AMLODIPINE-ATORVASTATIN	TABLET	N
amlodipine/atorvastatin	CADUET	TABLET	N
amlodipine/valsartan/hcthiazid	AMLODIPINE-VALSARTAN-HCTZ	TABLET	N
atenolol/chlorthalidone	ATENOLOL W/CHLORTHALIDONE	TABLET	N
atenolol/chlorthalidone	ATENOLOL-CHLORTHALIDONE	TABLET	N
atenolol/chlorthalidone	TENORETIC 100	TABLET	N
atenolol/chlorthalidone	TENORETIC 50	TABLET	N
azilsartan med/chlorthalidone	EDARBYCLOR	TABLET	N
bisoprolol/hydrochlorothiazide	BISOPROLOL FUMARATE/HCTZ	TABLET	N
bisoprolol/hydrochlorothiazide	BISOPROLOL-HYDROCHLOROTHIAZIDE	TABLET	N
candesartan/hydrochlorothiazid	ATACAND HCT	TABLET	N
candesartan/hydrochlorothiazid	CANDESARTAN-HYDROCHLOROTHIAZID	TABLET	N
captopril/hydrochlorothiazide	CAPTOPRIL/HYDROCHLOROTHIAZIDE	TABLET	N
captopril/hydrochlorothiazide	CAPTOPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
fosinopril/hydrochlorothiazide	FOSINOPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
irbesartan/hydrochlorothiazide	AVALIDE	TABLET	N
irbesartan/hydrochlorothiazide	IRBESARTAN-HYDROCHLOROTHIAZIDE	TABLET	N

metoprolol/hydrochlorothiazide	METOPROLOL-HYDROCHLOROTHIAZIDE	TABLET	N
propranolol/hydrochlorothiazid	PROPRANOLOL HCL W/HCTZ	TABLET	N
quinapril/hydrochlorothiazide	ACCURETIC	TABLET	N
quinapril/hydrochlorothiazide	QUINAPRIL-HYDROCHLOROTHIAZIDE	TABLET	N
telmisartan/amlodipine	TELMISARTAN-AMLODIPINE	TABLET	N
trandolapril/verapamil HCl	TRANDOLAPRIL-VERAPAMIL ER	TAB BP 24H	N
valsartan/hydrochlorothiazide	DIOVAN HCT	TABLET	N
valsartan/hydrochlorothiazide	VALSARTAN-HYDROCHLOROTHIAZIDE	TABLET	N
telmisartan/amlodipine/indapam	WIDAPLIK	TABLET	

Calcium Channel Blockers – Dihydropyridine, Oral

Generic	Brand	Form	PDL
amlodipine besylate	AMLODIPINE BESYLATE	TABLET	Y
amlodipine besylate	NORVASC	TABLET	Y
nicardipine HCl	NICARDIPINE HCL	CAPSULE	Y
nifedipine	NIFEDIPINE ER	TAB ER 24	Y
nifedipine	PROCARDIA XL	TAB ER 24	Y
nifedipine	NIFEDIPINE ER	TABLET ER	Y
amlodipine benzoate	KATERZIA	ORAL SUSP	N
amlodipine besylate	SDAMLO	POWDER CON	N
amlodipine besylate	NORLIQVA	SOLUTION	N
felodipine	FELODIPINE ER	TAB ER 24H	N
isradipine	ISRADIPINE	CAPSULE	N
levamlodipine maleate	LEVAMLODIPINE MALEATE	TABLET	N
nifedipine	NIFEDIPINE	CAPSULE	N
nisoldipine	NISOLDIPINE	TAB ER 24H	N
nisoldipine	SULAR	TAB ER 24H	N
nimodipine	NIMODIPINE	CAPSULE	
nimodipine	NIMOTOP	CAPSULE	
nimodipine	NIMODIPINE	SOLUTION	
nimodipine	NYMALIZE	SOLUTION	N
nimodipine	NYMALIZE	SYRINGE	N

Calcium Channel Blockers – Non-dihydropyridine, Oral

Generic	Brand	Form	PDL
diltiazem HCl	CARDIZEM SR	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM 12HR ER	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM 12HR ER	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 12H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 12H	Y

diltiazem HCl	CARDIZEM CD	CAP ER 24H	Y
diltiazem HCl	CARTIA XT	CAP ER 24H	Y
diltiazem HCl	CARTIA XT	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER (CD)	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER (CD)	CAP ER 24H	Y
diltiazem HCl	DILTIAZEM HCL	CAP ER 24H	Y
diltiazem HCl	DILACOR XR	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER (XR)	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER (XR)	CAP ER DEG	Y
diltiazem HCl	DILT-XR	CAP ER DEG	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP SA 24H	Y
diltiazem HCl	DILTIAZEM 24HR ER	CAP SA 24H	Y
diltiazem HCl	TIADYLT ER	CAP SA 24H	Y
diltiazem HCl	TIAZAC	CAP SA 24H	Y
diltiazem HCl	CARDIZEM	TABLET	Y
diltiazem HCl	DILTIAZEM HCL	TABLET	Y
diltiazem HCl	DILTIAZEM HCL	TABLET	Y
verapamil HCl	VERAPAMIL ER	CAP24H PEL	Y
verapamil HCl	VERAPAMIL HCL	CAP24H PEL	Y
verapamil HCl	VERAPAMIL SR	CAP24H PEL	Y
verapamil HCl	VERAPAMIL SR	CAP24H PEL	Y
verapamil HCl	VERAPAMIL HCL	TABLET	Y
verapamil HCl	VERAPAMIL HCL	TABLET	Y
verapamil HCl	CALAN SR	TABLET ER	Y
verapamil HCl	ISOPTIN S.R.	TABLET ER	Y
verapamil HCl	VERAPAMIL ER	TABLET ER	Y
verapamil HCl	VERAPAMIL ER	TABLET ER	Y
diltiazem HCl	CARDIZEM LA	TAB ER 24H	N
diltiazem HCl	DILTIAZEM 24HR ER (LA)	TAB ER 24H	N
diltiazem HCl	DILTIAZEM 24HR ER (LA)	TAB ER 24H	N
diltiazem HCl	MATZIM LA	TAB ER 24H	N
verapamil HCl	VERAPAMIL ER PM	CAP24H PCT	N
verapamil HCl	VERELAN PM	CAP24H PCT	N

Beta-blockers, oral

Generic	Brand	Form	PDL
acebutolol HCl	ACEBUTOLOL HCL	CAPSULE	Y
atenolol	ATENOLOL	TABLET	Y
atenolol	TENORMIN	TABLET	Y

carvedilol	CARVEDILOL	TABLET	Y
labetalol HCl	LABETALOL HCL	TABLET	Y
metoprolol succinate	METOPROLOL SUCCINATE	TAB ER 24H	Y
metoprolol succinate	TOPROL XL	TAB ER 24H	Y
metoprolol tartrate	LOPRESSOR	TABLET	Y
metoprolol tartrate	METOPROLOL TARTRATE	TABLET	Y
nadolol	NADOLOL	TABLET	Y
propranolol HCl	INDERAL LA	CAP SA 24H	Y
propranolol HCl	PROPRANOLOL HCL ER	CAP SA 24H	Y
propranolol HCl	PROPRANOLOL HCL	SOLUTION	Y
propranolol HCl	PROPRANOLOL HCL	TABLET	Y
betaxolol HCl	BETAXOLOL HCL	TABLET	N
bisoprolol fumarate	BISOPROLOL FUMARATE	TABLET	N
carvedilol phosphate	CARVEDILOL ER	CPMP 24HR	N
labetalol HCl	LABETALOL HCL	TABLET	N
metoprolol succinate	KAPSPARGO SPRINKLE	CAP SPR 24	N
metoprolol tartrate	LOPRESSOR	SOLUTION	N
metoprolol tartrate	METOPROLOL TARTRATE	TABLET	N
nebivolol HCl	BYSTOLIC	TABLET	N
nebivolol HCl	NEBIVOLOL HCL	TABLET	N
pindolol	PINDOLOL	TABLET	N
propranolol HCl	INDERAL XL	CAP ER 24H	N
propranolol HCl	INNOPRAN XL	CAP ER 24H	N
propranolol HCl	HEMANGEOL	SOLUTION	N
sotalol HCl	SOTYLIZE	SOLUTION	N
sotalol HCl	BETAPACE	TABLET	N
sotalol HCl	BETAPACE AF	TABLET	N
sotalol HCl	SOTALOL	TABLET	N
sotalol HCl	SOTALOL AF	TABLET	N
timolol maleate	BLOCADREN	TABLET	N
timolol maleate	TIMOLOL MALEATE	TABLET	N
propranolol HCl	HEMANGEOL	SOLUTION	N

Appendix 2: New Comparative Clinical Trials

A total of 110 citations were manually reviewed from the initial literature search. After further review, 110 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Beta Blockers
Ovid MEDLINE(R) ALL <1946 to May 15, 2026>

1	exp Acebutolol/	862
2	exp Atenolol/	5401
3	exp Carvedilol/	3059
4	exp Labetalol/	1969
5	exp Metoprolol/	5882
6	exp Betaxolol/	688
7	exp Bisoprolol/	1299
8	exp Nadolol/	839
9	exp Nebivolol/	919
10	exp Pindolol/	3719
11	exp Propranolol/	33401
12	exp Sotalol/	2184
13	Timolol/	3994
14	exp Administration, Oral/	167345
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	57850
16	14 and 15	2017
17	limit 16 to (english language and humans and yr="2022 -Current")	72

Calcium Channel Blockers
Ovid MEDLINE(R) ALL <1946 to May 15, 2026>

1	Calcium Channel Blockers/ or Amlodipine, Valsartan Drug Combination/ or Amlodipine Besylate, Olmesartan Medoxomil Drug Combination/ or Amlodipine/	40961
2	Nicardipine/	2624
3	Nifedipine/	16035
4	Felodipine/	1298
5	Isradipine/	1379
6	levamlodipine.mp.	33
7	nisodipine.mp.	3
8	Nimodipine/	2971
9	Diltiazem/	6384
10	Verapamil/	17149

11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	69584
12	Administration, Oral/	163357
13	11 and 12	1870
14	limit 13 to (english language and humans)	1264
15	limit 14 to yr="2015 -Current"	196
16	limit 15 to (comparative study or guideline or meta-analysis or practice guideline or "systematic review")	38

Appendix 4: Key Inclusion Criteria

Population	**Adults with hypertension**
Intervention	Beta-blockers and calcium channel blockers in Appendix 1
Comparator	Beta-blockers and calcium channel blockers in Appendix 1, diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers
Outcomes	Reductions in blood pressure
Timing	4- 8 weeks
Setting	Outpatient

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: Potassium and K-Phos, Oral

Date of Review: August 2026

Literature Search: 1/1/2014 – 6/17/2026
Date of Last Review: September 2014

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- The purpose of this literature scan is to review evidence for potassium and phosphorus supplement safety and effectiveness since the last review in 2014.
- Potassium tablets are used to treat or prevent low blood potassium (hypokalemia). Potassium is a mineral that is important for proper functioning of the heart, kidneys, muscles, nerves, and digestive system.
- Most people get enough potassium in their diet; however, low blood potassium can occur with extended vomiting or diarrhea. Some medicines, like diuretics or water pills, can remove potassium from the body, so a potassium supplement must be taken with these types of medicines.
- Side effects with potassium tablets include nausea, gas, vomiting, stomach pain, and diarrhea.
- Low blood phosphorous (hypophosphatemia) can be caused by malnutrition, alcoholism, sepsis, and diabetic ketoacidosis. Certain medications can cause low phosphorus including insulin, diuretics, and antacids. Phosphate supplements contain different ratios of sodium and potassium.
- Phosphate supplements are also used to treat high blood calcium and calcium-based kidney stones.
- Oregon Health Plan (OHP) pays for potassium chloride tablets and all phosphate replacement formulations. Providers must submit documentation to OHP to document why other potassium supplements are medically necessary. This process is called prior authorization.

Conclusions:

- No recently published high-quality systematic reviews or clinical guidelines were identified.

Recommendations:

- No changes to the Preferred Drug List (PDL) are recommended.
- Review drug costs in executive session.

Summary of Prior Reviews and Current Policy

- The Pharmacy and Therapeutics (P & T) Committee reviewed vitamins and electrolytes including potassium and phosphate at the September 2014 meeting. The following conclusions were shared with the Committee:

Author: Deanna Moretz, PharmD, BCPS

- There is moderate- to high-quality evidence that increased potassium intake reduces blood pressure in adults and low-quality evidence for reduced risk of stroke.
- It is recommended to get potassium intake from dietary sources. There is additional evidence that potassium supplementation with oral potassium supplements has no significant effect on blood pressure.
- Patients with drug-related hypokalemia (therapy with a diuretic) should receive potassium supplementation. Potassium chloride is the most effective for replacing acute potassium loss and is effective for the most common causes of potassium depletion.
- All potassium formulations (liquid and tablets) are readily absorbed.
- Potassium phosphate is most commonly used to replace phosphate losses and potassium bicarbonate is recommended in the setting of metabolic acidosis.
- Mild to moderate hypophosphatemia in ambulatory patients can be treated with oral phosphate replacement therapy. There is no evidence of improved outcomes for routine supplementation in patients without hypophosphatemia

- At that time, comparative costs were reviewed in executive session to determine preferred and non-preferred agents on the PDL. Due to different clinical considerations, different formulations of potassium salt supplements were designated as preferred. Potassium chloride packets and potassium gluconate were designated as non-preferred. Over-the-counter potassium supplements are not covered. All phosphorous products were designated as preferred.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews: No recently published, high-quality systematic reviews were identified that evaluated comparative safety and efficacy of potassium or phosphorous supplements.

After review, 16 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[1-16]

New Guidelines:
High Quality Guidelines: No new high-quality guidelines have been published to guide management of hypokalemia or hypophosphatemia.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
potassium bicarbonate/cit ac	EFFER-K	TABLET EFF	Y
potassium bicarbonate/cit ac	KLOR-CON-EF	TABLET EFF	Y
potassium chloride	KLOR-CON M10	TAB ER PRT	Y
potassium chloride	KLOR-CON M15	TAB ER PRT	Y
potassium chloride	KLOR-CON M20	TAB ER PRT	Y
potassium chloride	POTASSIUM CHLORIDE	TAB ER PRT	Y
potassium chloride	KLOR-CON 10	TABLET ER	Y
potassium chloride	KLOR-CON 8	TABLET ER	Y
potassium chloride	POTASSIUM CHLORIDE	TABLET ER	Y
potassium phosphate,monobasic	K-PHOS ORIGINAL	TABLET SOL	Y
potassium phosphate,monobasic	PHOSPHO-TRIN K500	TABLET SOL	Y
sod phos di, mono/K phos mono	K-PHOS NEUTRAL	TABLET	Y
sod phos di, mono/K phos mono	PHOSPHA 250 NEUTRAL	TABLET	Y
sod phos di, mono/K phos mono	PHOSPHO-TRIN 250 NEUTRAL	TABLET	Y
sod phos di, mono/K phos mono	WES-PHOS 250 NEUTRAL	TABLET	Y
sod phos,m-b/K phos,monob	K-PHOS NO.2	TABLET	Y
potassium bicarbonate/cit ac	EFFER-K	TABLET EFF	N
potassium chloride	POTASSIUM CHLORIDE	CAPSULE ER	N
potassium chloride	KAOCHLOR	LIQUID	N
potassium chloride	POTASSIUM CHLORIDE	LIQUID	N
potassium chloride	K-LOR	PACKET	N
potassium chloride	KLOR-CON	PACKET	N
potassium chloride	K-VESCENT	PACKET	N
potassium chloride	POKONZA	PACKET	N
potassium chloride	POTASSIUM CHLORIDE	PACKET	N
potassium chloride	POTASSIUM CHLORIDE	TABLET ER	N
potassium gluconate	KAON	ELIXIR	N
potassium	POTASSIUM	TABLET	
potassium chloride	POKONZA	LIQUID	

Appendix 2: New Comparative Clinical Trials

A total of 236 citations were manually reviewed from the initial literature search. After further review, 236 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 16, 2026>

1	potassium bicarbonate.mp. or Potassium Compounds/ or Potassium/	111099
2	Potassium Chloride/	18381
3	potassium phosphate.mp. or Phosphates/	73071
4	potassium gluconate.mp. or Hypokalemia/	9567
5	1 or 2 or 3 or 4	202788
6	limit 5 to (english language and humans and yr="2014 -Current")	12327
7	limit 6 to (guideline or practice guideline or "systematic review")	236

Ovid MEDLINE(R) ALL <1946 to June 16, 2026>

1.	exp Hypokalemia/th [Therapy]	418
2.	Hypophosphatemia/th [Therapy]	170
3.	1 or 2	579
4.	limit 3 to (english language and humans and yr="2014 -Current")	164
5.	limit 4 to (guideline or practice guideline or "systematic review")	4

ProDUR Report for April through June 2026
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	7	3	0	4	0.0%	N/A
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Syndrome	Set alert/Pay claim	2,191	471	0	1,719	1.2%	N/A
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	9,264	2,645	0	6,604	5.1%	N/A
ER (Early Refill)	**Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)**	**Set alert/Deny claim**	**112,893**	**22,322**	**118**	**90,451**	**62.3%**	**19.8%**
ID (Ingredient Duplication)	Oxycodone IR 15 mg billed and patient had Oxycodone 40 mg ER filled in past month	Set alert/Pay claim	41,932	11,016	3	30,852	23.1%	N/A
LD (Low Dose)	Divalproex 500 mg ER billed for 250 mg daily (#15 tablets for 30 day supply)	Set alert/Pay claim	950	191	0	759	0.5%	N/A
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later	Set alert/Pay claim	5	5	0	0	0.0%	N/A
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	809	226	0	583	0.4%	N/A
MX (Maximum Duration of Therapy)		Set alert/Pay claim	425	138	0	287	0.2%	N/A
PA (Drug/Age Precaution)	Products containing Codeine being billed and patient is less than 18 years of age	Set alert/Pay claim	10	3	0	7	0.0%	N/A
PG (Pregnancy/Drug Interaction)	**Accutane billed and client has recent diagnosis history of pregnancy**	**Set alert/Deny claim**	**201**	**83**	**0**	**118**	**0.1%**	**41.3%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim	Set alert/Pay claim	12,489	3,678	0	8,802	6.8%	N/A
		Totals	**181,176**					

ProDUR Report for April through June 2026
Top Drugs in Enforced DUR Alerts

Antidepressants: SSRI

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Zoloft (Sertraline)	8,947	1,606	7,341	86,034	10.4%	18.0%
ER	Lexapro (Escitalopram)	6,900	1,143	5,757	65,393	10.5%	16.6%
ER	Prozac (Fluoxetine)	6,621	1,189	5,432	66,313	10.0%	18.0%
ER	Celexa (Citalopram)	1,597	270	1,327	18,159	8.7%	16.9%

Antidepressants: Other

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Wellbutrin (Bupropion)	10,219	1,659	8,560	100,490	10.1%	16.2%
ER	Trazodone	7,842	1,601	6,240	80,648	9.7%	20.4%
ER	Cymbalta (Duloxetine)	5,420	1,006	4,413	51,999	10.4%	18.6%
ER	Effexor (Venlafaxine)	2,857	493	2,364	28,662	9.9%	17.3%
ER	Remeron (Mirtazapine)	2,515	441	2,074	20,698	12.1%	17.5%
ER	Elavil (Amitriptyline)	1,503	272	1,231	16,611	9.0%	18.1%

Antipsychotics

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Seroquel (Quetiapine)	5,547	1,341	4,206	38,135	14.5%	24.2%
ER	Abilify (Aripiprazole)	4,695	868	3,827	36,618	12.8%	18.5%
ER	Zyprexa (Olanzapine)	3,030	848	2,182	22,907	13.2%	28.0%
ER	Risperdal (Risperidone)	2,175	577	1,598	15,088	14.4%	26.5%

Anxiolytic

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Buspar (Buspirone)	4,572	757	3,815	44,642	10.2%	16.6%
ER	Lorazepam	271	61	210	12,802	2.1%	22.5%
ER	Alprazolam	146	22	124	7,198	2.0%	15.1%
ER	Diazepam	114	36	78	4,416	2.6%	31.6%

Miscellaneous

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lamictal (Lamotrigine)	7,810	1,449	6,361	60,376	12.9%	18.6%
ER	Intuniv (Guanfacine ER)	2,687	422	2,265	22,750	11.8%	15.7%
ER	Depakote (Divalproex)	1,692	467	1,225	12,720	13.3%	27.6%
ER	Suboxone (Buprenorphine/Naloxone)	97	36	61	1,555	6.2%	37.1%

ProDUR Report for April through June 2026
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC- Other
ER	April	4,943	100	275	745	7	3,632	19	8	157
ER	May	5,531	165	302	837	12	3,976	27	0	212
ER	June	4,813	215	278	711	12	3,421	14	0	162
	Total	**15,287**	**480**	**855**	**2,293**	**31**	**11,029**	**60**	**8**	**531**
	Percentage of Total Overrides		**3.1%**	**5.6%**	**15.0%**	**0.2%**	**72.1%**	**0.4%**	**0.1%**	**3.5%**

ProDUR Report for April through June 2026			
DUR Alert Cost Savings Report			
Month	**Alert Type**	**Prescriptions Not Dispensed**	**Cost Savings**
April	DC	1	$10.59
	DD	41	$3,657.84
	ER	51	$10,596.89
	ID	13	$2,962.06
	PG	1	$1,937.69
	TD	3	$7,135.29
	April	**110**	**$26,300.36**
May	DC	1	$735.49
	DD	78	$20,280.22
	ER	393	$176,618.30
	HD	2	$98.98
	ID	34	$6,259.43
	LR	1	$120.42
	MC	1	$24.90
	MX	2	$63.93
	TD	15	$3,216.08
	May Total	**527**	**$207,417.75**
June	DD	56	$8,419.55
	ER	27	$3,551.38
	HD	1	$1,960.45
	ID	4	$410.70
	TD	6	$1,369.04
	June Total	**94**	**$15,711.12**
	Total 2Q2026 Savings		**$249,429.23**

Drug Use Research & Management Program
Oregon State University
500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-1119

Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Billing Correction Review	High Cost OCC 3	Total Patients Identified	66	67	67	9
		Total Claims Identified	66	70	69	9
		Claims reviewed	16	7	10	
		Estimated Savings	$0	$0	$15,600	
	OCC 4 with OCC 2 for different NDC	Total Patients Identified	7	13	10	
		Total Claims Identified	7	14	12	
		Claims reviewed	1	2		
		Estimated Savings	$0	$0		
	OCC 4 with OCC 2 for the same NDC	Total Patients Identified	6	12	6	
		Total Claims Identified	7	13	10	
		Claims reviewed	2			
		Estimated Savings	$0			
	OCC 4 with Primary Payer Rejection Code	Total Patients Identified	8	6	7	1
		Total Claims Identified	9	6	7	1
		Claims reviewed	3	2	2	
		Estimated Savings	$0	$0	$0	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Aripiprazole Rapid Dissolve Tabs to Oral Tabs	Unique Prescribers Identified	23	29	36	4
		Unique Patients Identified	24	29	36	4
		Total Faxes Successfully Sent	20	20	23	4
		Prescriptions Changed to Recommended Within 6 Months of Intervention	10	12	7	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$10,094	$3,057	$1,123	
	Desvenlafaxine Salt Formulations	Unique Prescribers Identified	132	138	137	30
		Unique Patients Identified	138	142	139	30
		Total Faxes Successfully Sent	105	108	108	27
		Prescriptions Changed to Recommended Within 6 Months of Intervention	66	71	37	2
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$56,707	$45,448	$11,320	$441

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	965	981	1010	
		High risk patients identified	4	9	7	
		Prescribers successfully notified	4	9	5	
		Patients with continued antipsychotic therapy in the following 90 days	4	9	5	
		Patients with discontinuation of antipsychotic therapy in the following 90 days		2		

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	32	74	57	6
		Total prescribers identified	31	74	57	6
		Prescribers successfully notified	31	72	57	
		Patients with claims for the same antipsychotic within the next 90 days	12	32	27	
		Patients with claims for a different antipsychotic within the next 90 days	2	2	5	

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Retro-DUR Intervention History by Quarter FFY 2025 - 2026

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children in foster care under age 12 antipsychotic	RetroDUR Profiles Reviewed	65	55	70	
	Children in foster care under age 18 on 3 or more psychotropics	RetroDUR Profiles Reviewed	24	29	27	
	Children in foster care under age 18 on any psychotropic	RetroDUR Profiles Reviewed	150	325	219	
	Children in foster care under age 6 on any psychotropic	RetroDUR Profiles Reviewed	37	27	26	
	High Risk Patients - Bipolar	RetroDUR Profiles Reviewed	28	13	12	
		Letters Sent To Providers	19	6	10	
	High Risk Patients - Mental Health	RetroDUR Profiles Reviewed	28	25	15	
		Letters Sent To Providers	29	27	21	
	High Risk Patients - Opioids	RetroDUR Profiles Reviewed	26	23	15	
		Letters Sent To Providers	10	11	16	
	High Risk Patients - Polypharmacy	RetroDUR Profiles Reviewed	26	23	14	
		Letters Sent To Providers	8	8	6	
	Lock-In	RetroDUR Profiles Reviewed	7	7	4	
		Locked In	0	0	0	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotics for ages <=5 years	Patients identified with an ending PA	34	29	24	2
		Total prescribers identified	32	29	24	2
		Prescribers successfully notified	25	25	21	
		Patients with paid claims within next 60 days	19	23	16	
		Patients with denied claim within next 60 days	26	23	10	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	53	114	74	14
		Total prescribers identified	53	114	74	14
		Prescribers successfully notified	52	114	72	
		Patients with discontinuation of therapy within next 90 days	13	28	25	14
		Patients with new prescription for naloxone within next 90 days	5	6	1	
		Average number of sedative drugs dispensed within next 90 days	18	14	12	0
		Average number of sedative prescribers writing prescriptions in next 90 days	18	14	12	0
	Oncology Denials	Total patients identified	1			
		Total prescribers identified	1			
		Prescribers successfully notified	1			
	TCAs in Children	TCA Denials in Children	23	27	36	4
		Total patients identified	6	14	17	
		Total prescribers identified	6	14	17	
		Prescribers successfully notified	3	9	10	
		Patients with claims for a TCA within the next 90 days	3	6	3	
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1	2	

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Update on Targeted Immune Modulators Used to Manage Selected Autoimmune Conditions

Deanna Moretz, PharmD, BCPS

Targeted immune modulators (TIMs) are used to treat autoimmune disorders including atopic dermatitis (AD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), plaque psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD), and ulcerative colitis (UC). A summary of TIMs approved for management of selected auto-immune conditions is presented in **Table 5.** Targeted immune modulators include biologic disease-modifying anti-rheumatic drugs (DMARDs) and targeted synthetic DMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. Targeted synthetic DMARDs are small chemical molecules that can be taken orally. In the past 2 years substantial information about specific agents within this class of drugs has been published due to expanded indications, including new pediatric approvals. This newsletter will provide an update on recent Food and Drug Administration (FDA)-approved TIMs and updated indications for TIMs that occurred in 2024 and 2025. In addition, revisions to the Oregon Health Plan (OHP) Fee-for-Service (FFS) prior authorization (PA) criteria for the TIMs used to manage auto-immune conditions are summarized.

Guideline-Directed Therapy with TIMs

Standard of care for treatment of RA, AS, PsO, or PsA is to initiate therapy with a tumor necrosis factor inhibitor (TNF-I) or appropriate interleukin inhibitor if a conventional DMARD (i.e., methotrexate) has failed or if the patient has contraindications to conventional therapy.[17-19] Nonsteroidal anti-inflammatory drugs and exercise are recommended as first-line therapies to alleviate pain and stiffness in patients with AS.[20,21] Janus kinase (JAK) inhibitors can be considered to manage autoimmune conditions that are FDA-approved, but pertinent risk factors (cardiovascular events and malignancies) should be evaluated prior to starting therapy.[17] Other targeted synthetic DMARDs approved to manage PsO include the phosphodiesterase-4 inhibitor, apremilast and the recently approved tyrosine kinsase-2 inhibitor, deucravacitinib.

The 2019 American College of Gastroenterology (ACG)[22] and the National Institute for Health and Care Excellence (NICE)[23] guidelines recommend the use of TIMs for treating moderately to severely active UC in adults whose disease has responded inadequately to conventional therapy including aminosalicylates (i.e., sulfasalazine, mesalamine), corticosteroids, azathioprine or mercaptopurine. For management of CD, NICE guidance recommends TNFi for induction, but only after failure of conventional therapy with corticosteroids, aminosalicylates, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[24] The American College of Gastroenterology (ACG) strongly recommends induction with a TNFi to maintain remission in patients who have moderate-to-severe CD despite treatment with conventional therapy.[25]

New Targeted Immune Modulators

Ustekinumab Biosimilars

Eight new intravenous and subcutaneous (SC) biosimilar products for the reference product of STELARA (ustekinumab) received FDA approval in 2024 and 2025.[1] These products include: OTULFI (ustekinumab-aauz), IMULDOSA (ustekinumab-srlf), SELARSDI (ustekinumab-aekn), YESTINTEK (ustekinumab-kfce), STEQEYMA (ustekinumab-stba), WEZLANA (ustekinumab-auub), PYZCHIVA (ustekinumab-ttwe) and STARJEMZA (ustekinumab-hmny).[1] According to the FDA, all of the STELARA biosimilar products have FDA interchangeable status except for IMULDOSA.[1] The means they can be substituted for STELARA at the pharmacy level without requiring a prescription change from the healthcare provider. All the ustekinumab biosimilar products are indicated for treatment of adults with moderate to severe PsO, CD, UC, or active PsA and pediatric patients 6 years and older with moderate to severe PsO or active PsA.[2]

New Interleukin-31 Inhibitor: Nemolizumab

NEMLUVIO (nemolizumab) is an interleukin (IL)-31 receptor antagonist FDA-approved for: 1) adults with prurigo nodularis (PN)[3] and 2) patients 12 years of age and older with moderate-to-severe AD in combination with a topical corticosteroid (TCS) and/or a topical calcineurin inhibitor (TCI) when AD is not adequately controlled with topical therapies alone.[4]

Moderate-quality evidence from 2 randomized, double-blind, multi-center, placebo-controlled, phase 3 trials (OLYMPIA 1 and OLYMPIA 2) showed nemolizumab is effective for treating PN over 16 weeks.[5,6] Patients were randomized 2:1 to receive nemolizumab or placebo. After completion of either randomized controlled trial (RCT), patients were eligible to enter an ongoing long-term extension trial (OLYMPIA LTE). The co-primary endpoints were decreased itching and improvement in PN skin lesions. Pruritus was evaluated using the patient-reported itch response (a reduction of ≥ 4 points on the Peak Pruritus Numerical Rating Scale [PP-NRS; scores range from 0 to 10, with higher scores indicating more severe itch]) and skin lesions were evaluated using an Investigator's Global Assessment

(IGA) response (a score of 0 [clear] or 1 [almost clear] on the IGA [scores range from 0 to 4] and an IGA reduction from baseline to week 16 of ≥2 points).[5,6] Study results are presented in **Table 1.** For both assessments nemolizumab was significantly more effective in decreasing itching and improving skin lesions compared with placebo.

Table 1. Results from OLYMPIA 1 and 2 Trials[5,6]

	Percent of Patients with Itch Response at Week 16	Percent of Patients with IGA Response at Week 16
OLYMPIA 1[5] N=276	Nemolizumab vs Placebo: 58.4% vs. 16.7% Difference 41.7% 95% CI 29.4 to 50.8 P<0.001; NNT = 2	Nemolizumab vs Placebo: 26.3% vs 7.3% Difference 19% 95% CI 6.7 to 22.6 P=0.003; NNT = 3
OLYMPIA 2[6] N=274	Nemolizumab vs Placebo: 56.3% vs. 20.9% Difference 35.4% 95% CI 26.3 to 48.5 p<0.001; NNT = 5	Nemolizumab vs Placebo: 37.7% vs. 11.0% Difference 26.7% 95% CI 18.8 to 38.2 P<0.001; NNT =4
Abbreviations: CI = Confidence Interval; IGA = Investigators Global Response; NNT = Number Needed To Treat		

The most frequently reported adverse events with nemolizumab in the PN trials were headache (nemolizumab 6% vs. placebo 3%) and worsening AD (nemolizumab 4% vs placebo 0.5%).[3] In the United States, PN may disproportionally affect more Black than White patients (3:1 ratio) and may be less common in other race/ethnic groups.[6] However, people identifying as Black were underrepresented in both RCTs (9.8% in Olympia 1 and 4.4% in Olympia 2).[5,6] As PN is a chronic disease, studies of longer duration are needed to support long-term use.[5] An open-label extension study of 184-week duration is ongoing.

Moderate-quality evidence from 2 identical, multicenter, phase 3 RCTs (ARCADIA 1 and ARCADIA 2) showed nemolizumab is effective in treating moderate-to-severe AD over 16 weeks.[7] Patients at least 12 years of age with moderate-to-severe AD were randomized 2:1 to receive nemolizumab 30 mg SC every 4 weeks (after a loading dose of 60 mg at week 0) plus a TCS or TCI, or matching placebo plus a TCS or TCI over 16 weeks.[7] Skin clearance was measured by IGA success as defined above and Eczema Area and Severity Index (EASI)-75 response at 16 weeks.[7] Study results are presented in **Table 2**. For both assessments nemolizumab was significantly more effective in achieving a response compared with placebo, though the number needed to treat was higher than that for PN.

Table 2. Results from ARCADIA 1 and 2 Trials[7]

	People with IGA Success at Week 16	People with EASI-75 Response at Week 16
ARCADIA 1 N=941	Nemolizumab vs Placebo 35.6% vs. 24.6% Difference 11% 97.5% CI 4.7 to 18.3 P=0.0003; NNT = 9	Nemolizumab vs Placebo 43.5% vs. 29% Difference 14.5% 97.5% CI 7.8 to 22.0 P<0.0001; NNT = 9
ARCADIA 2 N=787	Nemolizumab vs Placebo 37.7% vs. 26% Difference 11.7% 97.5% CI 4.6 to 19.8 P=0.0006; NNT = 7	Nemolizumab vs Placebo 42.1% vs. 30.2% Difference 11.9% 97.5% CI 4.6 to 20.3 P=0.0006; NNT = 9
Abbreviations: CI = Confidence Interval; EASI = Eczema Area and Severity Index; IGA = Investigators Global Response; NNT = Number Needed to Treat		

In clinical trials for AD efficacy, the most commonly reported events reported were headache, arthralgia, urticaria, and myalgia.[4]

Limitations of the AD trials include the absence of long-term safety data.[7] A long-term extension study is ongoing. People enrolled in trials were predominantly White and other races and ethnicities were under-represented.[7] Patients with uncontrolled asthma were excluded from enrollment for safety reasons, presumably due to the risk of hypersensitivity reactions with administration of a monoclonal antibody. In addition, people who received 16-week treatment with dupilumab and experienced worsening of AD or failed to achieve improvement were excluded from trial enrollment. Investigators did not justify the reasons for excluding this patient population. Comparative trials with other TIMs approved for AD with nemolizumab have not been conducted.

New Interleukin-13 Inhibitor: Lebrikizumab

EBGLYSS (lebrikizumab) is a monoclonal antibody that targets IL-13. Lebrikizumab is approved for the treatment of moderate to severe AD in patients ≥ 12 years old who weigh ≥ 40 kg and are not adequately controlled with topical prescription therapies.[8] It can be used with or without other topical therapies (TCS or TCI).[8] Dosing is 500 mg SC at week 0 and Week 2, followed by 250 mg SC every 2 weeks until Week 16 or later, when adequate clinical response is achieved.[8] The maintenance dose is 250 mg SC every 4 weeks.[8]

Data from 3 high-quality, randomized, double-blind clinical trials (ADvocate 1 ADvocate 2, and ADhere) indicate that 16-week induction of lebrikizumab (administered every 2 weeks) is significantly more effective than placebo for improving skin clearance.[9,10] In these 3 RCTs, patients 12 years and older with moderate-to-severe AD uncontrolled with topical therapies were randomized 2:1 to lebrikizumab or placebo.[9,10] In the ADvocate trials co-administration of TCS/TCI was not permitted, while in the ADhere trial patients were permitted to use TCS or TCI.[9,10] Study results are presented in **Table 3**. In all 3 trials lebrikizumab was significantly more effective in achieving a response compared with placebo.

Table 3. Results from ADvocate and ADhere Trials[9,10]

	Percent of Patients with IGA Success at Week 16	Percent of Patients with EASI-75 Response at Week 16
ADvocate 1[9] N=424	Lebrikizumab vs Placebo 43.1% vs. 12.7% Difference 29.7% 95% CI 21.6 to 37.8 P<0.001; NNT = 4	Lebrikizumab vs Placebo 58.8% vs. 16.2% Difference 42% 95% CI 33.3 to 50.6 P<0.001; NNT = 3
ADvocate 2[9] N=427	Lebrikizumab vs Placebo 33.2% vs 10.8% Difference 21.9% 95% CI 14.2 to 29.6 P<0.001; NNT = 5	Lebrikizumab vs Placebo 52.1% vs. 18.1% Difference 33.3% 95% CI 14.23 to 29.6 P<0.001; NNT = 3
ADhere[10] N=228	Lebrikizumab vs Placebo 41.2% vs. 22.1% Difference 18.3% 95% CI 5.1 to 31.5 P<0.05; NNT = 6	Lebrikizumab vs Placebo 69.5% vs. 42.2% Difference 26.4% 95% CI 12.1 to 40.8 P<0.01; NNT = 4
Abbreviations: CI = Confidence Interval; EASI = Eczema Area and Severity Index; IGA = Investigators Global Response; Number Needed to Treat		

One 52-week trial, which re-randomized responders from the 2 ADvocate induction trials, indicated that continuing lebrikizumab (every 4 weeks) was associated with significantly better skin clearance, itching, and quality of life outcomes (Strength of Evidence: moderate) relative to placebo withdrawal.[11] In this trial lebrikizumab was generally well tolerated; the most commonly reported adverse effects were conjunctivitis (5.9%) and herpes (5.9%).[8] No head-to-head trials comparing lebrikizumab to other TIMs or other immunosuppressives have been conducted.

Expanded FDA-Approved Indications

The FDA continues to review and approve expanded indications and age ranges for the TIMs. Table 4 summarizes recently approved indications for TIMS to manage auto-immune conditions.

Table 4. Expanded FDA-Approved Indications

Drug	New Indication	Prexisting Indication(s)
Apremilast[12]	▪ PsA in patients ≥ 6 yo and weighing at least 20 kg	▪ PsA in adults ▪ PsO in patients ≥ 6 yo ▪ Oral ulcers associated with Bechet's Disease in adults
Guselkumab[13]	▪ UC in adults ▪ CD in adults ▪ PsO in patients ≥ 6 yo ▪ PsA in patients ≥ 6 yo	▪ PsO in adults ▪ PsA in adults
Certolizumab Pegol[14]	▪ pJIA in patients ≥ 2 yo	▪ CD in adults ▪ PsA in adults ▪ PsO in adults ▪ AS in adults ▪ Nr-axSpA in adults
Bimekizumab[15]	▪ PsA in adults ▪ AS in adults ▪ nr-axSpA in adults ▪ HS in adults	▪ PsO in adults
Mirkizumab[16]	▪ CD in adults	▪ UC in adults
Abbreviations: AS = Ankylosing Spondylitis; CD = Crohn's Disease; HS = Hidradenitis Suppurativa; nr-axSpA = Non-Radiographic Axial; pJIA = Polyarticular Juvenile Idiopathic Arthritis; SpondyloArthritis; PsA = Psoriatic Arthritis; PsO = Plaque Psoriasis; UC = Ulcerative Colitis		

Changes to OHP Prior Authorization Criteria

At the October 2025 Pharmacy and Therapeutics (P & T) Committee meeting, the committee approved adding nemolizumab and lebrikizumab to the Preferred Drug List (PDL) as non-preferred therapies. The PA criteria for the "TIMs for Severe Asthma and Atopic Dermatitis" were updated to include these 2 medications. In addition, based upon recent guidance, pediatric patients were removed from a trial and failure of an oral immunosuppressant (e.g. methotrexate, azathioprine) prior to initiating dupilumab for management of AD in children and adolescents. The requirement for a concurrent prescription for an EpiPen was modified to only apply to omalizumab requests. All the TIMs approved for management of moderate-to-severe AD (abrocitinib, dupilumab, tralokinumab, upadacitinib) are non-preferred and require PA prior to starting therapy.

At that same meeting, the P & T committee reviewed new evidence for the PDL class of "TIMs for Auto-Immune Conditions". Prior authorization criteria were updated to include expanded indications for the recent FDA approvals outlined in this newsletter. All TIMs are subject to PA before OHP FFS will pay for the claims. After executive session, where overall comparative costs and drug rebates were assessed, the following recommendations for updating the PDL were approved by the Committee and will become effective January 1, 2026:

Three agents were designated as preferred using the following definitions:

- Tier 1 agents are preferred, first line medications.
- Tier 2 agents are preferred, second line medications.
- Tier 3 agents are nonpreferred, third line medications.

The following recommendations were implemented:

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DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy Sentena
sentenak@ohsu.edu

- Make infliximab preferred, Tier 1
- Make ustekinumab biosimilar (PYZCHIVA) syringes and vials preferred, Tier 2 and
- Make guselkumab (TREMFYA) preferred, Tier 2.

Complete evidence reviews, the OHP FFS Drug Class list and PA criteria can be accessed at this website: https://orpdl.org/drugs/

Oregon Health Plan Prior Authorization Criteria for TIMs for Autoimmune Conditions

- Humira and Enbrel are preferred, Tier 1.
- Infliximab-axxq (AVSOLA), generic infliximab, Simlandi (branded only), AMJEVITA (100 mg/mL aka "high-concentration" only), and non-branded adalimumab-fkjp (50 mg/mL aka "low-concentration" only) are preferred, Tier 1.
- Ixekizumab (TALTZ), apremilast (OTEZLA), tofacitinib citrate (XELJANZ), ustekinumab biosimilar (PYZCHIVA), and guselkumab (TREMFYA) are designated as preferred, Tier 2.
- All other products are designated as non-preferred, Tier 3.

Conclusion

In the past 2 years, two new TIMs, nemolizumab and lebrikizumab, received FDA-approval to manage moderate-to-severe AD in adults and adolescents. Eight new biosimilar products for the reference product of STELARA (ustekinumab) are now available in the United States market. New therapies and expanded indications have provided more options for managing many auto-immune conditions, as presented in **Table 5.** Oregon Health Plan PA criteria are based on guideline-directed therapy, with an emphasis on using the most cost-effective therapies for appropriate indications.

Table 5. FDA-Approved TIMs for Selected Auto-Immune Conditions

Drug – Route of Administration	Molecular Target	Common Approved Indication(s)
Biologic DMARDs		
Adalimumab (HUMIRA) - SC	TNFα	AS, RA, PsA, PsO, CD, UC
Certolizumab Pegol (CIMZIA) - SC		AS, RA PsA, PsO, CD
Golimumab - (SIMPONI and SIMPONI ARIA) - IV or SC		AS, RA, PsA, UC
Infliximab (REMICADE) – IV, SC		AS, RA, PsA, PsO, CD, UC
Etanercept (ENBREL) - SC	TNFα, TNFβ	AS, RA, PsA, PsO
Anakinra (KINERET) - SC	IL-1 receptor	RA
Dupliumab (DUPIXENT) – SC	IL-4 receptor α subunit	AD
Sarilumab (KEVZARA) - SC	IL-6 receptor	RA
Tocilizumab (ACTEMRA) – IV or SC		RA
Lebrikizumab (EBGLYSS) -SC	IL-13	AD
Tralokinumab (ADBRY) – SC		AD
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO, CD, UC
Bimekizumab (BIMZELX) - SC	IL-17A, IL-17F, IL-17AF	AS, PsO, PsA
Brodalumab (SILIQ) - SC	IL-17 receptor	PsO
Ixekizumab (TALTZ) - SC	IL-17A	AS, PsA, PsO
Secukinumab (COSYNTEX) - SC		AS, PsA, PsO
Guselkumab (TREMFYA) – SC and IV	IL-23	PsA, PsO, CD, UC
Mirikizumab (OMVOH) – IV (initial dose) followed by SC		UC, CD
Risankizumab (SKYRIZI) - SC		PsA, PsO, CD, UC
Tildrakizumab (ILUMYA) - SC		PsO
Nemolizumab (NEMLUVIO) – SC	IL-31 receptor	AD, PN
Vedolizumab (ENTYVIO) – IV	Integrin receptor	CD, UC
Natalizumab (TYSABRI) – IV		CD
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	RA, PsA
Rituximab (RITUXAN) - IV	B-lymphocyte	RA
Spesolimab (SPEVIGO) – IV for acute flares, SC for maintenance to prevent flares	IL-36 receptor	GPP
Targeted Synthetic DMARDs		
Abrocitinib (CIBINQO) - PO	JAK 1	AD
Baricitinib (OLUMIANT) - PO	JAK 1,2	RA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	RA, PsA, UC
Upadacitinib (RINVOQ) - PO	JAK 1	AS, RA, PsA, CD, UC, AD
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Ozanimod (ZEPOSIA) – PO	S1P receptor	UC
Etrasimod (VELSIPITY)– PO		UC
Deucravacitinib (SOTYKTU) – PO	TYK2	PsO

Abbreviations: Atopic Dermatitis; AS=ankylosing spondylitis; CD=Crohn's Disease; DMARD=Disease-Modifying Antirheumatic Drug; FDA=Food and Drug Administration; IL=interleukin; GPP= Generalized Pustular Psoriasis;

IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PN=Prurigo Nodularis; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; S1P=sphingosine 1-phosphate; RA=rheumatoid arthritis; SC=subcutaneous; TNF=tumor necrosis factor; TYK2=tyrosine kinase 2; UC=Ulcerative Colitis

Peer Reviewed By: Spandana Daryani, MD
Assistant Professor, Department of Dermatology
Oregon Health & Science University

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Chronic Kidney Disease Pharmacotherapy: Guideline Updates & Practical Application

Hannah Allen PharmD Candidate 2026, and Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management Group

In the United States, an estimated 1 in 7 adults, about 35 million people, have chronic kidney disease (CKD), This condition is more prevalent in adults aged 65 years and older.[1] CKD is defined as abnormalities of kidney structure or function for a minimum of 3 months and is classified based on estimated glomerular filtration rate (eGFR) (G1-G5) and albuminuria (A1-A3).[2] Patients with CKD have a profoundly increased risk of cardiovascular disease (CVD), as 50% of patients with stage 4 and 5 CKD have some type of CVD.[3]. Death from cardiovascular events accounts for 40-50% of mortality in CKD.[3]

In 2024, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines were updated for the management of CKD, with signficiant emphasis on medications that improve CKD outcomes .[2] The guidelines include graded recommendations based on a systematic review of the evidence and practice points based on expert consensus or limited evidence. This newsletter summarizes key guideline updates with a focus on pharmacotherapy.

Renin-angiotensin system inhibitors (RASi))

Consistent with previous versions of the KDIGO guidelines, renin-angiotensin system (RAS) inhibition with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) for people with CKD and moderate (urine albumin-to-creatine ratio [UACR] 30-300 mg/kg) to severe (UACR > 300 mg/kg) albuminuria is recommended (**Table 1**).

Table 1: KDIGO Guideline Recommendations for Renin-Angiotensin System Inhibitors.[2]

Recommendation	Evidence Grade
• We recommend starting RASi for people with CKD and severely increased albuminuria without diabetes	1B
• We suggest starting RASi for people with CKD and moderately increased albuminuria without diabetes	2C
• We recommend starting RASi for people with CKD and moderately-to-severely increased albuminuria with diabetes	1B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: CKD – chronic kidney disease; RASi – renin-angiotensin system inhibitors

There is strong and consistent evidence that RASi slow CKD progression and decrease the risk of kidney failure with a greater benefit when patients have albuminuria. Less evidence is available for those without diabetes, but data still supports benefit, particularly with more severe albuminuria.[2] KDIGO guidelines recommend avoiding any combination of ACEi and ARB due to a risk of acute kidney injury (AKI) and hyperkalemia without any therapeutic benefits.[2]

Due to risks of hyperkalemia and acute kidney injury (AKI), RASi are often discontinued in advanced CKD. A practice point in the guidelines recommends continuing ACEi or ARB in people with CKD even if the eGFR falls below 30 ml/min.[2] This is based upon data from the STOP-ACEi trial, a multicenter, open-label trial randomizing 411 patients with stage 4 or 5 CKD to continue or discontinue RASi.[4] After a follow up of 3 years, there was no benefit in eGFR in the discontinuation group compared to those who continued RASi therapy (mean eGFR 12.6 ml/min versus 13.3 ml/min; p=0.42).[4] There was also no significant difference in end stage renal disease (ESRD) events, cardiovascular events, or adverse safety events between groups. The lack of a clear kidney benefit or harm from RASi in advanced CKD highlights the need to evaluate specific indications for these medications (e.g. CKD, hypertension, heart failure) and the importance of shared decision making.

It is recommended to monitor serum creatinine and potassium levels within 2-4 weeks after starting or changing the dose of RASi and to increase to maximally tolerated doses if there is a <30% decrease in eGFR.[2] A greater decrease in eGFR should trigger an investigation into other causes (e.g. renal artery stenosis, use of NSAIDs, hypovolemia, heart failure exacerbation, or urinary obstruction).[2] Patients unable to tolerate a higher dose of RASi may still benefit from lower doses or retrials in the future, especially if confounding factors are reversed.

Sodium-Glucose Cotransporter-2 (SGLT2i) Inhibitors

Through direct and indirect effects, SGLT2i reduce the risk of kidney disease progression, CV death, and all-cause mortality in adults with CKD, with or without diabetes.[2] A recent Cochrane systematic review found high quality evidence of a reduced risk of all-cause death (relative risk [RR] 0.86; 95% confidence interval [CI] 0.81 – 0.92) and kidney outcomes (RR 0.68; 95% CI 0.59 – 0.78) with SGLT2i in patients with CKD and diabetes.[5] Moderate quality evidence showed a reduction in major adverse cardiovascular events (MACE), likely due to deaths due to heart failure and sudden cardiac death.[5] The

SGLT2i's probably have little to no effect on fatal or nonfatal myocardial infarction (MI) and fatal or nonfatal stroke.

Studies support dapagliflozin and empagliflozin use in patients with CKD without diabetes. In a meta-analysis including the EMPA-KIDNEY and the DAPA-CKD trials, SGLT2i's showed a 37% reduction in risk of kidney disease progression (RR 0.63; 95% CI 0.58 – 0.69) with similar relative risks in patients with and without diabetes, a 23% reduction in the risk of AKI, and a 23% reduced risk of CV death or hospitalization for heart failure, regardless of diabetes status.[6]

These benefits are seen across the spectrum of kidney function and albuminuria levels and extend to patients with an eGFR as low as 20 ml/min. A systematic review and meta-analysis of 10 trials found a reduced incidence of a composite kidney outcome across all UACR groups, including < 30mg/kg (hazard ratio (HR) 0.62; 95% CI 0.50- 0.78).[7] Due to this evidence, KDIGO guidelines recommend SGLT2i in patients with CKD, with or without diabetes (**Table 2**).[2]

Table 2: Recommendations for Sodium-glucose Co-Transporter 2 Inhibitors[2]

Recommendation	Evidence Grade
• We recommend treating patients with T2D, CKD, and an eGFR ≥ 20 ml/in with an SGLT2i	1A
• We recommend treating adults with CKD with an SGLT2i with urine ACR ≥ 200 mg/g, or heart failure	1A
• We suggest treating adults with eGFR 20 to 45 ml/min with urine ACR < 200 mg/g with an SGLT2i	2B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: ACR – albumin to creatine ratio; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; SGLT2i – sodium-glucose cotransporter-2 inhibitor; T2D – type 2 diabetes.

The guidelines include a practice point that once an SGLTi is initiated, it is reasonable to continue if the eGFR falls below 20ml/min, unless it is not tolerated. [2] There is an increased risk of mycotic genital infections with SGLTi but these are generally mild and responsive to treatment. Other risks, including ketoacidosis and acute kidney injury (AKI) are low and the benefits of therapy outweigh these risks. [2] Similar to RASi, there is an expected hemodynamically mediated bump in serum creatinine (i.e. permissive AKI) after initiation with SGLT2i. If it remains stable, there is not volume depletion, and the rise in serum creatinine is less than 30%, it is not harmful. There is a low overall risk of hypoglycemia with SGLT2i but the risk is increased when used in combination with insulin and sulfonylureas. In advanced CKD, SGLTi loses its glucose lowering benefits and the A1c reduction is diminished.

Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid Receptor Antagonists (MRAs) reduce BP and albuminuria in CKD. Finerenone is a nonsteroidal MRA approved for CKD associated with T2DM and heart failure with preserved ejection fraction.[2] Compared to spironolactone, which is a steroidal MRA, finerenone is more cardioselective with a lower risk of sexual and hormonal side effects, including gynecomastia and decreased libido. In a large, phase 3 randomized controlled trial (RCT) (n=5,734) in patients with T2DM and CKD on maximally tolerated RASi, patients were randomized to finerenone or placebo.[8] Over a follow up of 2.6 years, there was a reduction in the primary renal composite outcome (renal death, decrease in eGFR of 40% or more, or dialysis) with finerenone compared to placebo (17.8% vs 21.1%; hazard ratio [HR] 0.82; 95% CI 0.73 – 0.93).[8] In a similarly designed trial, finerenone reduced the risk of the composite of CV death, non-fatal MI,stroke, and heart failure hospitalizations compared to placebo (12.4% vs. 14.2%; HR 0.87; 95% CI 0.76 to 0.98).[9] This was driven by heart failure hospitalizations with little effect on myocardial infarction (MI) or stroke. These studies only included patients with diabetes and participants had an eGFR ≥ 25 ml/min. In clinical trials, 2.3% and 11% of participants in the finerenone group discontinued or held treatment due to hyperkalemia compared to 0.9% and 5.2% in the placebo group. [9] To reduce the risk of hyperkalemia, patients should have a normal serum potassium at baseline (≤ 4.8 mmol/l) and serum potassium should be monitored within 1 month of initiating an MRA and then every 4 months. [2] Finerenone has no glucose lowering effects or substantial impact on blood pressure, and other medications with these benefits may be preferred.

Table 3: Recommendations for Mineralocorticoid Receptor Antagonists[2]

Recommendation	Evidence Grade
• We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 m2, **normal** serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor	2A

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest
Abbreviations: eGFR – estimated glomerular filtration rate; RAS – renin angiotensin system; T2D – type 2 diabetes.

Typically, MRAs are reserved for persistent albuminuria despite optimized therapy with RASi and SGLT2 inhibitors. A recent RCT randomly assigned participants with CKD, albuminuria, and T2DM on a RASi to receive finerenone, empagliflozin, or a combination of finerenone and empagliflozin.[10] Overall, the combination of finerenone and empagliflozin in addition to background RASi, was more effective at reducing the UACR compared to both agents

alone.[10] Although further studies are needed to evaluate if this benefit translates to a reduction in kidney and CV outcomes, this initial data supports combination therapy.

While spironolactone, a steroidal MRA, may decrease albuminuria when added to an ACEi or ARB in CKD, there is a lack of large, high-quality trials demonstrating improvements in renal or CV outcomes in CKD populations. Given its proven efficacy for resistant hypertension, spironolactone may be preferred when additional blood pressure reduction is a primary therapeutic goal.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

The 2024 KDIGO guidelines recommend a long-acting GLP-1 RA to reach glycemic targets in patients with CKD and T2DM (**Table 4**).[2]

Table 4: Recommendations for Glucagon-Like Peptide-1 Receptor Agonists[2]

Recommendation	Evidence Grade
• We recommend a long-acting GLP-1 RA in adults with T2DM and CKD who have not achieved glycemic targets despite use of metformin and SGLT2 inhibitor	1B

Certainty of Evidence: A: High; B: Moderate; C: Low; D: Very Low
Evidence Grade: Level I: We Recommend; Level 2: We Suggest

However, since the guidelines were released, semaglutide was FDA approved to reduce risk of sustained eGFR decline, ESRD, and CV death in patients with T2DM and CKD. This approval was based on a phase 3, placebo-controlled, RCT (n=3534) that randomized patients with T2DM and high-risk CKD on maximal RASi to semaglutide or placebo.[11] The baseline mean eGFR was 47 ml/min and the median UACR was 568. While most patients were on an ACEi or ARB (95%), only 15% were on a SGLT2 inhibitor. Overall, there was a reduction in kidney disease events with semaglutide compared to placebo (18.7% vs. 23.2%; HR 0.76; 95% CI 0.66 – 0.88) and a reduction in MACE (12% vs. 14.4%; HR 0.82; 95% CI 0.68 to 0.98).[11]

While both SGLT2i and GLP-1 RA are recommended in CKD and DM, cost may limit use of both agents. SGLT2i are generally favored when albuminuria or CKD progression is present, while GLP-1 RA may be favored when additional glycemic control or weight loss is needed.

Conclusion

With new evidence supporting multiple pharmacologic treatments for reducing renal and CV outcomes in patients with CKD, treatment of CKD is shifting from a stepwise approach to a pillar approach using a combination of medications, analagous to heart failure management . The four pillars of CKD treatment include RASi, SGLT2i, nonsteroidal MRA, and long-acting GLP-1 RA. Additional evidence is needed to better define the clinical implications of combination therapy, the optimal order of initiation, the level of benefit in patients without albuminuria, and if this data can be applied to patients with CKD without T2DM.

Peer Reviewer: Rob Rope, MD, Associate Professor of Medicine, Division of Nephrology and Hypertension, School of Medicine and Medical Director, General Nephrology Ambulatory Clinics, Oregon Health and Science University

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Eating Disorders and Disordered Eating Behaviors In Patients with Diabetes

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group and Samara Stevens, ND, Medical Director, Holistic Mental Health

Eating disorders and disordered eating behaviors are common in individuals with diabetes but are frequently under-recognized in clinical practice. Having diabetes increases the risk of developing an eating disorder, especially in people with type 1 diabetes (T1D). Estimates are that 20-40% of young women with T1D have an eating disorder and up to one-third of women with T1D withhold insulin for weight control.[1] People with type 2 diabetes mellitus (T2D) have also been found to have a higher level of disordered eating, with up to 26% having a binge-eating disorder.[2] Eating disorders in people with diabetes complicate glycemic control and weight management and are associated with increased morbidity and mortality.[3] Clinicians should incorporate routine screening for eating disorders and disordered eating in their patients with diabetes.

This newsletter will present the intricate relationship between eating behaviors and blood sugar control in patients with T1D and T2D, as well as screening and treatment options.

Disordered Eating and Eating Disorders

Eating disorders are a mental health condition affecting the relationship that an individual has with food and body image, which is more common in women than men.[2] Epidemiological studies suggest that people with diabetes have an increased risk of bulimia, anorexia, and binge eating disorders compared to nondiabetics.[2] People with T1D are more likely to be diagnosed with diabetes before the development of an eating disorder, while the reverse may be true for T2D, when the eating disorder (i.e., binge-eating) may contribute to the development of diabetes.[2]



Diabetes management itself may lead to a higher risk and leave patients more vulnerable to the development of an eating disorder. In patients with T1D the need to count carbohydrates, monitor weight, constant attention to food and the reality of insulin related weight gain creates a uniquely high-risk environment. The realization that insulin omission creates an effective and accessible method of weight control contributes to the problem. One study found that 36% of females intentionally omitted insulin for this purpose.[4] Avoidance of testing may accompany withholding insulin to avoid acknowledgement of high blood sugar. The results of withholding insulin leads to complications such as hyperglycemia, ketoacidosis, vascular complications and mortality in extreme cases.[5]

Disordered Eating and Altered Glucose Response

Metabolism disturbances have been identified in patients with disordered eating but commonly do not meet the traditional diagnosis for diabetes. Early-phase insulin hypersecretion often precedes pancreatic beta-cell decline.[6] Often these patients will have fasting glucoses of 80 mg/dL or less and fasting insulin levels ranging from 30-40 µU/mL suggesting insulin resistance (normal fasting insulin levels are 10 µU/mL or less). Evidence suggests that insulin resistance may be detectable 10-15 years prior to T2D diagnosis.[6] This represents an important opportunity for earlier intervention. Patients may not present with elevated hemoglobin A1c (HbA1c) but may have metabolic findings listed below for several years prior to a prediabetes diagnosis.[6]

Indicators of metabolic dysfunction:

- Elevated fasting insulin levels
- Glucose/insulin ratios less than 7 (suggesting insulin resistance)
- Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores 1.9 or above[7]
- Abnormal Quantitative Insulin Sensitivity Check Index (QUICKI) with lower values indicating increased insulin resistance[8]
- Reactive hypoglycemia after a mixed-meal tolerance test at 30, 60 and 90 minutes. Blood sugar drop after 30 minutes due to exaggerated insulin response[9]
- Strong family history of T2D
- History of restrictive eating patterns

Key Points:

- Hyperinsulinemia and insulin resistance often precede elevations in fasting glucose or increases in HbA1c by **many years**
- A normal HbA1c does not exclude early metabolic dysfunction
- Reactive hypoglycemia, elevated fasting insulin or abnormal insulin sensitivity may indicate early warning signs long before prediabetes is diagnosed

Impact on Blood Sugar

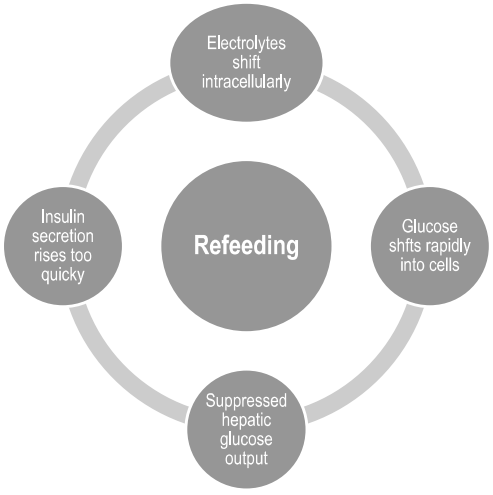
Patterns of metabolic instability associated with restrictive eating, binge-restrict cycles, insulin omission, and recurrent reactive hypoglycemia can contribute to glycemic variability, exaggerated insulin response, and progressive insulin resistance.[6,9] The metabolic response when food is consumed, as a result of the body compensating for calorie restriction or lack of insulin, are outlined in **Table 2.** This reactive hypoglycemia response may represent an early pre-diabetic metabolic phenotype in some patients.

Table 2. Metabolic Responses in People with Disordered Eating[9]

Condition	Response
Starvation	Glucose production is primary concern
Refeeding	Glucose is stored immediately
Refeeding Hypoglycemia	Hyperinsulinemia + Suppressed hepatic glucose output + depleted glycogen
Reactive Hypoglycemia	Low blood sugar (<70 mg/dL) occurring 2-5 hours after a meal due to over-production of insulin

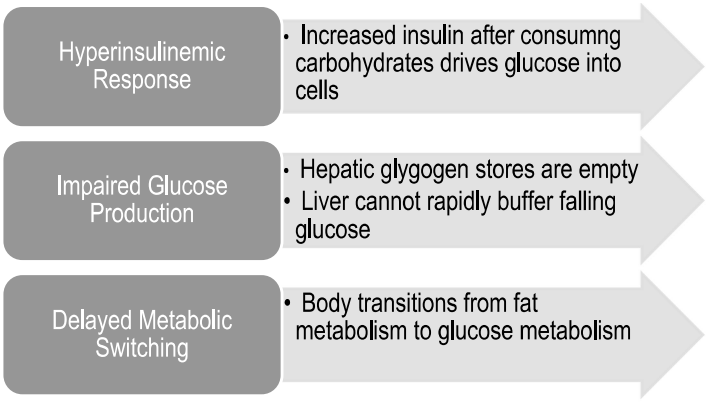
Normal glucose regulation can be disrupted in people with an eating disorder or disordered eating, causing stress to the pancreas contributing to insulin dysregulation.[9] During starvation the body responds by lowering insulin output, and increasing its level of glucagon and cortisol to maintain energy. Therefore, energy comes from fat oxidation, ketone production and gluconeogenesis. Introducing carbohydrates and other food back into the body affects the metabolism in an altered way (**Figure 1**).[5]

Figure 1. Metabolic Effects when Refeeding from a Starved State



Metabolic changes from adapting to prolonged starvation in anorexia can predispose patients to refeeding hypoglycemia.[9] During prolonged starvation hepatic glucose production becomes suppressed and glycogen stores are depleted. When carbohydrates are reintroduced, an exaggerated insulin response may occur, causing rapid peripheral glucose uptake before hepatic glucose production can adequately respond. This imbalance can lead to post-refeeding hypoglycemia.[9] In this scenario, when carbohydrates are consumed the body responds with an exaggerated rapid insulin release from the pancreas.[9] This can cause glucose to leave the bloodstream rapidly without the ability of hepatic glucose to respond accordingly due to suppressed glucose production by the liver in the starvation state.[9] Therefore, reduced production of hepatic glucose and increased peripheral uptake may cause hypoglycemia with reduced hypoglycemia awareness.[10] This can lead to cravings and urgent hunger.[9] Physiologic hunger signals triggered by reactive hypoglycemia may contribute to episodes of urgent or loss-of-control eating in some individuals. The physiology is described in **Figure 2.**

Figure 2. Mechanism of Reactive Hypoglycemia in Anorexia[9]



Elevated cortisol levels associated with disordered eating can promote increases in blood glucose, insulin resistance, and visceral fat accumulation - contributing to a lower basal metabolic rate. These metabolic changes may impair insulin sensitivity and results in glycemic variability over time, potentially leading to gradual increases in HbA1c.[7] Insulin resistance and compensatory hyperinsulinemia often precede elevations in fasting glucose or HbA1c by 5-15 years.[6]

Early metabolic changes may be present for many years before abnormalities appear in traditional glycemic screening measures. By the time impaired fasting glucose or prediabetes is identified, metabolic dysfunction may have already been present for over a decade.[6] Repeated insulin surges and glycemic variability associated with disordered eating may disrupt glucose regulation and can occur in patients across the weight spectrum, including those who are lean, normal-weight, or overweight.

It is also important to recognize that some patients with restrictive eating behaviors may meet behavioral criteria for eating disorders without developing the degree of weight loss typically associated with conditions such as anorexia nervosa. In the presence of metabolic dysregulation - including insulin

resistance, glycemic variability, or recurrent reactive hypoglycemia - expected weight trajectories may be altered.

As a result, restrictive eating disorders may be underrecognized in patients whose body weight does not fall into the ranges clinicians traditionally associate with anorexia nervosa.

Clinical indicators of metabolic dysregulation may include:

- Normal or slightly elevated fasting glucose levels
- Increased insulin levels
- Reactive hypoglycemia after meals
- Rising HbA1c over time

Early metabolic evaluation is warranted when patients present with any of the following:

- Postprandial fatigue (OR avoidance of meals because it makes them tired)
- Urgent hunger after meals
- Symptoms suggestive of reactive hypoglycemia
- Feelings of loss of control when eating higher carbohydrate foods

Risk factors for all types of disordered eating include being female and younger age.[5] People with diabetes and comorbid anxiety or depression have also demonstrated a higher risk of developing an eating disorder.[5]

Clinical Red Flags for Disordered Eating in Diabetes

- Recurrent diabetic ketoacidosis
- Unexplained rise in HbA1c
- Marked glycemic variability
- Insulin omission or dose manipulation
- Fear of weight gain associated with insulin use
- Postprandial "crashes" suggestive of reactive hypoglycemia
- Avoidance of glucose monitoring

Screening Tools can be used to assist in diagnosing disordered eating. They are listed in **Figure 3**.[3,5]

Figure 3. Screening Tools

- Diabetes Eating Problems Survey-Revised (DEPS-R): 16-item survey used in adults and adolescents with T1D with a cut-off score of 20 or higher identifying those at risk for an EDO
- Screen for Early Eating Disorder Signs (SEEDS) tool: Can be used in T1D and T2D and thought to be more predictive than other screening tools
- Modified SCOFF (Sick, Control, One, Fat and Food) (mSCOFF): 5-item questionnaire that can be used with as a first-step screening tool in patients with T1D (includes questions related to insulin use). Scores of 2 or more suggestive of disordered eating.

Because eating disorders and metabolic dysregulation often develop in parallel, screening for disordered eating behaviors may also provide an early window into emerging metabolic instability.

Clinical approach to screening conversations

Using neutral and non-judgmental language when screening for disordered eating behaviors can improve patient disclosure. Rather than asking direct yes/no questions about behaviors (e.g., "Do you skip insulin to lose weight?"), clinicians may normalize the behavior and ask whether the experience occurs for the patient. For example: "Some people with diabetes notice that concerns about food, weight, or blood sugar control can influence how they eat or how they use insulin. Has anything like that ever happened to you? If it has, what tends to be going on around that time?" This approach may reduce stigma and encourage patients to speak more openly about behaviors that might otherwise go unreported.

Management

Early identification, intervention and support are important in the treatment of disordered eating behaviors in people with diabetes. A multidisciplinary approach including psychotherapy, glucose management, nutritional counseling, and diabetes education is often required.[2] The emotional distress associated with disordered eating may need treatment with cognitive-behavioral therapy and/or medication.[2,11]

Some patients may consume fewer calories than expected while struggling to achieve a desired weight due to underlying metabolic dysregulation. This pattern may be misinterpreted as excessive caloric intake, leading to frustration and inappropriate treatment adjustments. In patients with a history of disordered eating, therapies that modify postprandial glucose dynamics (e.g., acarbose, miglitol, or metformin) have been used to address symptoms such as postprandial fatigue or early hunger.

Medication strategies for individuals with reactive hypoglycemia include drugs such as acarbose, miglitol, metformin, or glucagon-like peptide-1 (GLP-1) receptor agonists. Metformin has also been shown to prevent diabetes by 31% when compared to placebo in individuals at high risk.[12] Careful clinical assessment is important, however, as reactive hypoglycemia related to exaggerated postprandial insulin secretion may require targeted management of the insulin response rather than empiric treatment with insulin-sensitizing agents alone.

Population Health Considerations

Early identification of metabolic dysregulation in patients with disordered eating may represent an important opportunity for prevention and reduction in health care costs. Because diagnostic thresholds for diabetes identify disease relatively late in the biological progression of metabolic dysfunction, earlier recognition of insulin dysregulation and disordered

eating behaviors may allow intervention at a stage when metabolic changes remain more reversible.

The estimate of long-term clinical and economic burden of diabetes is substantial with national estimates exceeding $327 billion annually in direct medical costs and lost productivity.[13] Preventing costly complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy has demonstrated a reduction in healthcare expenditures. Early intervention for prevention or delay is crucial.

Provider Pearls

In patients with a history of an eating disorder or suspected disordered eating, with or without diabetes, it is important to encourage open conversations about eating behaviors during routine visits. Normalizing these conversations may improve disclosure of eating-related behaviors that patients might otherwise feel reluctant to discuss. Asking how often a patient weighs themselves and how being weighed during medical appointments affects them can help identify signs of eating-related distress.[11] Excessive or compulsive exercising is a common symptom of an eating disorder as well.

Patients with a history of eating disorders may experience anxiety related to weight measurements in clinical settings. In these situations, offering blinded weight assessments and avoiding the inclusion of weight or BMI on the after-visit summary may help reduce distress and improve engagement in care. If a patient is identified as having an urgent and/or severe eating disorder, referral for specialized management may be necessary (**Figure 4**).

Figure 4. Referral Information

National Alliance for Eating Disorders: Inpatient treatment centers and outpatient practitioners

https://www.findedhelp.com

Eating Disorder Outpatient Services: State availability

https://www.aedweb.org/expert-directory

Conclusion

Eating disorders and disordered eating behaviors occur in individuals with T1D and T2D and may be reinforced by glucose-management practices required for diabetes care. As our understanding of metabolic disease progression continues to evolve, it is becoming increasingly clear that some of the earliest physiological signals of dysregulated glucose metabolism may appear well before traditional diagnostic thresholds are reached.

Routine screening for disordered eating behaviors in patients with diabetes may therefore represent an important opportunity to identify both emerging eating disorders and early metabolic dysregulation before traditional glycemic markers become abnormal. Appropriate counseling and targeted medical therapy, when indicated, are important components of care for individuals with eating disorders and disordered eating behaviors.

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Policy Update: Healthier Oregon Program

Program Updates and Changes:

Healthier Oregon is a program that offers free health coverage through the Oregon Health Plan (OHP) for people of any immigration status who live in Oregon and meet income and other eligibility requirements for OHP. Unlike traditional Medicaid, non-emergency services (including most drug coverage) for members enrolled through Healthier Oregon are funded by the state and are not eligible for federal matching funds or Medicaid drug rebates.

In April 2026, about 99,400 members in Healthier Oregon were enrolled in coordinated care organizations (CCOs). However, beginning in January 2027, these members will move to OHP Open Card (also called the fee-for-service program). This will double the current OHP Open Card population which enrolls about 98,700 members through the Medicaid program.

As a result of these changes and because of the differences in funding between the Healthier Oregon and Medicaid populations, the Pharmacy and Therapeutics (P&T) Committee will need to re-evaluate choice of products on the preferred drug list (PDL). The P&T Committee is charged with evaluating comparative efficacy and safety of prescription drugs to inform PDL decisions. In the absence of differences in efficacy or safety, the P&T committee evaluates comparative drug costs. With such a large proportion of members enrolled through Healthier Oregon who are not eligible for Medicaid rebates, the most cost effective products for the state may be those with the lowest upfront costs.

PDL classes for which the P&T Committee has recently reviewed evidence of efficacy and safety will be brought back to the P&T committee as old business to evaluate utilization for Healthier Oregon members and pricing. The following classes have been recently reviewed by the Pharmacy and Therapeutics Committee. Included drugs, PDL status, and prior authorization criteria are referenced in the previous P&T documents.

PDL Class	Last P&T Review Date
Antifungals, Oral	December 2025

Recommendation:

- Evaluate comparative costs in executive session.

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

New Drug Evaluation: Redemplo (plozasiran), subcutaneous injection

Date of Review: August 2026
Generic Name: Plozasiran

End Date of Literature Search: 04/15/26
Brand Name (Manufacturer): REDEMPLO (Arrowhead Pharmaceuticals)
Dossier Received: yes

Plain Language Summary:

- REDEMPLO (plozasiran) is a new medicine used to reduce triglyceride levels in patients with a genetic condition causing very high triglyceride levels. This condition is called Familial Chylomicronemia Syndrome. People with very high triglyceride levels of 1000 mg/dL or higher have increased risk for inflammation of the pancreas, known as pancreatitis.
- There is only one other medication that works like plozasiran to reduce triglyceride levels in this condition. Dietary and fat restrictions are currently the only other recommended treatments. These dietary restrictions are difficult for patients to maintain.
- In one study, plozasiran injected subcutaneously, or under the skin, every 3 months reduced triglyceride levels by a meaningful amount when compared to placebo over 12 months in patients who were also following a low-fat diet.
- Side effects with plozasiran include an increase in blood sugars, injection site reactions, and nausea.
- We recommend plozasiran will be covered for people with familial chylomicronemia syndrome who are enrolled in the fee-for-service Oregon Health Plan after a prior authorization request by the prescriber is approved.

Research Questions:

1. Is there evidence demonstrating the efficacy of plozasiran in reducing triglyceride (TG) levels and episodes of acute pancreatitis in patients with Familial Chylomicronemia Syndrome (FCS)?
2. Is there evidence that plozasiran is safe for reducing TG levels and episodes of acute pancreatitis in patients with FCS?
3. Are there specific subpopulations for which plozasiran is better tolerated or more effective when used for FCS?

Conclusions:

- There is low-quality evidence that plozasiran at the FDA-approved dose of 25 mg subcutaneous (SC) every 3 months lowers TG levels significantly more than placebo at 10 months (least squares mean [LSM] difference -59%; 95% confidence interval [CI] -90 to -28; $p<0.001$) in participants with FCS.[1]
- There is low-quality evidence that plozasiran resulted in a nominal decrease in pancreatitis in adults with FCS (5 subjects in placebo group versus 2 in the pooled plozasiran group; odds ratio [OR] 0.17; 95% CI 0.03 to 0.94).[1] Given the small of subjects with pancreatitis events, the precise magnitude of risk reduction is uncertain.

Author: Megan Herink, PharmD, MBA, BCPS

- There is insufficient evidence for the long-term safety of plozasiran. Safety concerns include elevated hepatic transaminases and hyperglycemia. There were low rates of serious adverse events and discontinuations due to adverse events in one small trial (n=75) in adults with FCS.
- There is supportive data from two phase 2 trials that plozasiran 25 mg every 12 weeks results in clinically meaningful reduction in TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dL) and severe hypertriglyceridemia (TG level ≥ 500 mg/dL) without FCS on background lipid lowering therapy.[2,3] At the time of this review, plozasiran is not FDA-approved for this indication and phase 3 trials are ongoing. There is insufficient evidence that plozasiran lowers the risk of cardiovascular events or pancreatitis in patients with moderate to severe hypertriglyceridemia.
- There are no studies comparing the efficacy or safety of plozasiran to olezarsen for the treatment of FCS.

Recommendations:
- Make plozasiran as non-preferred in the "*Other Dyslipidemia Drug*" preferred drug list (PDL) class. Review costs in executive session.
- Include plozasiran in the apolipoprotein C-III clinical prior authorization criteria to ensure it is used according to supporting evidence and FDA labeling **(Appendix 3**).

Background:
Familial chylomicronemia syndrome is a rare autosomal recessive genetic disorder that causes a deficiency in lipoprotein lipase (LPL) enzyme activity through inactivation of the LPL gene resulting in persistence of triglyceride rich chylomicrons.[4] Although the onset of symptoms usually occurs in childhood or adolescence, FCS is often underdiagnosed or the diagnosis is delayed. Up to 30% of patients with FCS remain undiagnosed until adulthood.[4] FCS affects an estimated 1 to 13 individuals per 1,000,000 in the United States and is characterized by severely elevated chylomicrons and plasma TGs and an increased risk of pancreatitis.[4,5] Clinical presentation includes a TG level greater than 885 mg/dL repeatedly, or a one-time greater than 1000 mg/dL, lack of response to standard treatments, and history of acute pancreatitis. Patients have a 60% to 90% lifetime risk of pancreatitis. There is often a lack of other secondary risk factors, such as obesity and diabetes. Other manifestations can include eruptive cutaneous xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly.[4,5]

Genetic testing remains the gold standard for diagnosing FCS. The North American Familial Chylomicronemia Score (NAFCS) calculator was developed to use clinical criteria to determine a diagnosis of FCS and may be useful for patients who have not been tested genetically or in whom genetic testing was inconclusive.[4] The calculator is recommended only when patients are not responsive to fibrates and high-dose omega-3 fatty acids (< 20% reduction in TGs). The NAFCS calculator includes the following variables: young age of onset, BMI less than 25 kg/m^2, history of abdominal pain or pancreatitis, absence of secondary risk factors, persistent fasting TG greater than 885 mg/dL, TG to total cholesterol ratio greater than 3.5 mg/dL, apolipoprotein B (apoB) < 1 g/L, and nonresponse to conventional medications.[4]

The goal of treatment in FCS is to prevent acute pancreatitis and reduce plasma TG levels to less than 885 mg/dL. There is no current evidence-based definitive TG target and there are no high-quality clinical guidelines addressing FCS. There are currently no Food and Drug Administration (FDA)-approved treatments for FCS. Standard triglyceride-lowering treatments with fibrates, niacin, and omega-3 fatty acids are typically not effective in FCS due to a lack of LPL activity in FCS patients. Standard of care remains a restrictive low-fat diet (< 20 grams daily) to reduce the accumulation of chylomicrons, physical activity, and complete avoidance of alcohol. While standard lipid-lowering drugs are generally not effective for patients with FCS as they have no impact on chylomicron metabolism, they may be beneficial in patients with concomitant risk factors for atherosclerotic cardiovascular disease (ASCVD).[4,5]

Inhibiting APOC3 reduces TG levels by enhancing LPL activity and reducing serum apolipoprotein C-III protein, a key regulator of TG metabolism. Volanesorsen is an APOC3 inhibitor approved in Europe for the treatment of FCS. It was not approved in the United States because of concerns about thrombocytopenia.[4] In

December 2024, Olezarsen was the first FDA-approved treatment for FCS in adults. It is an antisense oligonucleotide targeting apolipoprotein C-III (APOC3) mRNA to reduce APOC3 production. Olezarsen was approved through expedited approval pathways, including fast-track, breakthrough therapy, and priority review.[5] Olezarsen is a second generation APO3 inhibitor targeting hepatic APOC3 mRNA. It has the same chemical composition as volanesorsen but differs with the addition of a triantennery N-acetyl galactosamine, which allows for lower dosing. Olezarsen 80 mg subcutaneous once monthly lowered TG levels more than placebo at 6 months (difference -43.5%; 95% CI -69.1 to -17.9; p<0.001) in subjects with FCS with insufficient evidence on decreasing pancreatitis and no effect on LDL-C.[6] There is supportive data that olezarsen 50 mg and 80 mg reduce TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dl) at high cardiovascular (CV) risk and severe hypertriglyceridemia (TG level ≥ 500 mg/dl) without FCS on background lipid lowering therapy.[7,8] Olezarsen was recently FDA approved to reduce TGs and the risk of acute pancreatitis in adults with severe hypertriglyceridemia (TG levels of at least 500 mg/dl).[9]

Also targeting APOC3, Plozasiran is a small interfering RNA (siRNA) that degrades APOC3 mRNA through RNA interference, resulting in increased clearance of serum TGs. It was FDA approved in November 2025 for the treatment of FCS in adults through expedited FDA approval pathways.[10] There is no data comparing plozasiran to olezarsen and neither drug has demonstrated a reduction in cardiovascular or clinical outcomes.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
Plozasiran 25 mg administered subcutaneously every 3 months received approval based on one randomized, phase 3, double-blind, controlled trial (**Table 1**). Subjects were randomized 2:1 to plozasiran 25 mg or volume matched placebo or plozasiran 50 mg or volume-matched placebo subcutaneously every 3 months for 12 months.[1] Adults 18 years of older with FCS and fasting TG levels greater than 880 mg/dL with and without a history of pancreatitis were included. Subjects with both genetically confirmed and clinical diagnoses were included. A clinical diagnosis included fasting TG level greater than 1000 mg/dL and one of the following: recurrent episodes of acute pancreatitis, recurrent hospitalizations for abdominal pain, childhood pancreatitis, or family history of hypertriglyceridemia-induced pancreatitis.[1] The FDA typically requires 2 adequate and well controlled trials to provide substantial evidence for efficacy. However, the FDA allowed one study due to the rarity of the condition and lack of alternative treatment options for FCS.[10]

If the study participant was not already following a low-fat diet, they were enrolled in a 4-week dietary run-in period. Subjects were instructed to consume no more than 20 g of fat per day, and alcohol use was discouraged.[1] Of the 123 screened subjects, 75 were randomized to plozasiran or placebo. The most common reason for screen failure was not meeting the TG requirement or diagnosis of FCS. Seventy-three percent of the enrolled population was White, the median TG level was 2044 mg/dL, and 49% were enrolled based on a previous genetic confirmation.[1] Thirty four subjects had a clinical diagnosis of FCS that was not genetically confirmed. Most subjects (88%) had a previous episode of pancreatitis.[1]

The percent change in baseline TG level was -80% with plozasiran 25 mg (LSM difference -59%; 95% CI -90 to -28), -78% with plozasiran 50 mg (LSM difference -53%; 95% CI -83 to -22), and -17% with placebo, resulting in a statistically significant mean difference in both treatment groups.[1] There were also statistically significant differences in percent change from baseline in APO3 for both plozasiran 25 mg (LSM difference -95%; 95% CI -108.3% to -72.7%) and plozasiran 50 mg (LSM difference -93.4%; 95% CI -109.4% to -77.4%) compared to placebo at month 10.[1] Subgroup analysis demonstrated a similar treatment effect in those with genetically confirmed FCS and clinically diagnosed FCS. Plozasiran resulted in an increase in low density lipoprotein (LDL) from baseline compared to placebo.

There was a total of 9 positively adjudicated acute pancreatitis events, occurring in 5 (20%) subjects in the placebo group and in 2 (4%) in the pooled plozasiran groups (OR 0.17; 95% CI 0.03 to 0.94; p=0.03).[1] Given the small of subjects with pancreatitis events, the precise magnitude of risk reduction is uncertain.

Two phase 2 trials in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL) (n=226) and moderate hypertriglyceridemia (TG ≥ 150 mg/dL and ≤ 400 mg/dL) (n=353) were used by the FDA as confirmatory evidence.[2,3] Subjects with a history of clinical ASCVD or an elevated 10-year ASCVD risk score were required to be on appropriate lipid lowering therapy according to standard of care. There were high rates of screening failures in both trials (66.2% in severe hypertriglyceridemia trial and 52% in moderate hypertriglyceridemia).[10] Both trials demonstrated statistically significant reductions in TG levels from baseline at week 24 with plozasiran administered subcutaneously every 12 weeks (total of 2 doses given). In moderate hypertriglyceridemia, the placebo-adjusted percent change in fasting TG from baseline to week 24 was -56% (95% CI -65.1 to -46.8) and in severe hypertriglyceridemia, the difference was -53.1% (95% CI -65.1% to -38). There are ongoing phase 3 trials evaluating plozasiran for moderate and severe hypertriglyceridemia.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Acute pancreatitis
2) Hospitalization due to pancreatitis
3) Serious adverse events
4) Study withdrawal due to an adverse event
5) Reduction in TG level

Primary Study Endpoint:
1) Percent change in fasting triglyceride level from baseline to month 10

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Endpoints	ARR/NNH	Risk of Bias/ Applicability
1. Palisade Study[1] Phase 3, DB, PC, RCT	1. Plozasiran 25 mg SC Q 3 months 2. Plozasiran 50 mg SC Q 3 months 3. placebo * 4-week run-in period for diet stabilization prior to randomization 12 months	Demographics: 51% women, 73% white, mean age 46 years, median TG 2044 mg/dL, 59% genetically confirmed FCS, 88% h/o pancreatitis Key Inclusion Criteria: -Genetically or clinically confirmed diagnosis of FCS -Fasting TG ≥880 mg/dL, refractory to standard lipid lowering therapy	ITT: 1. 26 2. 24 3. 25 PP: 1. 23 2. 22 3. 19 Attrition: 1. 3 (12%) 2. 2 (8%) 3. 6 (24%)	Primary Endpoint: Percent change in fasting TG from baseline at Month 10 1. -80% 2. -78% 3. -17% Mean difference: 25 mg vs placebo: -59% 95% CI, -90 to -20; P<0.0001 50 mg vs. Placebo: -53%; 95% CI, -83 to -22; p=0.0002 Secondary Endpoint:	N/A	Discontinued due to AE: 1. 2 (7.7%) 2. 1 (4.2%) 3. 0 Serious adverse effects: 1. 5 (19%) 2. 2 (8%) 3. 7 (28%)	NS NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear; randomized using an interactive web response system, allocation performed using a block randomization algorithm; small numbers resulted in imbalances at baseline in TG lowering therapy and percent of subjects with diabetes Performance Bias: Low; double blinded using matching placebo volume. Detection Bias: Low; blinded assessors for adjudication of pancreatitis Attrition Bias: Low; low overall attrition and similar between groups. Reporting Bias: Low. Protocol available online and all outcomes prespecified. Other Bias: High. Study financially supported by drug manufacturer. Arrowhead

		-Age ≥18 years old - ≤ 20g of fat/ day <u>Key Exclusion Criteria</u>: -Active pancreatitis - HbA1c ≥ 9% - AST/ALT > 3 x ULN - Bilirubin > 1.5 x ULN -eGFR < 30 ml/min - Coagulopathy - Malignancy within 2 years - Active HIV, HCV, or HBV - Use of GLP-1 - NYHA Class II, III, or IV HF or EF < 30% - > 14 units of alcohol per week		Acute Pancreatitis (pooled plozasiran vs. pooled placebo) Plozasiran: 2 (4%) Placebo: 5 (25%) OR 0.17; 95% CI 0.03 to 0.94; p=0.03	N/A			Pharmaceuticals involved in data interpretation and preparation of manuscript. **Applicability**: <u>Patient</u>: Rare disease limits sample size. 54% of screened patients did not meet randomization criteria. FCS is often present in adolescents, who were excluded. The 4-week diet stabilization run-in period limits applicability. <u>Intervention</u>: Doses selected based on phase 1 studies. However, no clear dose response in phase 3 study and only the 25 mg dose was FDA approved. <u>Comparator</u>: Placebo group comparator appropriate <u>Outcomes:</u> Reduction in TG levels is a surrogate outcome. Uncertainty around magnitude of benefit on acute pancreatitis. <u>Setting</u>: 58 centers in 21 countries; 12% of subjects from the United States.

<u>Abbreviations</u> : ACS = acute coronary syndrome; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; CI = confidence interval; CV = cardiovascular; DC = discontinuation; DB = double-blind; EF = ejection fraction; eGFR = estimated glomerular filtration rate; FCS = Familial Chylomicronemia Syndrome; GLP-1 = glucagon like peptide-1; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HF = heart failure; HIV = human immunodeficiency virus; ITT = intention to treat; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NYHA = New York heart association; OR = odds ratio; PC = placebo controlled; PP = per protocol; RR: rate ratio; SAE = serious adverse events; SC = subcutaneous; TG = triglyceride; ULN = upper limit of normal.

Clinical Safety:

In the small pivotal study, plozasiran was well tolerated. Common side effects that occurred more frequently than placebo are included in **Table 2.** Side effects of concern with plozasiran include hyperglycemia, elevated in liver transaminases, and increases in LDL-C. In the pivotal trial, there were 3 discontinuations due to adverse events in subjects receiving plozasiran and none in subjects receiving placebo. Two of the discontinuations were due to hyperglycemia. Average fasting glucose and HbA1c values increased by 7.6 mg/dl and 0.33%, respectively in the plozasiran 25 mg group.[10] There were more subjects receiving plozasiran who experienced a composite hyperglycemia outcome consisting of adverse events, new antidiabetic medication, and laboratory values in a subgroup without diabetes compared to placebo (40% vs. 20%), suggesting worsening glycemic control with plozasiran.[10] Plozasiran was associated with mean increases in ALT, (alanine aminotransferase) AST (asparte aminotransferase), and direct bilirubin within the first 3 months, which stabilized, and remained on average within normal range. Increases in LDL-C of 125% from baseline was noted in the FCS population treated with plozasiran 25 mg compared to 46% in those treated with placebo. Despite increases in the LDL-C, the average LDL-C value at Month 12 was less than 50 mg/dL.[10]

The proportion of subjects reporting serious adverse events was 28% in the placebo, 19% in the 25 mg plozasiran group, and 8% in the plozasiran 50 mg group. While thrombocytopenia is a safety concern of antisense oligonucleotides, platelet levels remained unchanged from baseline and there was no difference in the frequency of thrombocytopenia between plozasiran and placebo. The safety of plozasiran has not been established in pediatric patients with FCS.

Table 2: Adverse reactions that occurred in > 10 % of patients and at a higher frequency than placebo[11]

Adverse reaction	Plozasiran (n=43)	Placebo (n=23)
Hyperglycemia	10 (20%)	2 (8%)
Headache	8 (16%)	2 (8%)
Nausea	7 (14%)	2 (8%)
Injection site reaction	1 (4%)	5 (10%

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use REDEMPLO® safely and effectively. See full prescribing information for REDEMPLO.

REDEMPLO (plozasiran) injection, for subcutaneous use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
REDEMPLO is an apolipoprotein C-III *(apoC-III)*-directed small interfering ribonucleic acid (siRNA) indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of REDEMPLO is 25 mg injected subcutaneously once every 3 months. (2.1)
- Inject REDEMPLO subcutaneously into the front of the thigh or abdomen. The outer area of the upper arm can be used as an injection site if a healthcare provider or caregiver administers the injection. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 25 mg/0.5 mL solution in a single-dose pre-filled syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Most common adverse reactions in REDEMPLO treated patients (incidence ≥10% of patients treated with REDEMPLO and >5% more frequently than with placebo) are hyperglycemia, headache, nausea, and injection site reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arrowhead Pharmaceuticals Inc. at 1-844-REDEMPLO (1-844-733-3675), or https://arrowheadpharma.com/safetyreporting, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.[11]

Parameter	
Mechanism of Action	Plozasiran is an siRNA conjugated with GalNAc that binds and degrades ApoC-III mRNA through the RNA interference mechanism resulting in reduced levels of hepatic and serum ApoC-III protein. Reduction of serum and liver ApoC-III protein leads to increased clearance of plasma TGs
Oral Bioavailability	N/A; subcutaneous administration
Distribution and Protein Binding	Volume of distribution is 146 L; Plozasiran is 78% protein bound
Elimination	16% - 19% excreted in the urine
Half-Life	3 to 4 hours
Metabolism	Plozasiran is primarily metabolized by nucleases to shorter oligonucleotides of varying lengths.

Abbreviations: ApoC-III - apolipoprotein C-III; L – liter; N/A – not applicable; RNA - Ribonucleic acid; siRNA – small interfering RNA; TG - triglyceride

APOLIPOPROTEIN C-III (APOC3) Inhibitors

Goal(s):
- Promote use of APOC3 Inhibitors that is consistent with medical evidence and FDA-approved indications.
- Promote use of high value products.

Length of Authorization:
- Up to 12 months

Requires PA:
- Olezarsen (Tryngolza)
- Plozasiran (Redemplo)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved FFS prior authorization?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have a diagnosis of familial chylomicronemia syndrome (FCS), confirmed by genetic testing? Please submit a copy of the genetic testing results	**Yes**: Go to #4	**No:** Go to #7
4. Is the medication prescribed by or in consultation with a specialist in familial chylomicronemia syndrome (FCS)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have a current triglyceride level of 1000 mg/dL or greater within the previous 6 months?	**Yes:** Go to #6 **Recent TG Level**_____ **Date** _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient agree to adhere to a low-fat diet (≤ 20 g of fat per day)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an FDA-approved indication?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have clinically diagnosed severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL on at least 2 occasions within the previous 6 months?	**Yes:** Go to #9 **Recent TG Level**_____ **Date** _____	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient on maximally tolerated statin therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient failed to have adequate benefit with (triglycerides remain > 500 mg/dl), or have a contraindication to, an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) and high-dose omega 3 fatty acid (4 gm daily)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of a positive clinical response (i.e. clinically meaningful reduction in triglyceride level or reduction in episodes of acute pancreatitis) within the previous 6 months?	Yes: Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Newer Drugs for Heart Failure

Date of Review: August 2026

Date of Last Review: June 2022 (Diuretics, Oral)
Feb 2022 (Inhibitors of the Renin-Angiotensin-Aldosterone System)
Literature Search: 01/01/22 – 03/31/2026

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This literature scan looks at recently published evidence for medicines used to treat heart failure. When the heart muscle cannot pump as well as it should to meet the body's needs for nutrients and oxygen from the blood, it is called heart failure. Heart failure may be caused by many different things. Examples are increased blood pressure (hypertension), damaged heart valves, coronary artery disease, irregular heartbeat, a heart attack, and inflammation of the heart muscle.
- Symptoms of heart failure include feeling tired, shortness of breath, coughing, swelling in the legs, ankles, or feet, and rapid weight gain because not enough fluid is removed from the body. Everyday activities such as walking or climbing stairs can become very difficult.
- There are many medicines used to treat the symptoms of heart failure, and they work in different ways to improve the heart's ability to pump blood to the rest of the body. People with heart failure often need more than one medicine to treat their symptoms.
- Diuretics are medicines that decrease the amount of the blood the heart must pump by removing extra sodium and fluid from the body. Diuretics used to treat heart failure include furosemide, torsemide, and bumetanide.
- Spironolactone and finerenone block the effects of aldosterone, a hormone that controls the body's release of sodium and water. These medicines help decrease blood pressure and decrease fluid buildup (edema).
- Other medicines used to treat heart failure relax the blood vessels to make it easier for the heart to pump blood. These medicines are called angiotensin converting enzyme (ACE) inhibitors (e.g., lisinopril, enalapril) and angiotensin II receptor blockers (ARBs) (e.g., losartan, valsartan). Sacubitril/valsartan can replace an ACE inhibitor or ARB in the treatment of heart failure. It is a combination medicine called an angiotensin-receptor neprilysin inhibitor (ARNi). This medicine can improve blood flow, reduce extra fluids in the body, and decrease the strain on the heart.
- Vericiguat is a newer medicine approved for adults after being discharged from the hospital for treatment of heart failure symptoms. When taken with other heart failure medicines, vericiguat can decrease the risk of future hospital admissions and dying from heart failure complications.
- Sodium-glucose costransporter-2 (SGLT-2) inhibitors (i.e., empagliflozin, dapagliflozin), are approved to lower blood sugar in people with diabetes. These medicines have also been shown to reduce hospitalizations due to heart failure symptoms.
- The use of finerenone, vericiguat, and SGLT-2 inhibitors have been added as recommendations to the latest heart failure treatment guidelines.
- Oregon Health Plan provides coverage for several diuretics, ACE inhibitors, and ARBs including furosemide, spironolactone, bumetanide, chlorthalidone, torsemide, ramipril, quinapril, candesartan, irbesartan, benazepril, olmesartan, losartan, valsartan, enalapril, and lisinopril. For all other heart failure

Author: Deanna Moretz, PharmD, BCPS

medicines, including sacubitril/valsartan, finerenone, vericiguat, and SGLT2 inhibitors, the provider must submit documentation why the patient needs the medicine. This process is called prior authorization.

Conclusions:

- Three high-quality systematic reviews[1-3] and 5 high-quality clinical guidelines[4-8] have been published since the last Pharmacy and Therapeutics (P and T) review of guideline-directed medical therapy (GDMT) for heart failure.
- A 2025 systematic review and meta-analysis of comparative randomized controlled trials (RCTs) of furosemide and torsemide assessed differences in clinical outcomes in patients treated with these diuretics for management of heart failure.[1] Moderate-quality evidence from pooled RCTs, showed that torsemide compared with furosemide did not result in a statistically significant difference in all-cause mortality or all cause rehospitalization rates in patients with heart failure.[1]
- A 2023 systematic review and meta-analysis evaluated the association of ARNis with atherosclerotic cardiovascular disease (ASCVD) events in patients with heart failure.[2] The major findings from moderate-quality evidence were as follows: (1) the incidence of ASCVD events was not significantly different between patients with heart failure receiving ARNi therapy versus those receiving ACE inhibitor/ARB therapy; (2) patients with heart failure receiving ARNi therapy had a higher incidence of peripheral artery disease compared to patients treated with ACE inhibitor/ARB therapy (risk ratio [RR] 1.63, 95% confidence interval [CI] 1.05 to 2.52, p = 0.03); and (3) findings were generally consistent when stratified by ACE inhibitor/ARB type, length of follow-up, and type of heart failure based on ejection fraction.[2]
- A 2021 Cochrane review assessed the effects of beta-blockers, ACE inhibitors, ARBs, ARNis, and mineralocorticoid receptor antagonists (MRAs) in people with heart failure and preserved ejection fraction (HFpEF).[3] There is moderate certainty evidence that MRA and ARNi treatment in HFpEF probably reduces heart failure hospitalization compared to placebo/usual care but probably has little or no effect on cardiovascular (CV) mortality (moderate certainty evidence) and quality of life (high certainty evidence).[3] Low certainty evidence shows beta-blocker treatment may reduce the risk of CV mortality compared to placebo/usual care.[3] Although MRAs and ARNis are probably effective at reducing the risk of heart failure hospitalization (moderate certainty evidence), the treatment effect sizes are modest.[3]
- In recently published guidance (2026), Canada's Drug Agency (CDA) recommends that finerenone be reimbursed by public drug plans as an add-on to standard of care in adults with heart failure with left ventricular ejection fraction (LVEF) ≥ 40% to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits.[4]
- Guidance from CDA (2023) recommends that vericiguat be reimbursed for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or intravenous (IV) diuretic therapy.[5]
- Recommendations for treating heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and HFpEF were revised in the updated National Institute for Health and Care Excellence (NICE) guidance for management of adults with chronic heart failure in 2025.[6] Recommendations include:
    - Offer an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFrEF.[6]
    - Consider an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFmrEF.[6]
    - For people who have an intolerance to an ACE inhibitor, or if the ACE inhibitor is ineffective at maximally tolerated doses, consider switching to an ARB or ARNi.[6]
- Focused guidance was developed by the European Society of Cardiology (ESC) in 2023.[7] Recommendations for the use of SGLT2 inhibitors and finerenone in heart failure management were added to the treatment recommendations.[7]

- The 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guideline consolidated 2013 and 2017 recommendations into a new document along with recently published evidence for updated heart failure treatment strategies.[8] Pharmacologic recommendations for management of HFrEF, HFmrEF, and HFpEF are presented in **Tables 1, 2, and 3,** respectively. Recent changes include:
    - Guideline-directed medical therapy (GDMT) for HFrEF includes the following 4 medication classes: renin-angiotensin-aldosterone system (RAAS) inhibitors/ARNis, beta blockers, MRAs, and SGLT2 inhibitors.[8]
    - SGLT2 inhibitors are strongly recommended in HFmrEF. Weaker recommendations are made for ARNi, ACE inhibitor, ARB, MRA, and beta blocker therapy for patients with HFmrEF.[8]
    - New recommendations for treatment of HFpEF are made for SGLT2 inhibitors, MRAs, and ARNis.[8]
    - Heart failure with improved LVEF (HFimpEF) refers to patients with previous HFrEF who now have an LVEF > 40%. These patients should continue their HFrEF treatment.[8]
- New formulations approved by the Food and Drug Administration (FDA) include:
    - 10/2025: LASIX ONYU is a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours via an infusion device.[9] LASIX ONYU is indicated for the treatment of edema in adult patients with heart failure.[9]
    - 9/2025: ENBUMYST is a new dosage form of bumetanide nasal spray which contains 0.5 mg/0.1 mL per each unit of use device.[10] ENBUMYST is indicated for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease, including nephrotic syndrome in adults.[10]
    - 7/2025: VOSTALLY is a new dosage form of ramipril oral suspension 1 mg/mL, indicated for the treatment of hypertension in adults; to reduce the risk of myocardial infarction (MI), stroke or death from CV causes in patients 55 years or older at high risk of developing major CV events; and to reduce the risk of CV death and hospitalization for heart failure in adults with post-MI heart failure.[11]
    - 3/2025: ARBLI, a new dosage form of losartan oral suspension 10 mg/mL, is indicated for the treatment of hypertension in adults and children greater than 6 years old; reduction of stroke in patients with hypertension and left ventricular hypertrophy (there is evidence that this benefit does not apply to Black patients); and treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes mellitus (T2DM) and a history of hypertension.[12]
    - 3/2025: HEMICLOR, a new oral dosage form of chlorthalidone 12.5 mg tablets, is indicated for the treatment of hypertension in adults.[13] The manufacturer did not conduct any clinical studies for this dosage form, instead a literature-based review was submitted to the FDA to support the efficacy of 12.5 mg dosing of chlorthalidone to control hypertension alone or in combination with other antihypertensive medications.[13]
    - 1/2025: INZIRQO, a new dosage form of hydrochlorothiazide oral suspension 10 mg/mL, is indicated for the treatment of hypertension in adults and pediatric patients and for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease in adults and pediatrics.[14]
    - 10/2022: FUROSCIX, a single-use, subcutaneous injection form of furosemide is designed to administer 80 mg over 5 hours.[15] FUROSCIX is indicated for the treatment of congestion due to fluid overload in adults with New York Heart Association (NYHA) Class II/III chronic heart failure.[15]
- New FDA-approved indications include:
    - 12/2025: The expanded use of FUROSCIX for the treatment of edema in pediatric patients weighing 43 kg and above with chronic heart failure.[15] Previously, FUROSCIX was FDA-approved for treatment of edema in adults with chronic heart failure or chronic kidney disease (CKD), including nephrotic syndrome.[7] (The CKD indication was added in March 2025.[7]) FUROSCIX has not been studied in pediatric patients.[15] Use of FUROSCIX in pediatric patients is supported by efficacy, safety, and pharmacokinetic data of IV furosemide in adults.[15]
    - 7/2025: An expanded indication of finerenone for reduction of risk of CV death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure and LVEF $\geq$ 40%.[16] Prior to this expanded indication, finerenone was approved to reduce the risk of sustained estimated

glomerular filtration (eGFR) decline, end stage kidney disease, CV death, non-fatal MI and hospitalization for heart failure in adults with CKD associated with type 2 diabetes mellitus (T2DM).[16] The safety and efficacy of finerenone in patients with heart failure was evaluated in a double-blind, placebo-controlled, multicenter RCT.[16] The primary endpoint was the composite of CV death and total (first and recurrent) heart failure events comprised of hospitalization for heart failure and urgent heart failure visits.[16] Finerenone reduced the risk of the primary composite endpoint compared to placebo (RR 0.84; 95% CI 0.74 to 0.95; p = 0.007).[16] The overall safety profile of finerenone in this study was largely consistent with the adverse reactions reported in patients with CKD and T2DM.[16]

- 4/2021: Expanded approval of valsartan to include children aged 1 year and older for the treatment of hypertension.[17] Previously, the treatment was indicated for patients 6 years of age and older with hypertension.[17] The antihypertensive effects of valsartan were evaluated in 3 single-arm clinical studies in pediatric patients aged 1 to 5 years.[17] In all 3 RCTs, valsartan reduced systolic blood pressure.[17] The adverse event profile of valsartan in children was similar to adverse events reported in adult studies.[17]

Recommendations:

- Rename "Diuretics, Oral" to "Diuretics, Outpatient" to accommodate new subcutaneous and nasal formulations intended for outpatient use.
- Revise finerenone prior authorization (PA) criteria to include use in the expanded FDA-approved indication to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits in patients with LVEF $\geq$ 40%.
- Maintain the following new formulations of diuretics and RAAS inhibitors as nonpreferred on the preferred drug list (PDL): chlorthalidone 12.5 mg tablet (HEMICLOR); subcutaneous forms of furosemide (FUROSCIX, LASIX ONYU); oral suspensions and oral solutions of HCTZ, losartan, and ramipril (INZIRQO, ARBLI, VOSTALLY); and bumetanide nasal spray (ENBUMYST). Make a metolazone product preferred based upon AHA the recommendation that metolazone or chlorothiazide may be added to loop diuretics in patients with heart failure and refractory edema unresponsive to loop diuretics alone.[8]
- Based on guideline recommendations that support the use of ARNIs (sacubitril/valsartan) as part of GDMT in heart failure, retire PA criteria for sacubitril/valsartan.
- Evaluate medication costs in executive session.

Summary of Prior Reviews and Current Policy

- At the June 2022 meeting the Pharmacy and Therapeutics (P & T) Committee evaluated evidence for the safety and efficacy of diuretics for the prevention of mortality and CV disease in patients with hypertension, heart failure, and CKD. In addition, evidence for a new selective MRA, finerenone, was reviewed. No changes to the PDL were made based on the clinical evidence presented at the meeting. Finerenone was maintained as non-preferred on the PDL with prior authorization (PA) to limit use to patients with CKD and T2DM on background therapy with an ACE inhibitor or ARB (see **Appendix 6**).
- At the February 2022 P & T Committee meeting the committee reviewed evidence for RAAS inhibitors. After review of evidence and evaluation of costs in executive session, fosinopril, quinapril, and candesartan were made preferred on the PDL.
- At the June 2021 P & T Committee meeting evidence was presented for vericiguat, a soluble guanylate stimulator, indicated to reduce the risk of CV death and hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic heart failure and LVEF less than 45%. The committee accepted the recommendation to maintain vericiguat as non-preferred on the PDL and require PA to ensure appropriate use in patients on goal directed therapy with advanced symptomatic HFrEF (see **Appendix 6**).
- Preferred agents in the oral diuretic class include tablet and capsule formulations of hydrochlorothiazide (HCTZ), triamterene, triamterene/HCTZ, furosemide, spironolactone, amiloride, amiloride/HCTZ, bumetanide, chlorthalidone, indapamide, spironolactone/HCTCZ, and torsemide (see **Appendix 1**). All other diuretics and formulations are subject to nonpreferred PA criteria.

- Preferred agents in the RAAS inhibitor drug class include fosinopril, ramipril, quinapril, candesartan, irbesartan, benazepril, olmesartan, losartan, valsartan, enalapril, lisinopril, telmisartan (see **Appendix 1**). All other RAAS inhibitors are subject to nonpreferred PA criteria.
- Current PA criteria limit use of sacubitril/valsartan to patients with heart failure and LVEF less than 40%, on maximally tolerated ACE inhibitor or ARB and a recommended beta-blocker with evidence of efficacy and safety in patients with heart failure (see **Appendix 6**).

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Furosemide Versus Torsemide on Hospitalizations and Mortality in Patients With Heart Failure (2025)
A systematic review and meta-analysis of comparative RCTs of furosemide and torsemide assessed differences in clinical outcomes in patients treated with these diuretics for management of patients with any type of heart failure.[1] Literature was searched through August 5, 2023 and 188 studies were initially identified.[1] Only the RCTs comparing furosemide and torsemide in adult patients with heart failure that measured mortality and hospitalizations were included in the analysis.[1] Twelve RCTs met inclusion criteria with a total of 5,424 patients.[1] Ten of the 12 studies were open-label RCTs, which increased the risk of bias.[1] Otherwise, the risk of bias in other domains was low.[1]

There was no significant difference in all-cause mortality between furosemide and torsemide (RR 0.98; 95% CI 87 to 1.10; p = 0.73; 9 RCTs; moderate-quality evidence).[1] Pooled analysis of RCTs that assessed the risk for rehospitalization did not show any statistically significant difference between torsemide and furosemide groups (RR 0.95, 95% CI 0.88 to 1.02; p = 0.16; 7 RCTs; moderate-quality evidence).[1] In summary, considering the moderate-quality evidence from pooled RCTs, torsemide compared with furosemide did not result in a statistically significant difference in all-cause mortality or all cause rehospitalization rates in patients with heart failure.

Angiotensin Receptor-Neprilysin Inhibitor Effects on Atherosclerotic Cardiovascular Disease Events (2023)
This systematic review and meta-analysis evaluated the association of ARNis with ASCVD events in patients with heart failure.[2] Literature was searched through January 4, 2023 for studies comparing ARNis with ACE inhibitors or ARBs in terms of MI, stroke, angina pectoris, peripheral artery disease, and the composite end point of all 4 events in patients with HF.[2] A total of 8 RCTs met inclusion criteria, with 17,541 patients assigned to either the ARNi (n=8,764) or ACE inhibitor/ARB (n=8,777) groups.[2] Five RCTs included patients with HFrEF and 3 studies included only patients with HFpEF.[2] The ACE inhibitors and ARBs used in the control group were enalapril in 5 studies, valsartan in 2 studies, and enalapril/valsartan in one trial.[2] The follow-up durations ranged from 8 weeks to 35

months.[2] Six RCTs were identified as having moderate risk of bias and 2 RCTs were identified as having a low risk of bias.[2] There was no study with a high risk of bias in any domain.[2]

The incidence of composite end point (RR 1.03, 95% CI 0.93 to 1.13, p = 0.63), MI (RR 1.02, 95% CI 0.81 to 1.30, p = 0.85), angina pectoris (RR 0.96, 95% CI 0.80 to 1.17, p = 0.70), and stroke (RR 0.99, 95% CI 0.85 to 1.16, p = 0.93) were not statistically different between the ARNi and ACE inhibitor/ARB groups.[2] However, ARNi therapy was associated with a higher incidence of peripheral artery disease (RR 1.63, 95% CI 1.05 to 2.52, p = 0.03).[2] In the subgroup analyses for the composite end point of MI, stroke, angina, or peripheral artery disease, there was no statistical difference between groups according to the type of ACE inhibitor/ARB used (enalapril [RR 0.99, 95% CI 0.85 to 1.16, p = 0.95, I^2 = 10%] or valsartan [RR 1.05, 95% CI 0.92 to 1.21, p = 0.47, I^2 = 0%] compared to ARNi therapy.[2] There was no statistical difference between groups for the length of follow-up (8 to 12 weeks [RR 0.73, 95% CI 0.19 to 2.74, p = 0.64, I^2 = 35%]; 24 to 36 weeks [RR 0.96, 95% CI 0.50 to 1.81, p = 0.89, I^2 = 0%]; and 108 to 140 weeks [RR 1.03, 95% CI 0.93 to 1.14, p = 0.57, I^2 = 0%;].[2] There was no statistical difference between ARNi vs ACE inhibitor/ARB for the classification of the heart failure based on ejection fraction (HFpEF [RR 0.99, 95% CI 0.86 to 1.16, p = 0.94, I^2 = 0%] and HFrEF [RR 1.05, 95% CI 0.92 to 1.20, p = 0.47, I^2 = 7%]).[2]

In summary, for this meta-analysis the major findings from moderate-quality evidence were as follows: (1) the incidence of ASCVD events was not significantly different between patients with heart failure receiving ARNi therapy versus those receiving ACE inhibitor/ARB therapy; (2) patients with heart failure receiving ARNi therapy had a higher incidence of peripheral artery disease compared to patients treated with ACE inhibitor/ARB therapy (RR 1.63, 95% CI 1.05 to 2.52, p = 0.03); and (3) findings were generally consistent when stratified by ACE inhibitor/ARB type, length of follow-up, and heart failure based on ejection fraction.[2]

Beta-Blockers and Inhibitors Of The Renin-Angiotensin Aldosterone System For Chronic Heart Failure With Preserved Ejection Fraction (2021)
A Cochrane review assessed the effects of beta-blockers, ACE inhibitors, ARBs, ARNis, and MRAs in people with HFpEF.[3] Literature was searched through May 2020 and 41 RCTs met inclusion criteria.[3] The risk of bias was frequently unclear and only 5 studies had a low risk of bias in all domains.[3]

<u>Beta-blockers</u>
Ten studies (n=3087) investigated beta-blockers. Five studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The age of participants ranged from 30 years to 81 years.[3] A possible reduction in CV mortality was observed with beta-blockers compared to placebo/usual care (RR 0.78, 95% CI 0.62 to 0.99; number needed to treat for an additional benefit (NNTB) 25; n=1046; 3 studies), however, the certainty of evidence was low.[3] There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; n=1105; 4 studies; low-certainty evidence).[3] The effects on heart failure hospitalization, hyperkalemia, and quality of life remain uncertain.[3]

<u>Mineralocorticoid Receptor Antagonists</u>
Thirteen studies (n = 4459) investigated MRAs in HFpEF.[3] Eight studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The age of participants ranged from 54.5 to 80 years.[3] Pooled analysis indicated that MRA treatment probably reduces heart failure hospitalization compared to placebo/usual care (RR 0.82, 95% CI 0.69 to 0.98; NNTB = 41; n= 3714; 3 studies; moderate-certainty evidence).[3] However, MRA treatment probably has little or no effect on all-cause mortality compared to placebo/usual care (RR 0.91, 95% CI 0.78 to 1.06; n=4207; 5 studies; moderate-certainty evidence) and cardiovascular mortality (RR 0.90, 95% CI 0.74 to 1.11; n=4070; 3 studies; moderate-certainty evidence).[3] MRA treatment may have little or no effect on quality of life measures compared to placebo/usual care (mean difference [MD] 0.84, 95% CI -2.30 to 3.98; n=511; 3 studies; low-certainty evidence).[3] MRA treatment was associated with a higher risk of hyperkalemia compared to placebo/usual care (RR 2.11, 95% CI 1.77 to 2.51; number needed to treat for an additional harmful outcome [NNTH] = 11; n=4291; 6 studies; high-certainty evidence).[3]

Angiotensin-Converting Enzyme Inhibitors

Eight studies (n = 2061) investigated ACE inhibitors.[3] Three studies used a placebo comparator and in 5 studies the comparator was usual care.[3] The mean age of participants ranged from 70 to 82 years.[3] Pooled analyses with moderate-certainty evidence suggest that ACE inhibitor treatment likely has little or no effect on cardiovascular mortality compared to placebo/usual care (RR 0.93, 95% CI 0.61 to 1.42; n=945; 2 studies), all-cause mortality (RR 1.04, 95% CI 0.75 to 1.45; n=1187; 5 studies) and heart failure hospitalization (RR 0.86, 95% CI 0.64 to 1.15; n=1019; 3 studies), and may result in little or no effect on the quality of life (MD -0.09, 95% CI -3.66 to 3.48; n=154; 2 studies; low-certainty evidence).[3] The effects of ACE inhibitors on hyperkalemia remain uncertain.[3]

Angiotensin Receptor Blockers

Eight studies (n = 8755) investigating ARBs were included.[3] Five studies used a placebo comparator and in 3 studies the comparator was usual care.[3] The mean age of participants ranged from 61 to 75 years.[3] Pooled analyses with high certainty of evidence suggest that ARB treatment has little or no effect on cardiovascular mortality compared to placebo/usual care (RR 1.02, 95% 0.90 to 1.14; n=7254; 3 studies), all-cause mortality (RR 1.01, 95% CI 0.92 to 1.11; n=7964; 4 studies), heart failure hospitalization (RR 0.92, 95% CI 0.83 to 1.02; n=7254; 3 studies), and quality of life (MD 0.41, 95% CI -0.86 to 1.67; n=3117; 3 studies).[3] ARBs were associated with a higher risk of hyperkalemia compared to placebo/usual care (RR 1.88, 95% CI 1.07 to 3.33; n=7148; 2 studies; high-certainty evidence).[3]

Angiotensin Receptor Neprilysin Inhibitors

Three studies (n = 7702) investigating ARNis were included.[3] Two studies used ARBs as the comparator and one used standardized medical therapy, based on participants' established treatments at enrollment.[3] The mean age of participants ranged from 71 to 73 years.[3] Results suggest that ARNis may have little or no effect on cardiovascular mortality compared to ARBs/standard medical therapy (RR 0.96, 95% CI 0.79 to 1.15; n=4796; one study; moderate-certainty evidence), all-cause mortality (RR 0.97, 95% CI 0.84 to 1.11; n=7663; 3 studies; high-certainty evidence), or quality of life (high-certainty evidence).[3] However, ARNi treatment may result in a slight reduction in heart failure hospitalization, compared to usual care (RR 0.89, 95% CI 0.80 to 1.00; n=7362; 2 studies; moderate-certainty evidence).[3] ARNi treatment was associated with a reduced risk of hyperkalemia compared with valsartan (RR 0.88, 95% CI 0.77 to 1.01; n=5054; 2 studies; moderate-certainty evidence).[3]

In summary, there is moderate certainty evidence that MRA and ARNi treatment in HFpEF probably reduces heart failure hospitalization but probably has little or no effect on cardiovascular mortality and quality of life (high-quality evidence) compared to placebo/usual care.[3] Low certainty evidence shows beta-blocker treatment may reduce the risk of cardiovascular mortality compared to placebo/usual care; however, further trials are needed.[3] The current evidence for beta-blockers, ACE inhibitors, and ARBs is limited and does not support their use in HFpEF in the absence of an alternative indication.[3] Although MRAs and ARNIs are probably effective at reducing the risk of heart failure hospitalization (moderate certainty evidence), the treatment effect sizes are modest.[3]

After review, 29 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), network meta-analysis, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Canada's Drug Agency: Finerenone Reimbursement Recommendation (2026)

Canada's Drug Agency (CDA) recommends that finerenone be reimbursed by public drug plans as an add-on to standard of care in adults with heart failure with LVEF ≥ 40% to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visits.[4] Finerenone should only be covered when initiated as an add-on to standard of care therapy in adults with NYHA class II to IV with mildly reduced or preserved ejection fraction (LVEF ≥ 40%).[4] Treatment should not be initiated in patients with serum or plasma potassium levels greater than 5.0 mmol/L (i.e., severe hyperkalemia) or with an eGFR less than 25 mL/min/1.73 m^2.[4]

Canada's Drug Agency: Vericiguat Reimbursement Recommendation (2023)

One phase 3, multicenter, double-blind, randomized placebo-controlled trial (VICTORIA; n=5,050) demonstrated that treatment with vericiguat when added to dual or triple background heart failure therapy resulted in added clinical benefit for patients with symptomatic chronic HFrEF who are stabilized after a recent heart failure decompensation event.[5] In the VICTORIA trial, background therapy included beta blockers; ACE inhibitors, ARBs, or an ARNI; and MRA.[5] In the VICTORIA trial, 91.4% of patients were receiving at least 2 medications, 60% of patients were receiving 3 medications, and 14% of patients were receiving sacubitril-valsartan as one of the medications.[5] No patients received background therapy with SGLT2 inhibitors in the VICTORIA trial; therefore, the cumulative benefit and potential harms of adding vericiguat to standard quadruple therapy or adding vericiguat instead of SGLT2 inhibitors to triple therapy remains unknown.[5] There was no evidence from the VICTORIA trial that demonstrated whether patients who are intolerant to one or more of the classes of medications included in standard heart failure therapy may benefit from the addition of vericiguat.[5] Compared with placebo, treatment with vericiguat was associated with a statistically significant and clinically meaningful reduction in the hazard of a first event of CV death or hospitalization for heart failure (hazard ratio [HR] = 0.90; 95% CI, 0.82 to 0.98).[5] Compared to placebo, the hazard of the first event of all-cause mortality or hospitalization for heart failure was lower in the vericiguat group (HR = 0.90; 95% CI, 0.83 to 0.98).[5]

- Canada's Drug Agency recommends that vericiguat be reimbursed for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy.[5]

National Institute for Health and Care Excellence (NICE): Management of Chronic Heart Failure in Adults (2025)

Recommendations for treating HFrEF, HFmrEF, and HFpEF were revised in the updated NICE guidance for management of adults with chronic heart failure.[6]

<u>Management of people with HFrEF:</u>

- Offer an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFrEF.[6]
- For people on maximum tolerated dose of the each of the 4 recommended medicines who continue to have symptoms of HFrEF, consider switching the ACE inhibitor to an ARNi.[6]
- For people with HFrEF who have angioedema after taking an ACE inhibitor, or who have symptoms of intolerance to ARNis, consider an ARB in addition to a beta blocker, MRA, and SGLT2 inhibitor.[6]
- For people with HFrEF who have symptoms of intolerance to ACE inhibitors (other than angioedema), offer an ARNi, a beta blocker, MRA, and SGLT2 inhibitor.[6]
- If ACE inhibitors, ARNis, and ARBs are not tolerated, consider hydralazine in combination with nitrate.[6]
- Offer digoxin to people with worsening or severe HFrEF despite optimized GDMT.[6]
- Avoid verapamil, diltiazem, and short-acting dihydropyridine agents in people with HFrEF.[6]

<u>Management of people with HFmrEF:</u>

- Consider an ACE inhibitor, beta-blocker, MRA, and SGLT2 inhibitor to people with HFmrEF.[6]

- For people with HFmrEF who have symptoms of intolerance to ACE inhibitors, consider an ARB, beta blocker, MRA, and SGLT2 inhibitor (empagliflozin or dapagliflozin).[6]

Management of people with HFpEF:

- Consider an MRA and SGLT2 inhibitor (empagliflozin or dapagliflozin) for treating HFpEF.[6]

Update of European Society of Cardiology: Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2023)

This focused guidance was developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the ESC.[7] Interim focused updates are created when the publication of new evidence could influence clinical practice before the next full update of a guideline is published.[7] Classes of recommendations (COR) and levels of evidence (LOE) are described below.

Classes of Recommendations[7]

- Class I: There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful
- Class IIa: There is a high probability of efficacy/usefulness based on evidence and opinion
- Class IIb: Effectiveness/usefulness is not well established based on evidence and opinion
- Class III: No Benefit: There is evidence or general agreement that the procedure or treatment is not effective and/or useful
- Class III: Harm: There is evidence and/or general agreement that the procedure or treatment is harmful

Levels of Evidence[7]

- Level A: Demonstrated by multiple high-quality RCTs or meta-analyses
- Level B-R: Demonstrated by 1 or more RCTs
- Level B-NR: Demonstrated by 1 or more well-designed, well-executed non-randomized, observational, or registry studies
- Level C-LD: Demonstrated by randomized or non-randomized, observational, or registry studies with design or methodological limitations
- Level C-EO: Consensus of expert opinion based on clinical experience

- Recommendation for the treatment of patients with symptomatic HFmrEF:
  - An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of heart failure hospitalization or CV death (COR: I; LOE: A).[7]
- Recommendation for the treatment of patients with symptomatic HFpEF:
  - An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of heart failure hospitalization or CV death (COR: I; LOE: A).[7]
- Recommendations for the prevention of heart failure in patients T2DM and CKD:
  - In patients with T2DM and CKD, SGLT2 inhibitors are recommended to reduce the risk of heart failure hospitalization and CV death (COR: I; LOE: A).[7]
  - In patients with T2DM and CKD, finerenone is recommended to reduce the risk of heart failure hospitalization (COR: I; LOE: A).[7]

American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Guideline for the Management of Heart Failure (2022)

The 2022 ACC/AHA/HFSA guideline consolidated 2013 and 2017 recommendations into a new document along with recently published evidence for new treatment strategies.[8] In the U.S., approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic CVD.[8] These are known risk factors with high relative risk and population attributable risk for development of heart failure.[8] Therefore, a large proportion of the U.S. population can be categorized as being at-risk for heart failure (stage A).[8] The common causes of heart failure include ischemic heart disease and MI, hypertension, and valvular heart disease (VHD).[8] Stage B or pre-heart failure, represents a phase of clinically asymptomatic structural and functional cardiac abnormalities that increases the risk for symptomatic heart failure.[8] Stages of heart failure were revised in the 2022 guidance to emphasize the new terminologies of at risk for heart failure (Stage A) and pre-heart failure (Stage B.)[8] Classes of recommendations (COR) and levels of evidence (LOE) are defined in the ESC guidance above.

- Pharmacologic recommendations for patients at risk of heart failure (Stage A) include:
    - In patients with hypertension, blood pressure should be controlled in accordance with GDMT for hypertension to prevent symptomatic heart failure (COR: I; LOE: A).[8]
    - In patients with T2DM and either established CVD or at high cardiovascular risk, SGLT2 inhibitors should be used to prevent hospitalizations for heart failure (COR: I; LOE: A).[8]

- Pharmacologic recommendations for patients in pre-heart failure (Stage B) include:
    - In patients with LVEF < 40%, ACE inhibitors should be used to prevent symptomatic heart failure and reduce mortality (COR: I; LOE: A).[8]
    - In patients with a recent or remote history of MI or acute coronary syndrome (ACS), statins should be used to prevent symptomatic heart failure and adverse CV events (COR: I; LOE: A).[8]
    - In patients with a recent MI and LVEF ≤40% who are intolerant to ACE inhibitors, ARB should be used to prevent symptomatic heart failure and reduce mortality (COR: I; LOE: B-R).[8]
    - In patients with a recent or remote history of MI or ACS and LVEF ≤ 40%, evidence-based beta blockers should be used to reduce mortality (COR: I; LOE: B-R).[8]
    - In patients with LVEF ≤40%, beta blockers should be used to prevent symptomatic heart failure (COR: I; LOE: C-LD).[8]
    - In patients with LVEF <50%, thiazolidinediones should not be used because they increase the risk of heart failure, including hospitalization (COE: 3-Harm; LOE: B-R).[8]
    - In patients with LVEF <50%, non-dihydropyridine calcium channel blockers with negative inotropic effects may be harmful (COE: 3-Harm; LOE: LD).[8]

Loop diuretics (bumetanide, furosemide, torsemide) are the preferred diuretic agents for use in most patients with heart failure.[8] Thiazide diuretics such as chlorthalidone or hydrochlorothiazide may be considered in patients with hypertension and heart failure and mild fluid retention.[8] Metolazone or chlorothiazide may be added to loop diuretics in patients with refractory edema unresponsive to loop diuretics alone.[8] The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euvolemia.[8] With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain.[8] As such, diuretics should not be used in isolation but always combined with other GDMT for heart failure that reduces hospitalizations and prolongs survival.[8]

Recommendations for diuretics and decongestion strategies in patients with heart failure include:

- In patients with heart failure who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening heart failure (COR: I; LOE: B-NR).[8]
- For patients with HF and congestive symptoms, addition of a thiazide (e.g., metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate- or high-dose loop diuretics to minimize electrolyte abnormalities (COR: I; LOE: B-NR).[8]

Heart Failure Classification by LVEF[8]

- HFrEF is defined as LVEF ≤ 40%.
- Heart failure with an LVEF of between 41% and 49% is classified as HFmrEF.
- HFpEF is defined as LVEF ≥ 50%.
- HFimpEF is defined as HF in patients whose initial LVEF was ≤ 40%, with a subsequent increase in LVEF ≥ 10% and a resulting LVEF greater than 40% based on longitudinal assessment.

Pharmacologic recommendations for management of HFrEF, HFmrEF, and HFpEF are presented in **Table 1, 2**, and **3,** respectively.
Recent changes include:

- Guideline-directed medical therapy for HFrEF includes the following 4 medication classes: RAAS/ARNIs, beta blockers, MRAs, and SGLT2 inhibitors.[8]
- SGLT2 inhibitors are recommended in HFmrEF (COR: IIa). Weaker recommendations are made for ARNi, ACE inhibitor, ARB, MRA, and beta blockers for patients with HFmrEF.[8]
- New recommendations for HFpEF are made for SGLT2 inhibitors (COR: IIa), MRAs (COR: IIb), and ARNi (COR: IIb).[8]
- Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF > 40%. These patients should continue their HFrEF treatment.[8]

Table 1. Pharmacotherapy Recommendations for Heart Failure with Reduced Ejection Fraction[8]

Recommendation	COR	LOE
In patients with HFrEF and NYHA class II–III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.	I	A
In patients with previous or current symptoms of chronic HFrEF, the use of an ACE inhibitor is beneficial to reduce morbidity and mortality when the use of an ARNi is not feasible.	I	A
In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACE inhibitor because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.	I	A
In patients with chronic symptomatic HFrEF, NYHA class II or III, who tolerate an ACE inhibitor or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.	I	B-R
An ARNi should not be administered concomitantly with an ACE inhibitor or within 36 hours of the last dose of an ACE inhibitor.	III Harm	B-R
ARNi or ACE inhibitor should not be administered to patients with any history of angioedema.	III Harm	C-LD
In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta-blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalization	I	A
In patients with HFrEF and NYHA class II-IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if estimated glomerular filtration rate is > 30 mL/min/1.73 m2 and serum potassium is < 5.0 mEq/L. Careful monitoring of potassium,	I	A

renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency.		
In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia.	III Harm	B-R
In patients with symptomatic chronic HFrEF, an SGLT2 inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.	I	A
For patients self-identified as African American with NYHA class III–IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.	I	A
In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.	IIb	C-LD
In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid (PUFA) supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations.	IIb	B-R
In patients with chronic HFrEF without a specific indication (e.g., venous thromboembolism, AF, a previous thromboembolic event, or a cardioembolic source), anticoagulation is not recommended.	3 No Benefit	B-R
For patients with symptomatic (NYHA class II to III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.	IIa	B-R
In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.	IIb	B-R
In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.	IIb	B-R
Abbreviations: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARBs = Angiotensin Receptor Blockers; ARNi = Angiotensin Receptor-Neprilysin Inhibitor; COR = Class Of Recommendation; GDMT = Guideline-Directed Medical Therapy; HF = Heart Failure; HFrEF = Heart Failure With Reduced Ejection Fraction; LOE = Level Of Evidence; MRA = Mineralocorticoid Receptor Antagonists; NYHA = New York Heart Association; SGLT2 = Sodium-Glucose Cotransporter 2		

Table 2. Pharmacotherapy Recommendations for HF with Mildly Reduced Ejection Fraction[8]

Recommendation	COR	LOE
In patients with HFmrEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.	IIa	B-R
In patients with current or previous symptomatic HFmrEF (LVEF, 41%–49%), use of evidence-based beta-blockers for HFrEF, ARNi, ACE inhibitor or ARB, and MRAs may be considered to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.	IIb	B-NR
Abbreviations: ACEi = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; ARNi = Angiotensin Receptor-Neprilysin Inhibitor; COR = Class of Recommendation; HF = Heart Failure; HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; MRAs = Mineralocorticoid Receptor Antagonists; SGLT2 = Sodium-Glucose Cotransporter 2		

Table 3. Pharmacotherapy Recommendations for HF with Preserved Ejection Fraction[8]

Recommendation	COR	LOE

In patients with HFpEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.	IIa	B-R
In selected patients with HFpEF, MRA may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of the spectrum.	IIb	B-R
In selected patients with HFpEF, ARNis may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum.	I	C-LD
In patients with HFpEF, management of AF can be useful to improve symptoms.	IIa	C-EO
In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly in patients with LVEF on the lower end of this spectrum	IIb	B-R
In patients with HFpEF, routine use of nitrates of phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective.	3 No Benefit	B-R
Abbreviations: ARB = Angiotensin Receptor Blocker; AF = atrial fibrillation; ARNis = Angiotensin Receptor-Neprilysin Inhibitors; COR = Class of Recommendation; HF = Heart Failure; HFpEF = Heart Failure with Preserved Ejection Fraction; LOE = Level of Evidence; LVEF = left ventricular ejection fraction; MRA = Mineralocorticoid Receptor Antagonist; SGLT2 = Sodium-Glucose Cotransporter 2		

After review, 2 guidelines were excluded due to poor quality.[18,19]

New Formulations and Indications:

New Formulations

- 10/2025: The FDA approved LASIX ONYU, a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours.[9] The single-use, prefilled cartridge contains furosemide 80 mg/2.67 mL.[9] The infuser device delivers furosemide 30 mg over the first hour, then 12.5 mg per hour for the subsequent 4 hours.[9] LASIX ONYU is indicated for the treatment of edema in adult patients with heart failure.[9] The FDA based the approval of LASIX ONYU on pharmacokinetic studies that showed subcutaneous administration of LASIX ONYU produced similar diuresis and natriuresis to IV furosemide administration at 8- and 24-hours post-dose in patients with edema due to heart failure.[9]

- 9/2025: The FDA approved ENBUMYST, a new dosage form of bumetanide nasal spray which contains 0.5 mg/0.1 mL per each unit of use device.[10] ENBUMYST indicated for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease, including nephrotic syndrome in adults.[10] The usual total daily dose of bumetanide is 0.5 mg to 2 mg once daily; the number of nasal spray devices needed for a single dose depends on the prescribed dose.[10] The nasal spray is not intended for chronic use, it should be replaced with oral diuretics as soon as practical.[10] The FDA based the approval of ENBYMYST on clinical trials that supported the safety and efficacy of oral bumetanide.[10] Pharmacokinetic studies demonstrated the bioequivalency of bumetanide nasal spray to oral and IV bumetanide formulations.[10]

- 7/2025: The FDA approved VOSTALLY a new dosage form of ramipril oral suspension 1 mg/mL, indicated for the treatment of hypertension in adults; to reduce the risk of MI, stroke or death from CV causes in patients 55 years or older at high risk of developing major CV events; and to reduce the risk of CV death and hospitalization for heart failure in adults with post-MI heart failure.[11] The FDA approval was based on pharmacokinetic studies demonstrating the bioequivalency of the oral suspension to oral forms of ramipril tablets and capsules.[11]

- 3/2025: The FDA approved ARBLI, a new dosage form of losartan oral suspension 10 mg/mL, indicated for the treatment of hypertension in adults and children greater than 6 years old; reduction of stroke in patients with hypertension and left ventricular hypertrophy (there is evidence that this benefit does

not apply to Black patients); and treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with T2DM and a history of hypertension.[12] The FDA based the approval of ARBLI on clinical trials that supported the safety and efficacy of losartan tablets.[10] Pharmacokinetic studies demonstrated the bioequivalency of losartan oral suspension to oral losartan tablet formulations.[10]

- 3/2025: The FDA approved HEMICLOR, a new oral dosage form of chlorthalidone 12.5 mg tablets indicated for the treatment of hypertension in adults.[13] The manufacturer did not conduct any clinical studies for this dosage form, instead a literature-based review was submitted to the FDA to support the efficacy of 12.5 mg dosing of chlorthalidone to control hypertension alone or in combination with other antihypertensive medications.[13]

- 1/2025: The FDA approved INZIRQO, a new dosage form of hydrochlorothiazide oral suspension 10 mg/mL, indicated for the treatment of hypertension in adults and pediatric patients and for the treatment of edema associated with congestive heart failure, hepatic cirrhosis, and renal disease in adults and pediatrics.[14] The approval was based on pharmacokinetic studies comparing the oral suspension to oral forms of generic hydrochlorothiazide tablets. Previous findings from published safety and efficacy studies for hydrochlorothiazide tablets also supported the FDA approval.[14]

- 10/2022: The FDA approved FUROSCIX, a single-use, subcutaneous injection form of furosemide designed to administer 80 mg over 5 hours.[15] The prefilled cartridge contains furosemide 80 mg/10 mL.[15] The on-body infuser device is a pre-programmed cartridge designed to deliver 30 mg of furosemide over the first hour, then 12.5 mg per hour for the subsequent 4 hours.[15] FUROSCIX is indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure.[15] This indication was later expanded (see next section). This device is not for chronic use and should be replaced with oral diuretics as soon as practical.[15] The FDA based the approval of FUROSCIX on pharmacokinetic studies that showed subcutaneous administration of FUROSCIX produced similar diuresis and natriuresis to IV furosemide administration at 8- and 24-hours post-dose in patients with edema due to heart failure.[9]

New Indications:

- 12/2025: The FDA approved the expanded use of FUROSCIX for the treatment of edema in pediatric patients weighing 43 kg and above with chronic heart failure.[15] Previously, FUROSCIX was FDA-approved for treatment of edema in adults with chronic heart failure or chronic kidney disease.[7] (The CKD indication was added in March 2025). FUROSCIX has not been studied in pediatric patients.[15] Use of FUROSCIX for this indication is supported by: 1) efficacy, safety, and pharmacokinetic data of furosemide in adult and pediatric patients and 2) population pharmacokinetic modeling which demonstrated no significant difference in furosemide exposure following FUROSCIX administration in a simulated pediatric population weighing 43 kg and above and aged 6 to <17 years compared to adult patients with chronic heart failure.[15]

- 7/2025: The FDA approved an expanded indication of finerenone for reduction of risk of CV death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure and LVEF $\geq$ 40%.[16] The target daily dose of finerenone for heart failure (LVEF $\geq$ 40%) is dependent on renal function at initiation of treatment. The target dose is 40 mg once daily for eGFR $\geq$ 60 mL/min/1.73m^2 and 20 mg once daily if eGFR $\geq$ 25 to < 60 mL/min/1.73m^2.[16] Prior to this expanded indication, finerenone was approved to reduce the risk of sustained eGFR decline, end stage kidney disease, CV death, non-fatal MI and hospitalization for heart failure in adults with CKD associated with T2DM.[16] The target dose is this population is 20 mg once daily, based on eGFR and serum potassium thresholds.[16]

The safety and efficacy of finerenone in patients with heart failure was evaluated in a double-blind, placebo-controlled, multicenter RCT, FINEARTS-HF, in which a total of 3003 patients were treated with a target dose of 20 mg or 40 mg once daily of finerenone with a mean duration of treatment of 2.7 years.[16] The primary endpoint was the composite of CV death and total (first and recurrent) heart failure events comprised of hospitalization for heart failure and urgent heart failure visits.[16] Finerenone reduced the risk of the primary composite endpoint compared to placebo (RR 0.84; 95% CI 0.74 to 0.95; p = 0.007).[16] The overall safety profile of finerenone in the FINEARTS-HF study was largely consistent with the adverse reactions reported in patients with CKD and T2DM.[16]

- 4/2021: The FDA expanded the approval of valsartan to include children aged 1 year and older for the treatment of hypertension.[17] Previously, the treatment was indicated for patients 6 years of age and older with hypertension.[17] The antihypertensive effects of valsartan were evaluated in 3 single-arm clinical studies in pediatric patients from 1 to less than 6 years of age.[17] In all 3 RCTs, valsartan reduced systolic blood pressure.[17] The adverse experience profile of valsartan was similar to that described for adults.[17]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts[20]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Spironolactone	CAROSPIR	8/2023	Use in Specific Populations	CAROSPIR is not recommended for the treatment of hypertension in pediatric patients because of the potential risks associated with the antiandrogenic, progestogenic, and estrogenic properties of spironolactone in pediatric patients.

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9. LASIX ONYU (furosemide) for subcutaneous injection. Prescribing Information. Burlington, MA; SQ Innovation, Inc. October 2025.
10. ENBUMYST (bumetanide) nasal spray. Prescribing Information. Henderson, NV; Corstasis Therapeutics. September 2025.
11. VOSTALLY (ramipril) oral solution. Prescribing Information. Watkinsville, GA; Metacel Pharmaceuticals, LLC. July 2025.
12. ARBLI (losartan potassium) oral suspension. Prescribing Information. Commack, NY; Scienture, LLC. February 2026.
13. HEMICLOR (chlorthalidone) oral tablets. Prescribing Information. Orlando, FL; Ingenus Pharmaceuticals, LLC. March 2025.
14. INZIRQO (hydrochlorothiazide) oral suspension. Prescribing Information. Baudette MN; ANI Pharmaceuticals, Inc. January 2025.
15. FUROSCIX (furosemide) subcutaneous injection. Prescribing Information. Burlington, MA; scPharmaceuticals, Inc. December 2025.
16. KERENDIA (finerenone) oral tablets. Prescribing Information. Whippany, NJ; Bayer HealthCare Pharmaceuticals, Inc. July 2025.
17. DIOVAN (valsartan) oral tablets. Prescribing Information. East Hanover, NJ; Novartis Pharmaceuticals Corportation. April 2021.
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Appendix 1: Current Preferred Drug List

Diuretics, oral

Generic	Brand	Route	Form	PDL
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	CAPSULE	Y
triamterene	TRIAMTERENE	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	CAPSULE	Y
furosemide	FUROSEMIDE	ORAL	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	SOLUTION	Y
spironolactone	ALDACTONE	ORAL	TABLET	Y
amiloride HCl	AMILORIDE HCL	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	ORAL	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
bumetanide	BUMETANIDE	ORAL	TABLET	Y
chlorthalidone	CHLORTHALIDONE	ORAL	TABLET	Y
furosemide	FUROSEMIDE	ORAL	TABLET	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	ORAL	TABLET	Y
indapamide	INDAPAMIDE	ORAL	TABLET	Y
furosemide	LASIX	ORAL	TABLET	Y
spironolactone	SPIRONOLACTONE	ORAL	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	ORAL	TABLET	Y
torsemide	TORSEMIDE	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	ORAL	TABLET	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	ORAL	TABLET	Y
spironolactone	CAROSPIR	ORAL	ORAL SUSP	N
spironolactone	SPIRONOLACTONE	ORAL	ORAL SUSP	N
furosemide	FUROSEMIDE	ORAL	SOLUTION	N
hydrochlorothiazide	INZIRQO	ORAL	SUSP RECON	N
eplerenone	EPLERENONE	ORAL	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	ORAL	TABLET	N
chlorthalidone	HEMICLOR	ORAL	TABLET	N
eplerenone	INSPRA	ORAL	TABLET	N
finerenone	KERENDIA	ORAL	TABLET	N
metolazone	METOLAZONE	ORAL	TABLET	N
chlorthalidone	THALITONE	ORAL	TABLET	N
metolazone	METOLAZONE	ORAL	TABLET	
hydroflumethiazide	SALURON	ORAL	TABLET	
furosemide	FUROSCIX	SUBCUT	KIT	

furosemide*	LASIX ONYU	SUBCUT	KIT	
bumetanide*	ENBUMYST	NASAL	SPRAY	

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

Generic	Brand	Route	Form	PDL
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
quinapril HCl	ACCUPRIL	ORAL	TABLET	Y
candesartan cilexetil	ATACAND	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
olmesartan medoxomil	BENICAR	ORAL	TABLET	Y
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
olmesartan medoxomil	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	ARBLI	ORAL	ORAL SUSP	N
sacubitril/valsartan	ENTRESTO SPRINKLE	ORAL	PEL DSP CP	N
enalapril maleate	ENALAPRIL MALEATE	ORAL	SOLUTION	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
aliskiren hemifumarate	ALISKIREN	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
sacubitril/valsartan	ENTRESTO	ORAL	TABLET	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N
perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N

sacubitril/valsartan	SACUBITRIL-VALSARTAN	ORAL	TABLET	N
aliskiren hemifumarate	TEKTURNA	ORAL	TABLET	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
valsartan	VALSARTAN	ORAL	SOLUTION	
lisinopril	LISINOPRIL	ORAL	TABLET	

Vasodilators: Coronary

Generic	Brand	Route	Form	PDL
vericiguat	VERQUVO	PO	TABLET	N

*Not currently a rebatable product

Appendix 2: New Comparative Clinical Trials

A total of 165 citations were manually reviewed from the initial literature search. After further review, 135 citations were excluded because of wrong study design (e.g., observational), comparator (ego, no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Mentz, RJ, et al[21] OL, RCT	1. Oral torsemide: dosing determined by provider N=1431 Vs. 2. Oral furosemide: dosing determined by provider N=1428 Dosing conversion guide: Torsemide 1 mg to Furosemide 2-4 mg	Inclusion Criteria: Patients over 18 yo with LVEF ≤ 40% within 24 mos Or Elevated BNP (baseline not described) Exclusions: -CKD requiring dialysis -History of heart transplant or LVAD Demographics: Median age: 65 yo Female: 37% Black: 34% Beta-blocker use: 82% RAAS use: 68% MRA use: 44% SGLT2i use: 8%	All-cause mortality in a time-to-event analysis over 30 months after discharge for HF exacerbation	All-cause mortality rates over 17.4 mos: 1. 373 (26.1%) 2. 374 (26.2%) HR: 1.02 95% CI 0.89 to 1.18 P= 0.76 Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months.	-Nonadherence at 30 days was 7% and at 6 mos was 9.5% of patients -7% crossover from torsemide to furosemide and 3.85% crossover from furosemide to torsemide -Variations in baseline GDMT among enrolled patients -Dosing discretion led to variations in how each diuretic was prescribed -Interpretation of these findings is limited by loss to follow-up, participant crossover to different diuretic therapy, and nonadherence to diuretic therapy
Pieske B, et al[22] PARALLAX RCT DB, AC/PC, RCT	1. Sacubitril/valsartan 97 mg/103 mg twice daily N=1281 Vs. 2. RAAS therapy (enalapril 10 mg,	Inclusion Criteria: -Patients 45 yo and older with HF and LVEF > 40% requiring diuretic treatment -NYHA Class II-IV -Plasma NT-proBNP > 220 pg/mL in NSR and > 600 pg/mL for	Co-primary end points were change from baseline in plasma NT-proBNP level at week 12 and in the 6-minute walk distance at week 24.	1. Change from baseline in NT-proBNP after 12 weeks Median baseline NT-proBNP = 786 pg/mL in the sacubitril/valsartan arm and 760 pg/mL in the comparator group. Median NT-proBNP at 12 weeks not reported for either arm.	--NT-proBNP is a prognostic biomarker in HF, surrogate endpoint -A clinically significant decrease in NT-proBNP is a drop of 25-30% -Results reported as change in geometric mean ratio which indicates a shift in the average rate of decline -Short trial duration (24 weeks)

	valsartan 160 mg, or placebo) N=1285 Enalapril: n = 510 Valsartan: n = 558 Placebo: n= 148 Trial Duration: 24 weeks 396 centers in 32 countries	patients with AF or atrial flutter -Structural heart disease (left atrial enlargement or left ventricular hypertrophy) -If on ACEi/ARB therapy, must have history of HTN Exclusions: -LVEF $\leq$ 40% -Acute coronary syndrome, cardiac surgery -Acute decompensated HF within 30 days of study entry -SBP $\geq$ 180 -Serum potassium > 5.2 mmol/L Demographics: -Mean age: 72.6 yo -Female: 51% -Baseline median NT-proBNP: 786 pg/mL (sacubitril/valsartan) vs. 760 pg/mL (RAAS)		Results reported as adjusted mean geometric ratio, where a ratio lower than 1 favors sacubitril/valsartan 1. Adjusted mean ratio to baseline: 0.82 pg/mL 2. Adjusted mean ratio to baseline: 0.98 pg/mL Adjusted geometric mean ratio: 0.84 95% CI 0.80 to 0.88 P<0.0001 2. Change from baseline in exercise capacity as assessed by the 6MWT at 24 weeks 1. Increased by 9.7 meters 2. Increased by 12.2 meters Mean Difference: -2.5 meters 95% CI -8.5 to 3.5 meters P=0.42 Compared with standard medical therapies, sacubitril/valsartan resulted in a significantly greater decrease in plasma N-terminal pro–brain natriuretic peptide at 12 weeks but did not improve submaximal exercise capacity at 24 weeks. The clinical significance of this change is not clear. Further research is needed to evaluate potential benefits of sacubitril/valsartan.	-Did not evaluate long term outcomes such as heart failure hospitalization or cardiovascular mortality
Abbreviations: 6MWT = 6 minute walk test; AC = active comparator; ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CI = confidence interval; CKD = chronic kidney disease; DB = double-blind; GDMT = Guideline Directed Medical Therapy; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; HTN = hypertension; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; mg = milligrams; mos = months; mL = milliliters; MRA = mineralocorticoid receptor antagonist; NSR = normal sinus rhythm; NT-proBNP = N-terminal pro b-type natriuretic peptide; OL = open-label; PC = placebo controlled; pg = picogram; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium glucose transporter 2 inhibitor; RAAS = RCT = randomized clinical trial; SBP = systolic blood pressure; Scr = serum creatinine; yo = years old				

Appendix 3: Abstracts of Comparative Clinical Trials

***Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: The TRANSFORM-HF Randomized Clinical Trial*[21]**

Objective: To determine whether torsemide results in decreased mortality compared with furosemide among patients hospitalized for heart failure.

Design, Setting, and Participants: TRANSFORM-HF was an open-label, pragmatic randomized trial that recruited 2859 participants hospitalized with heart failure (regardless of ejection fraction) at 60 hospitals in the United States. Recruitment occurred from June 2018 through March 2022, with follow-up through 30 months for death and 12 months for hospitalizations. The final date for follow-up data collection was July 2022.

Interventions: Loop diuretic strategy of torsemide (n = 1431) or furosemide (n = 1428) with investigator-selected dosage.

Main Outcomes and Measures: The primary outcome was all-cause mortality in a time-to-event analysis. There were 5 secondary outcomes with all-cause mortality or all-cause hospitalization and total hospitalizations assessed over 12 months being highest in the hierarchy. The prespecified primary hypothesis was that torsemide would reduce all-cause mortality by 20% compared with furosemide.

Results: TRANSFORM-HF randomized 2859 participants with a median age of 65 years (IQR, 56-75), 36.9% were women, and 33.9% were Black. Over a median follow-up of 17.4 months, a total of 113 patients (53 [3.7%] in the torsemide group and 60 [4.2%] in the furosemide group) withdrew consent from the trial prior to completion. Death occurred in 373 of 1431 patients (26.1%) in the torsemide group and 374 of 1428 patients (26.2%) in the furosemide group (hazard ratio, 1.02 [95% CI, 0.89-1.18]). Over 12 months following randomization, all-cause mortality or all-cause hospitalization occurred in 677 patients (47.3%) in the torsemide group and 704 patients (49.3%) in the furosemide group (hazard ratio, 0.92 [95% CI, 0.83-1.02]). There were 940 total hospitalizations among 536 participants in the torsemide group and 987 total hospitalizations among 577 participants in the furosemide group (rate ratio, 0.94 [95% CI, 0.84-1.07]). Results were similar across prespecified subgroups, including among patients with reduced, mildly reduced, or preserved ejection fraction.

Conclusions and Relevance: Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months. However, interpretation of these findings is limited by loss to follow-up and participant crossover and nonadherence.

***Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction: The PARALLAX Randomized Clinical Trial*[22]**

Objective: To evaluate the effect of sacubitril/valsartan on N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, 6-minute walk distance, and quality of life vs background medication–based individualized comparators in patients with chronic heart failure and LVEF of more than 40%.

Design, Setting, and Participants: A 24-week, randomized, double-blind, parallel group clinical trial (August 2017-October 2019). Of 4632 patients screened at 396 centers in 32 countries, 2572 patients with heart failure, LVEF of more than 40%, elevated NT-proBNP levels, structural heart disease, and reduced quality of life were enrolled (last follow-up, October 28, 2019).

Interventions: Patients were randomized 1:1 either to sacubitril/valsartan (n = 1286) or to background medication–based individualized comparator (n = 1286), i.e., enalapril, valsartan, or placebo stratified by prior use of a renin angiotensin system inhibitor.

Main Outcomes and Measures: Primary end points were change from baseline in plasma NT-proBNP level at week 12 and in the 6-minute walk distance at week 24. Secondary end points were change from baseline in quality-of-life measures and New York Heart Association (NYHA) class at 24 weeks.

Results: Among 2572 randomized patients (mean age, 72.6 years [SD, 8.5 years]; 1301 women [50.7%]), 2240 (87.1%) completed the trial. At baseline, the median NT-proBNP levels were 786 pg/mL in the sacubitril/valsartan group and 760 pg/mL in the comparator group. After 12 weeks, patients in the sacubitril/valsartan group (adjusted geometric mean ratio to baseline, 0.82 pg/mL) had a significantly greater reduction in NT-proBNP levels than did those in the comparator group (adjusted geometric mean ratio to baseline, 0.98 pg/mL) with an adjusted geometric mean ratio of 0.84 (95% CI, 0.80 to 0.88; P < .001). At

week 24, there was no significant between-group difference in median change from baseline in the 6-minute walk distance with an increase of 9.7 m vs 12.2 m (adjusted mean difference, −2.5 m; 95% CI, −8.5 to 3.5; P = .42). There was no significant between-group difference in the mean change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (12.3 vs 11.8; mean difference, 0.52; 95% CI, −0.93 to 1.97) or improvement in NYHA class (23.6% vs 24.0% of patients; adjusted odds ratio, 0.98; 95% CI, 0.81 to 1.18). The most frequent adverse events in the sacubitril/valsartan group vs the comparator group were hypotension (14.1% vs 5.5%), albuminuria (12.3% vs 7.6%), and hyperkalemia (11.6% vs 10.9%)

Conclusions and Relevance: Among patients with heart failure and left ventricular ejection factor of higher than 40%, sacubitril/valsartan treatment compared with standard renin angiotensin system inhibitor treatment or placebo resulted in a significantly greater decrease in plasma N-terminal pro–brain natriuretic peptide levels at 12 weeks but did not significantly improve 6-minute walk distance at 24 weeks. Further research is warranted to evaluate potential clinical benefits of sacubitril/valsartan in these patients.

Appendix 4: Medline Search Strategy

DIURETICS

Ovid MEDLINE(R) ALL <1946 to April 01, 2026>

1	Hydrochlorothiazide/tu [Therapeutic Use]	3266
2	Triamterene/ or Diuretics/	31072
3	exp Furosemide/tu [Therapeutic Use]	3952
4	exp Spironolactone/tu [Therapeutic Use]	3503
5	Amiloride/tu [Therapeutic Use]	660
6	exp Bumetanide/tu [Therapeutic Use]	272
7	exp Chlorthalidone/tu [Therapeutic Use]	885
8	exp Indapamide/tu [Therapeutic Use]	615
9	exp Torsemide/tu [Therapeutic Use]	40
10	exp Eplerenone/tu [Therapeutic Use]	148
11	exp Ethacrynic Acid/tu [Therapeutic Use]	408
12	Naphthyridines/ or finerenone.mp.	4956
13	exp Metolazone/tu [Therapeutic Use]	89
14	exp Hydroflumethiazide/tu [Therapeutic Use]	44
15	finerenone.mp. or Mineralocorticoid Receptor Antagonists/	7234
16	Diuretics, Potassium Sparing/ or Diuretics/ or Diuretics, Osmotic/	31303
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	49910
18	Heart Failure/th [Therapy]	32277
19	17 and 18	1246
20	limit 19 to (english language and humans and yr="2021 -Current")	142

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)

Ovid MEDLINE(R) ALL <1946 to March 31, 2026>

1	exp Ramipril/tu [Therapeutic Use]	1118
2	exp Quinapril/	639
3	candesartan.mp. or Angiotensin II Type 1 Receptor Blockers/	11799
4	exp Irbesartan/tu [Therapeutic Use]	85
5	Angiotensin-Converting Enzyme Inhibitors/ or benazepril.mp.	37931
6	Olmesartan Medoxomil/tu [Therapeutic Use]	24
7	exp Losartan/tu [Therapeutic Use]	2355
8	exp Valsartan/tu [Therapeutic Use]	724
9	exp Enalapril/tu [Therapeutic Use]	3263

10	exp Fosinopril/tu [Therapeutic Use]	215
11	exp Lisinopril/tu [Therapeutic Use]	852
12	exp Telmisartan/tu [Therapeutic Use]	170
13	exp Enalapril/tu [Therapeutic Use]	3263
14	exp Captopril/tu [Therapeutic Use]	3946
15	azilsartan.mp.	354
16	moexipril.mp.	123
17	exp Perindopril/tu [Therapeutic Use]	849
18	eprosartan.mp.	439
19	trandolapril.mp.	752
20	aliskiren.mp.	1352
21	Valsartan/	4145
22	sacubitril.mp.	2716
23	Soluble Guanylyl Cyclase/ or vericiguat.mp.	1855
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	59413
25	Heart Failure/th [Therapy]	32277
26	24 and 25	819
27	limit 26 to (english language and humans and yr="2021 -Current")	123

Appendix 5: Key Inclusion Criteria

Population	Adults and Children with Heart Failure
Intervention	Diuretics, ACE inhibitors, ARBs, MRAs, ARNis, Vericiguat
Comparator	Other active comparators used to manage heart failure
Outcomes	Resolution of heart failure systems, reduction in heart failure hospitalizations and CV events
Timing	6 months to 1 year
Setting	Outpatient

Finerenone

Goal(s):
- Promote use of finerenone that is consistent with medical evidence
- Promote use of high value products

Length of Authorization:
- 12 months

Requires PA:
Finerenone (Kerendia™)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Does the patient have a diagnosis of heart failure with LVEF ≥ 40%?	**Yes:** Go to #5	**No:** Go to #3
3. Is the patient 18 years or older with a diagnosis of type 2 diabetes?	**Yes:** Go to #4	**No:** Pass to RPh; deny for medical appropriateness
4. Does the patient have a diagnosis of chronic kidney disease?	**Yes:** Go to #5	**No:** Pass to RPh; deny for medical appropriateness.
5. Does the patient have a documented estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) < 25 ml/min **OR** require hemodialysis?	**Yes:** Pass to RPh; deny for medical appropriateness. Request eGFR if not provided	**No:** Document eGFR and go to #6 Recent eGFR: _____ Date:

Approval Criteria		
6. Is the patient currently on standard of care for heart failure including a maximally tolerated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor (ARNI) OR have a documented contraindication to these medications?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the patient's serum potassium ≤ 5.0 mEq/L?	**Yes:** Approve for up to 12 months Recent potassium:____ Date: _____	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *8/26 (DM); 06/22 (MH)*
Implementation: *TBD; 7/1/22*

Sacubitril/Valsartan (Entresto™) RET(RE

Goal(s):
- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:
- 3 to 12 months

Requires PA:
- Sacubitril/valsartan (Entresto™)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have chronic heart failure (New York Heart Association [NYHA] Class II-IV)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient 17 years of age or younger?	**Yes:** Go to #5	**No:** Go to # 7
5. Does the patient have left ventricular systolic dysfunction (ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the medication prescribed by or in consultation by a cardiologist or heart failure provider?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness
7. Has the patient tolerated a minimum daily dose of an ACE-inhibitor or ARB listed in Table 1 for at least 30 days? *Note: ACE inhibitors must be discontinued at least 36 hours prior to initiation of sacubitril/valsartan*	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have heart failure with reduced ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #9	**No:** Approve for 3 months *Note: Benefits of therapy are most clearly evident in patients with left ventricular ejection fraction below normal. Use judiciously with higher baseline ejection fraction*

Approval Criteria		
9. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and ACE-I/ARB) through pharmacy claims/refill history and provider assessment?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Is the patient 18 years or older or at least 50 kg?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
3. Is the patient currently taking sacubitril/valsartan at the target dose in Table 2 or to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
4. What is the clinical reason the drug has not been titrated to the target dose?	Document rationale and approve for up to 90 days. Prior authorization required every 90 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1,2]

ACE-inhibitor	Angiotensin-2 Receptor Blocker (ARB)

Captopril	100 mg/day	Candesartan	16 mg/day
Enalapril	10 mg/day	Losartan	50 mg/day
Lisinopril	10 mg/day	Valsartan	160 mg/day
Ramipril	5 mg/day	Olmesartan	10 mg/day
Trandolapril	2 mg/day	Irbesartan	150 mg/day
Fosinopril	20 mg/day		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:

- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of sacubitril/valsartan to reduce risk of angioedema.[3,4]

Table 2: Target dose of sacubitril/valsartan in pediatric heart failure[4]

Population	Target Dose
Patients less than 40 kg	3.1 mg/kg twice daily
Patients at least 40 kg, less than 50 kg	72/78 mg twice daily
Patients at least 50 kg	97/103 mg twice daily

References:

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2017;136(6): e137-e161.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012; 14:803-869. doi:10.1093/eurjhf/hfs105.
3. McMurray J, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Eng J Med*. 2014; 371:993-1004. doi:10.1056/NEJMoa1409077.
4. ENTRESTO (sacubitril and valsartan) [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, February 2021.

P&T / DUR Review: *8/26(DM); 6/21(MH); 05/17(DM), 09/15*
Implementation: *TBD; 7/1/21; 10/13/16; 10/1/15*

Vericiguat (Verquvo®)

Goal(s):

- Restrict use of vericiguat in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Vericiguat (Verquvo®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3.	
3. Does the patient have symptomatic New York Heart Association (NYHA) Class II to IV chronic heart failure?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have reduced ejection fraction (< 45%) assessed within the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have worsening heart failure defined as one of the following? a. History of previous heart failure hospitalization within the last 6 months b. Intravenous diuretic use within previous 3 months	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient on an angiotensin system inhibitor at maximally tolerated dose, such as: a. Angiotensin converting enzyme inhibitor (ACE-I) b. Angiotensin receptor blocker (ARB) c. Angiotensin receptor-neprilysin inhibitor (ARNI)	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #9	**No:** Pass to RPh. Deny, medical appropriateness
9. Is there evidence of adherence and tolerance to goal directed heart failure therapy (beta-blocker and angiotensin inhibitor) through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #10	**No:** Pass to RPh. Deny, medical appropriateness
10. Is the patient on long-acting nitrates such as isosorbide dinitrate, isosorbide 5-mononitrate, transdermal nitroglycerin, or other similar agents or phosphodiesterase-5 (PDE5) inhibitors (e.g. sildenafil, tadalafil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Does the patient have stage 5 chronic kidney disease (eGFR < 15 ml/min or on hemodialysis/peritoneal dialysis)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the patient of childbearing potential?	**Yes:** Go to #13	**No:** Approve for 6 months
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Has the patient developed symptomatic hypotension or syncope while on vericiguat?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #2
2. Has the patient experienced disease progression, defined as either worsening NYHA functional class or worsening signs and symptoms of heart failure requiring intensification of therapy?	**Yes:** Go to #3	**No:** Approve for 12 months
3. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *8/26 (DM); 06/21 (MH)*
Implementation: *TBD; 7/1/21*

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Teplizumab Prior Authorization Criteria Update

Date of Review: August 2026

Literature Search: 07/01/2018 – 05/15/26
Date of Last Review: Miscellaneous Antidiabetic Agents (July 2018)

Purpose of the Review: Teplizumab is a CD3-directed antibody initially approved in November of 2022 to delay the onset of Stage 3 type 1 diabetes (T1D) in adults and pediatric patients 8 years and older. Recently teplizumab has been approved for two additional indications. The purpose of this review is to update the prior authorization (PA) criteria to include these new indications.

New Indications:

Use in Stage 2 T1D
Teplizumab was approved in April 2026 to delay the onset of Stage 3 T1D in pediatric patients between 1 and 8 years, previously approved in patients 8 years and older, with Stage 2 T1D.[1] Approval was based on evidence from a single arm, open-label safety and pharmacokinetic study in pediatric patients with Stage 2 T1D (**Table 1**).[2]

The diagnosis of Stage 2 T1D should be confirmed by the following before administering teplizumab:
- Document at least two positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is not available.
- In patients who meet criteria for a diagnosis of Stage 2 T1D, ensure the patient's diagnosis confirms an autoimmune origin and does not suggest insulin resistance due to obesity, type 2 diabetes (T2D) or dysglycemia due to other forms of diabetes.

Use in Stage 3 T1D
In June 2026, teplizumab received an additional indication to delay the decline in endogenous insulin production in pediatric patients aged 8 to 17 years recently diagnosed with Stage 3 T1D.[1] Approval was granted via the accelerated approval program based on reduced C-peptide decline and may be contingent on confirmatory trials demonstrating benefit. Evidence was based on results of the PROTECT study shown in **Table 1** below. [3]

Teplizumab use in Stage 3 T1D should be confirmed by the following:
- Document at least one positive pancreatic islet cell autoantibody and peak C-peptide ≥0.2 pmol/mL on a mixed-meal tolerance test (MMTT) or alternative method if appropriate and MMTT is not available.

Author: Kathy Sentena, PharmD

Table 1. Studies used for Expanded Indications for Teplizumab

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Gitelman, et al[2] (PETITE-1D) MC, OL, Single arm	Teplizumab given once daily for 14-days Trial duration: 2 years	Children < 8 years with Stage 2 T1D (n=23)	Treatment-emergent adverse events (TEAE), TEAE treatment discontinuations and serious adverse events	- All participants experienced a TEAE that was mild to moderate in most cases - TEAE leading to discontinuation occurred in 3 (13%) patients (anemia, elevated liver enzymes and macro-papular rash) - Two patients (9%) had a severe adverse reaction	- Mean age 4.8 years - Safety was similar to other studies - Two patients developed Stage 3 T1D during study
Ramos, et al[3] (PROTECT) PC, Phase 3, RCT	Teplizumab given once daily as two 12-day treatment courses Vs. Placebo Trial duration: 78 weeks	Children and adolescents with newly diagnosed T1D (within 6 weeks) (n=328)	Change from baseline in beta-cell function, as measured by stimulated C-peptide levels at week 78	Teplizumab: -0.09 Placebo: -0.21 LSMD 0.13 pmol/ml; 95% CI, 0.09 to 0.17 P<0.001 -	- Mean age was 12.1 years - Baseline mean peak C-peptide level was 0.2 to 0.7 pmol/ml in 42.1% and >0.7 pmol/ml in 57.9% - Mean HbA1c was 9.0% - More patients treated with teplizumab maintained a C-peptide level of 0.2 pmol/ml or greater compared to placebo, 94.9% vs 79.2%
Abbreviations: CI = confidence interval; DB= double blind; HbA1c = hemoglobin A1C; LSMD = least square mean difference; MC = multi-center; PC = placebo controlled; RCT = randomized clinical trial; T1D = type 1 diabetes.					

Patients that are candidates for teplizumab should undergo additional laboratory testing prior to administration. Prior to teplizumab use, a complete blood count, liver enzyme tests, and evaluation for active Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection, including assessment of viral load (e.g., polymerase chain reaction testing) should be performed.[1] Teplizumab should not be used in patients with certain laboratory abnormalities. The use of teplizumab is contraindicated in patients who are immunocompromised or have active viral infection (such as EBV or CMV infection). Age-appropriate vaccinations should be given prior to teplizumab administration.[1] Live-attenuated vaccines should be given at least 8 weeks prior to teplizumab and inactivated vaccines should be given at least 2 weeks prior to treatment.[1]

Administration

Teplizumab should be given intravenously once a day for 14 days (Stage 2 T1D) or 12 days (Stage 3 T1D). The dose is based on body surface area (BSA) and titrated as described in the labeling.[1] For Stage 2 TID, only one 14-day teplizumab treatment course is recommended.[1] For Stage 3 T1D, it is recommended that the initial treatment be given as soon as possible following a Stage 3 diagnosis but no later than 8 weeks from diagnosis.[1] For Stage 3 T1D, 2 treatment courses

are recommended. The second treatment course should be given 6 months after the first treatment course. If the second course is delayed, administer the second treatment course within 6 to 12 months after the first treatment course.[1]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the evidence for these new indications. Maintain teplizumab as nonpreferred.
- Recommend updating the PA criteria to include the new indication for teplizumab for use in Stage 3 T1D (**Appendix 1**).

References:

1. TZIELD (teplizumab -mzwv) [prescribing information]. Morristown, NJ; Provention Bio, Inc. April 2026.

2. Gitelman S, Simmons K, Sherr J, et al. Safety and pharmacokinetics of teplizumab in children less than 8 years of age with stage 2 type 1 diabetes. *Diabetologia* . 2026 Feb;69(2):330-342.

3. Ramos E, Dayan C, Chatenoud L, et al. Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes. *N Engl J Med.* 2023;389:2151-2161.

Appendix 1: Prior Authorization Criteria

Teplizumab

Goal(s):

- To promote safe and effective use in populations with established benefit:
  - Teplizumab has benefit for *prevention* of Stage 3 type 1 diabetes mellitus (T1DM) in members with Sstage 2 T1DM~~disease~~ (defined below based on lab testing) in adult and pediatric patients 1 year of age and older.
  - Delay the decline in endogenous insulin production in pediatric patients ages 8 to 17 years recently diagnosed with Stage 3 T1D.

~~Benefit has not been established for symptomatic (stage 3) T1DM or members who do not meet the definition for stage 2 disease (defined below).~~

Length of Authorization:

- One 14-day treatment course (Stage 2) **OR**
- Two treatment courses of 12-days (Stage 3) separated by at least 6 months but not more than 12 months~~.~~

Requires PA:

- All provider-administered and pharmacy point-of-sale claims for teplizumab

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at

- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is the request for an FDA approved age? ~~(e.g. 8 years of age or older)?~~	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
~~2. Has the patient previously been treated with teplizumab (use beyond the original 14 day infusion)?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness. No evidence to support additional doses.~~	~~**No:** Go to #3~~
~~3.~~2. Is the medication prescribed by or in consultation with an endocrinologist?	**Yes:** Go to #~~3~~4	**No:** Pass to RPh. Deny; medical appropriateness.
3. Has the patient previously been treated with teplizumab?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have Stage 2 T1~~I~~D and is 1 year of age or older?	**Yes:** Go to #5	**No:** Go to #7
~~4.~~5. Does the patient meet the standard criteria for the diagnosis of type 1 diabetes as determined as having one of the following: - HbA1c of 6.5% or higher **OR** - Fasting plasma glucose (FPG) of 126 mg/dL or higher **OR** - Oral glucose tolerance test (OGTT) of 200 mg/dL or higher?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #~~6~~5

Approval Criteria		
6. Is the person at high risk of developing T1DM (e.g. Stage 2 diabetes) as determined by having the following: - Presence of two or more diabetes-related autoantibodies (e.g. insulin autoantibodies (IAA), islet cell antibodies (ICA), glutamic acid decarboxylase 65 (GAD) autoantibodies, insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A)) **AND** - Abnormal glucose confirmed within the last 2 months as determined by: - An abnormal glucose during an OGTT (140-199 mg/dL) **OR** - FPG 100-125 mg/dL **OR** - HbA1c 5.7-6.4% or ≥10% increase in HbA1c **OR** - 2-hour plasma glucose 140-199 mg/dL	**Yes: Go to** #8	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient aged 8 to 17 years and recently diagnosed with **Stage 3** T1D (within in the previous **8 weeks**) by documentation of: - at least one positive pancreatic islet cell autoantibody **AND** - peak C-peptide > 0.2 pmol/mL on a mixed-meal tolerance test (MMTT) or alternative method if appropriate and MMTT is not available	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~8. Have baseline liver function tests, ~~and~~ complete blood panel and evaluation for active EBV and CMV infection ~~been~~ assessed ~~evaluated~~ in the past 2 months?	**Yes:** Go to #~~9~~6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~6.~~9. Has the patient received, or have contraindications to, all routine immunizations recommended for their age based on provider attestation of immunization history? Note: - Teplizumab labeling recommends administration of live-attenuated vaccines at least 8 weeks prior to treatment and inactivated (killed) vaccines or mRNA vaccines at least 2 weeks prior to treatment. - Routine vaccinations for patients at least 8 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Approve for a 14-day course (**Stage 2**) **OR** for up to two 12-day treatment courses (**Stage 3**) separated by 6 months but not more than 12 months~~Go to #7~~ Document provider attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness
~~Is the person at high risk of developing T1DM (e.g. Stage 2 diabetes) as determined by having the following: Presence of two or more diabetes-related autoantibodies (e.g. insulin autoantibodies (IAA), islet cell antibodies (ICA), glutamic acid decarboxylase 65 (GAD) autoantibodies, insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A)) **AND** Abnormal glucose confirmed within the last 2 months as determined by: An abnormal glucose during an OGTT (140-199 mg/dL) **OR** FPG 100-125 mg/dL **OR** HbA1c 5.7-6.4% or ≥10% increase in HbA1c **OR** 2-hour plasma glucose 140-199 mg/dL Note: Teplizumab is preventative therapy and not approved at this time for people diagnosed with symptomatic T1DM (e.g. Stage 3)~~	~~**Yes:** Approve for one 14-day course.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Antivirals for HSV

Date of Review: August 2026

Date of Last Review: September 2019
Dates of Literature Search: 07/01/2019 - 04/13/2026

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class review is to identify new literature for the herpes simplex virus (HSV) class. Additionally, in anticipation of funding line changes in 2027, coverage parameters will be reviewed to determine oral and/or topical options as it relates to disease severity.

Plain Language Summary:
- Herpes simplex virus (HSV) is a common, lifelong infection that can cause painful blisters or sores. The most common form of herpes is herpes simplex virus type 1 (HSV-1), which usually appears around the mouth and lips. The other type of virus is herpes simplex virus type 2 (HSV-2), which occurs around the genitalia.
- Both HSV-1 and HSV-2 can be passed from person to person when there are symptoms and when there are no symptoms.
- Certain antiviral medicines like acyclovir and valacyclovir can treat HSV infections. They shorten the time the sores are present, may decrease symptoms and spreading of the infection. There is no cure for HSV.
- Antiviral medicines taken by mouth, like tablets, are more effective than topical antiviral medicines applied to the skin.
- This review found no new high-quality guidelines or systematic reviews for the treatment of HSV.
- There is one new antiviral formulation that was approved by the Food and Drug Administration (FDA) for acyclovir. It is used to treat HSV in the eye, which can occur but is not very common.
- There are two new safety warnings for the drugs acyclovir and valacyclovir. These drugs have been associated with severe skin reactions in rare cases.
- The Drug Research and Management (DURM) group does not recommend changes to the Preferred Drug List of antiviral medicines for HSV.

Research Questions:
1. What is the comparative evidence for efficacy of antivirals used to treat HSV?
2. What is the comparative evidence for the safety of antivirals used to treat HSV?
3. Are there groups of patients based on specific demographic characteristicss (e.g., age, racial or ethnic groups, gender, disease severity), for which antivirals are more effective or associated with less harm for the treatment of HSV?

Author: Kathy Sentena, PharmD

Conclusions:

- No new high quality systematic reviews or clinical practice guidelines for HSV were identified.
- A new formulation of acyclovir ophthalmic ointment (AVACLYR) was approved for the treatment of acute herpetic keratitis in patients with herpes simples (HSV-1 and HSV-2) virus.[1] Acyclovir was not previously available in an ophthalmic preparation.
- Two new safety alerts regarding risk of hypersensitivity for both acyclovir and valacyclovir were identified (**Table 2**). The same contraindication and warning were added to both drug's labeling.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the evidence.
- Update prior authorization criteria to accommodate future changes to the prioritized list of health services.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- There was no new evidence identified in the previous review done in September of 2019.
- Preferred drugs include acyclovir capsules, tablets and oral suspension. Valacyclovir tablets and VALTREX tablets are also preferred.

Background:

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) are common infections with an incidence of 520 million for HSV-1 and 3.8 billion for HSV-2 worldwide.[2] High-income countries have reported declining rates of HSV. Primary oral and genital herpes occurs at an increased incidence in adolescents and young adults. Children attending day care, adolescents and athletes involved in contact sports may be at increased risk for HSV-1.[3] The incidence of genital herpes increases with the number of sexual partners in women and in non-Hispanic Black patients.[4] Oral herpes is mainly caused by HSV-1 and is spread by oral contact. Genital herpes can be caused by HSV-1 but is more commonly due to HSV-2 and is spread by sexual contact.[2] The herpes virus is a chronic infection in the sensory ganglia. Infections can alternate between active symptoms and inactivity.[5] Most infections are asymptomatic (subclinical) but some present with painful blisters or ulcers, fever, local lymphadenopathy and headache that can often reoccur.[5] Initial infections usually last 2 to 12 days after exposure.[3] Recurrence of HSV-1 is rarely associated with systemic symptoms.[3] In rare cases HSV can cause severe disease such as encephalitis, meningitis, hepatitis, respiratory tract infections, and esophagitis.[5] Transmission can occur during asymptomatic viral shedding as well as with active infections.[3] Recurrent infections are more common with HSV-2 compared to HSV-1.[4] Reactivation of the virus from the latent state to active replication can be triggered by illness or fever, sun exposure, menstrual period, injury, emotional stress and surgery.[2]

Individuals that are immunocompromised are at increased risk of reactivation of HSV, including those with:[3]

- Human immunodeficiency virus (HIV) with advanced disease (CD4 count <200 cells/microL)
- Transplant recipients with history of previous HSV-1 infection
- Burns or other skin disorders
- Pregnancy

There is no cure for HSV-1 and HSV-2; however, antivirals are effective for decreasing symptom duration, severity of symptoms and virus transmission.[6] They are most effective when given within 48 hours of an outbreak. Primary treatment of a genital HSV infection should include antiviral therapy, ideally within 72 hours

of lesion appearance.[6] Oral acyclovir is appropriate for most infections; intravenous (IV) therapy indicated for complicated infections such as central nervous system disease or disseminated disease.

Considerations for when to treat HSV-1 include if it is the primary infection, recurrent infection, severity of symptoms, site of infection, frequency of recurrence and if there is a well-defined prodrome.[3] In immunocompetent patients, oral treatment is recommended for primary gingivostomatitis (mouth infection) who present within 72 hours of symptom onset (**Table 1**).[3] Treatment is commonly 7-10 days; however, treatment can be extended if the lesion is not healed. If the patient presents outside of the 72 hours and still has significant pain or new lesions, antiviral therapy should still be offered.[3] Topical antivirals are not recommended for HSV due to less efficacy compared to oral antiviral therapies and multiple times a day application.

Treatment of genital herpes is the same as for HSV-1 (**Table 1**). Oral antivirals recommended by the Centers for Disease Control and Prevention (CDC) for genital herpes (HSV-1 and HSV-2) are acyclovir, famciclovir, and valacyclovir.[6] For patients who have HSV recurrence, episodic or chronic suppressive therapy can be considered. Chronic suppressive therapy options for ongoing genital HSV include acyclovir, famciclovir or valacyclovir.[6]

Individuals with severe disease may be candidates for episodic or chronic suppressive therapy (**Table 1).**[3] Episodic therapy, given for 5 days, is considered for patients with occasional recurrence with mild to moderate symptoms with well-defined prodrome.[3] Daily suppressive therapy is recommended for patients with severe disease to reduce HSV episodes, symptoms, pain, and complications.[6] Suppressive therapy has been shown to decrease risk for transmitting HSV and decreasing recurrent episodes. Topical therapy is not indicated for genital HSV.

Table 1. Oral Medication Recommendations for the Treatment of HSV in Adolescents and Adults [3,6]

Indication	Medication and Dose
Primary HSV-1 Infection	Acyclovir 400 mg three times daily or 200 mg five times daily
	Famciclovir 250 mg three times daily or 500 mg twice daily
	Valacyclovir 1 gm twice daily
Genital HSV	Acyclovir 400 mg three times daily
	Famciclovir 250 mg three times daily
	Valacyclovir 1 gm twice daily
Recurrent HSV-1 infections	Acyclovir 400 mg three times daily for 5 days
	Famciclovir 750 mg twice daily for 1 day or 1500 mg as a single dose
	Valacyclovir 2 gm twice daily for 1 day
Episodic therapy for HSV-1 and HSV-2	Acyclovir 400 mg three times daily
	Famciclovir 750 mg twice a day for one day or 1500 mg as a single dose
	Valacyclovir 2 gm twice daily for one day
Chronic Suppressive Therapy for HSV-1 and HSV-2	Acyclovir 400 mg twice daily
	Valacyclovir 500 mg orally once daily

All antivirals used for HSV should have doses adjusted in patients with moderate to severe renal insufficiency.[3] Adverse reactions are usually mild and may include headache, diarrhea, vomiting , pain and dizziness.

The Antiviral for HSV drug class represents a small quarterly spend to the Oregon Health Plan for fee-for-service (FFS) patients of about $2500. Ninety-nine percent of claims were for preferred products prescribed to 267 patients.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
None identified.

After review, 9 systematic reviews were excluded due to poor quality (e.g., indirect network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[7–15]

New Guidelines:
No high-quality clinical practice guidelines were identified.

After review, one guideline was excluded due to poor quality.[16]

New Formulations or Indications:

AVACLYR (acyclovir ophthalmic ointment 3%): Topical acyclovir ophthalmic ointment was approved in March 2019.[1] Acyclovir ophthalmic ointment is an antiviral approved for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2) virus. Acyclovir is a herpes simplex virus nucleoside analog deoxyribonucleic acid (DNA) polymerase inhibitor.[1] Acyclovir ointment is applied in a 1 cm ribbon in the lower cul-de-sac of the affected eye 5 times daily till healed and then 3 times daily for 7 days. The approval of acyclovir ointment was based on 5 double-blind, RCTs (n=238) which enrolled patients with dendritic herpetic keratitis. Safety and efficacy in pediatric patients less than 2 years of age was not studied.[1] Evidence from 5 randomized trials demonstrated clinical resolution of healed ulcers. At day 7 resolution averaged 83% for acyclovir ophthalmic ointment 3% compared to 50% for idoxuridine ophthalmic ointment 0.5% and 1%.[1] Idoxuridine was the standard of care for treating ophthalmic herpes prior to the approval of acyclovir making it an appropriate comparator. In July 2021, labeling was updated to include a warning that patients should not wear contact lenses during treatment with acyclovir ophthalmic ointment if they have signs or symptoms of herpetic keratitis or during the course of therapy with treatment.[1]

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles
Acyclovir[17] and Valacyclovir[18]	ZOVIRAX VALTREX	November 2025	Contraindications	Acyclovir is contraindicated in patients who have had demonstrated clinically significant hypersensitivity reaction (e.g., anaphylaxis, severe cutaneous adverse reaction [SCARs]) to valacyclovir, acyclovir or any component of the formulation.
			Warnings and Precautions	Severe cutaneous adverse reactions (SCARs), including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported during postmarketing experience with valacyclovir. Discontinue immediately if painful rash with mucosal involvement or a progressive severe rash develops.

Randomized Controlled Trials:
A total of 62 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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14. Vernooij RWM, Michael M, Colombijn JMT, Owers DS, Webster AC, Strippoli GFM, Hodson EM. Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2025, Issue 1. Art. No.: CD005133.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
acyclovir	ACYCLOVIR	CAPSULE	Y
acyclovir	ACYCLOVIR	ORAL SUSP	Y
acyclovir	ACYCLOVIR	TABLET	Y
valacyclovir HCl	VALACYCLOVIR	TABLET	Y
valacyclovir HCl	VALTREX	TABLET	Y
acyclovir	ACYCLOVIR	CREAM (G)	N
acyclovir	SITAVIG	MA BUC TAB	N
acyclovir	ACYCLOVIR	OINT. (G)	N
docosanol	DOCOSANOL	CREAM (G)	N
famciclovir	FAMCICLOVIR	TABLET	N
penciclovir	DENAVIR	CREAM (G)	N
penciclovir	PENCICLOVIR	CREAM (G)	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 07, 2026

Search Strategy:

#	Searches	Results
1	acyclovir.mp. or Acyclovir/	13887
2	Valacyclovir/ or valacyclovir.mp.	1982
3	docosanol.mp.	123
4	Famciclovir/ or famciclovir.mp.	942
5	penciclovir.mp.	477
6	1 or 2 or 3 or 4 or 5	15066
7	limit 6 to (english language and humans and yr="2019 -Current")	1623
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	62

Appendix 3: Key Inclusion Criteria

Population	Patients diagnosed with herpes simplex virus (HSV)-1 or HSV-2
Intervention	Oral or topical antiviral used for the treatment of HSV
Comparator	Placebo or active treatment
Outcomes	Symptom improvement
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Antivirals for Herpes Simplex Virus

Goal(s):

- Cover oral and/or topical antivirals only for ~~funded~~ medically necessary diagnoses. HSV infections are ~~funded~~ medically necessary only when complicated by an immunocompromised host or there is documentation of impacts on quality of life.
- Support individual review under the EPSDT benefit.

Length of Authorization:

- Up to 12 months (criteria specific)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Immunocompromised Conditions

Cancer and undergoing chemotherapy or radiation
Solid organ transplant or an islet transplant
Advance or untreated HIV with CD4 cell counts <200/mm3, history of AIDs-defining illness without reconstitution or clinical manifestations of symptomatic HIV
Moderate or primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)

Centers for Disease Control and Prevention. People who are immunocompromised. May 2023. Available at: https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html. Accessed April 13, 2026.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for an FDA approved indication?	**Yes:** Go to #3	**No:** Deny; medical appropriateness.
2. 3. Has the patient tried and failed or have contraindications to at least 2 preferred products?~~Will the prescriber consider a change to a preferred product?~~ ~~3.~~ ~~4. Message:~~ ~~5. Preferred products do not require a PA.~~ ~~Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.~~	**Yes:** ~~Inform prescriber of covered alternatives in class.~~Go to #4	**No:** Deny; medical appropriateness. ~~I~~inform provider of preferred antivirals.~~Go to #3~~
4. Is the diagnosis uncomplicated herpes simplex virus infection (HSV-1 or HSV-2)?	**Yes:** Go to #5~~4~~	**No:** Go to #7~~6~~
~~8.~~ 5. Pass to RPh: Is the patient immunocompromised as listed in Table 1 (document ICD10 code)? ~~Examples:~~ ~~9. Diagnosis of cancer AND currently undergoing chemotherapy or radiation. Document therapy and length of treatment.~~ ~~10. Solid organ transplant~~ ~~HIV/AIDS~~	**Yes:** Approve for up to 12 months. ICD10 code:_____	**No:** Go to #6~~5~~

Approval Criteria		
~~12.~~6. Is the patient currently taking an immunosuppressive drug similar to the examples described below? ~~13.~~ Document name of drug. If is drug not in the list below, pass to RPh for evaluation. ~~14. Immunosuppressive drugs include, but are not limited to:~~	**Yes:** Approve for up to 90 days	**No:** Pass to RPh. Go to #~~6~~87.

~~Immunosuppressants~~	
~~Abatacept~~	~~Infliximab~~
~~Adalimumab~~	~~Leflunomide~~
~~Anakinra~~	~~Methotrexate~~
~~Apremilast~~	~~Natalizumab~~
~~Azathioprine~~	~~Rituximab~~
~~Basiliximab~~	~~Secukinumab~~
~~Certolizumab pegol~~	~~Sirolimus~~
~~Cyclosporine~~	~~Tacrolimus~~
~~Etanercept~~	~~Tocilizumab~~
~~Golimumab~~	~~Tofacitinib~~
~~Hydroxychloroquine~~	~~Ustekinumab~~
	~~Vedolizumab~~

Active treatment with high-dose corticosteroids (20 mg or more of prednisone or equivalent per day when administered for 2 weeks or more)
Alkylating agents
Antimetabolites
Transplant-related immunosuppressive drugs
Cancer chemotherapeutic agents
Tumor necrosis factor (TNF) blockers
Other biologic agents that are immunosuppressive or immunomodulatory

Approval Criteria		
7. RPh only: All other indications need to be evaluated as to whether they are ~~an OHP-funded condition~~supported by high-quality evidence (e.g., positive RCTs or guidelines). Note: Viral ICD-10 codes that do not appear on the OHP funding list pending a more specific diagnosis code should be treated as not funded by the OHP.	If funded and clinic provides supporting literature, approve for length of therapy or 3 months whichever is less. Note: deny non-viral diagnoses (medical appropriateness)	**No:** Pass to RPh. Deny; medical appropriateness. ~~Non-funded and not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP~~ ~~If eligible for EPSDT review: Go to #7.~~
8. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?	**Yes:** ~~If clinic provides supporting literature, a~~Approve for length of therapy or 3 months whichever is less. Note: deny non-viral diagnoses (medical appropriateness)	**No:** Pass to RPh. Deny; medical necessity.

P&T Review: *8/26 (KS), 9/19 (KS), 7/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *8/16; 1/1/11*

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Orphan Drug Evaluation: Enzyme Replacement Therapy for Hunter Syndrome

Date of Review: August 2026
Generic Name: Tividenofusp alfa-eknm
Idursulfase

End Date of Literature Search: 05/29/2026
Brand Name (Manufacturer): Avlayah (Denali Therapeutics Inc.)
Elaprase (Takeda Pharmaceuticals)

Dossier Received: No

Purpose for Review:

- To establish medically appropriate prior authorization (PA) criteria for 2 enzyme replacement therapies, idursulfase and tividenofusp alfa-eknm, which are Food and Drug Administration (FDA)-approved for management of symptoms associated with Hunter syndrome, also known as mucopolysaccharidosis type II (MPS II).
- The wholesale acquisition cost per 6 mg vial of idursulfase is $3,310.65. Idursulfase is dosed at 0.5 mg/kg once a week. For a 36 kg child, the dose would be 18 mg or 3 vials or $9,932 per week or $516,461 per year.
- Tividenofusp alfa-eknm has a maintenance dose of 15 mg/kg once weekly after administering the loading dose protocol. The cost for each 150 mg vial is $5,200. For a 36 kg child, the maintenance dose would be 4 vials (rounded to the nearest whole vial) and cost $20,800 per week or $1,081,600 per year.

Plain Language Summary:

- The Food and Drug Administration (FDA) has approved 2 medicines, idursulfase and tividenofusp alfa-eknm, to treat Hunter syndrome.
- Hunter syndrome is a rare condition caused by a gene mutation that is inherited from the mother. This condition mostly affects boys.
- In people with Hunter syndrome, the body cannot make enough of the enzyme (a type of protein) that normally breaks down long chains of complex sugar molecules. This causes a buildup of complex sugar which leads to tissue and organ damage (spleen, liver) and affects physical and mental development.
- Symptoms of Hunter syndrome begin to appear around 2 to 4 years of age. Symptoms can be mild or severe and include an abnormally large head, hearing loss, stiff joints, heart disease, damaged spinal cord, and slowed development in walking and talking.
- Idursulfase is an enzyme replacement therapy that replaces the missing enzyme in Hunter syndrome and slows down tissue damage. This medicine is given via an infusion into the vein (intravenously) once a week.
- In a year-long study of 96 patients with Hunter syndrome, people treated with idursulfase were able to walk 37 meters farther over 6 minutes, compared to people who received placebo. Side effects include fever, rash, and headaches.
- Tividenofusp alfa-eknm is another enzyme replacement therapy that was designed to treat specific symptoms of Hunter syndrome related to the nervous system and brain. This medicine is also given via an intravenous infusion once a week.
- In clinical studies, chemical signs of the disease called biomarkers were used to assess how well tividenofusp alfa-eknm works. Over 24 weeks, a harmful complex sugar called heparan sulfate decreased by 91% in the fluid surrounding the spinal cord and brain (cerebrospinal fluid).

Author: Deanna Moretz, PharmD, BCPS

- There are no published studies to determine whether tividenofusp alfa-eknm improves neurologic symptoms of Hunter syndrome such as seizures, trouble thinking or learning, and hyperactivity. The most common side effects were related to how the drug is given, known as infusion-related reactions, such as fever, hives, and vomiting.
- The Drug Use Research and Management group recommends that the Oregon Health Authority pay for idursulfase and tividenofusp alfa-eknm for patients with Hunter syndrome after their provider documents medical appropriateness through a process called prior authorization.

Research Questions:

1. What is the evidence for the safety and efficacy of idursulfase in treating MPS II (Hunter syndrome)?
2. What is the evidence for the safety and efficacy of tividenofusp alfa-eknm in treating neurologic manifestations of MPS II?
3. Are there specific subpopulations for which idursulfase or tividenofusp-alfa-eknm is better tolerated or more effective for management of symptoms associated with MPS II?

Conclusions:

- Two enzyme replacement therapies, idursulfase and tividenofusp alfa-eknm, are FDA-approved for management of symptoms associated with MPS II.

<u>Idursulfase</u>

- In patients 5 years and older with MPS II, there is moderate-quality evidence from a single phase 2/3 trial (n=96) that weekly infusions of idursulfase 0.5 mg/kg improves exercise capacity as assessed by the 6-meter walk test (6MWT) by an average of 37 meters compared to placebo (p=0.013; 95% confidence interval [CI], not reported) over the course of a year.[1] Idursulfase does not improve lung function as assessed by predicted percent of forced vital capacity (FVC) (low-quality evidence).[1]
- An established minimal clinically important difference (MCID) for the 6MWT in patients with MPS II has not been formally defined in the clinical literature; however, the idursulfase investigators determined that a walking distance improvement of 30 to 44 meters over 52 weeks represented meaningful clinical benefit.[2]
- The most commonly reported adverse events with idursulfase in the phase 2/3 randomized controlled trial (RCT) were: headache (28%), pruritus (25%), urticaria (16%), musculoskeletal pain (13%), diarrhea (9%) and cough (9%).[3] Idursulfase has a boxed warning for risk of anaphylaxis.[3] In postmarketing reports, patients experienced anaphylactic reactions for up to several years after initiating idursulfase treatment.[3] Some patients had repeated anaphylactic events over a 2 to 4 month time period.[3]
- The phase 2/3 RCT of idursulfase was conducted in patients who were ambulatory and could follow directions to complete the pulmonary function testing. The efficacy of idursulfase in MPS II patients who were non-ambulatory, or who had severe MPS II with neurocognitive impairment was not evaluated.
- In patients 16 months to 5 years of age, no data are available to demonstrate improvement in MPS II disease-related symptoms or long-term clinical outcome.[3] In 2 open-label studies enrolling 38 people, treatment with idursulfase reduced spleen volume in adults and children aged 5 years and older.[3-5] The safety and efficacy of idursulfase have not been established in pediatric patients less than 16 months of age with MPS II.[3]
- Idursulfase cannot cross the blood brain barrier, and IV administration does not mitigate neurologic manifestations of MPS II.[6]

<u>Tividenofusp alfa-eknm</u>

- Tividenofusp alfa-eknm is indicated for the treatment of neurologic manifestations of MPS II when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.[7] FDA-approval was based on the surrogate endpoint of reduction in cerebrospinal fluid (CSF) heparan sulfate levels from baseline to Week 24.[6] Heparan sulfate is theorized to be the toxic substrate responsible for neurodegeneration in MPS

II.[6] A key review issue for the FDA was whether reduction in CSF levels of heparan sulfate could reasonably predict clinical benefit in patients with severe MPS II.[6] Continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[7]

- There is insufficient evidence that tividenofusp alfa prevents or delays neurocognitive decline in people with MPS II.[6] Efficacy in people with advanced neurologic impairment is unknown. It is hypothesized that once irreversible central nervous system (CNS) damage has occurred, initiating an intervention to replace the deficient enzyme may not benefit patients.[6]
- There is low-quality evidence from a phase 1/2 single-arm, open-label trial (n=47) that CSF heparan sulfate levels were reduced with tividenofusp alfa treatment from 837.5 ng/mL at baseline to 69 ng/mL at Week 24, reflecting a mean percent reduction of 91.4%.[6,8] Levels of CSF heparan sulfate observed at 24 weeks are levels observed in healthy individuals, which range from 50 to 70 ng/mL, and are almost always below 200 ng/mL.[6,9]
- In the phase 1/2 study, 41 participants (87%) had at least one infusion-related reaction; symptom severity was moderate in 55% of participants and severe in 6% of participants (low-quality evidence).[8] Tividenofusp alfa has a boxed warning for risk of hypersensitivity reactions including anaphylaxis.[7] Other common adverse events reported with tividenofusp alfa include upper respiratory tract infection (60%), pyrexia (55%), cough (47%), vomiting (43%), diarrhea (40%), rash (40%), anemia (38%), coronavirus disease 2019 (38%), and rhinorrhea (38%).[8]
- Administration of tividenofusp may cause anemia and/or membranous nephropathy.[7] The manufacturer recommends obtaining baseline hemoglobin levels before starting therapy and monitoring serum creatinine levels and urine-to-protein creatinine ratio during therapy.[7] Tividenofusp alfa-eknm is not recommended for use in combination with other enzyme replacement therapies, as combination therapy has not been studied and could increase the risk of severe hypersensitivity reactions.[7]
- It is not clear if tividenofusp alfa will improve motor function in patients with MPS II, as those outcomes have not been studied to date.
- An ongoing phase 2/3, multicenter, double-blind, randomized trial of tividenofusp alfa compared with idursulfase will evaluate the relative effects on safety, cognitive, and behavioral outcomes in patients with MPS II.[8]

Recommendations:

- Create a Preferred Drug List (PDL) class of drugs for MPS II (Hunter syndrome).
- Implement prior authorization (PA) criteria for the use of idursulfase and tividenofusp alfa-eknm, based on the indications that are FDA-approved in patients with MPS II.

Background:

- Mucopolysaccharidosis type II is a rare, X-linked genetic disorder of lysosomal storage. An enzyme replacement therapy, idursulfase, was approved in 2006 by the FDA as a treatment for patients with MPS II.[3] A second enzyme replacement therapy, tividenofusp alfa-eknm, received FDA approval in March 2026 for the treatment of neurologic manifestations of MPS II.[7] Both medications are administered via IV infusion once a week, using a weight based dosing regimen.[3,7]
- There are currently 12 known enzyme deficiencies that cause MPS comprising 8 different clinical types. Other enzyme replacement therapies (i.e., laronidase, galsulfase) have been approved to treat MPS type I and MPS type IV, respectively.[1] These therapies are subject to the Oregon Health Plan (OHP) orphan drug policy and PA criteria.
- A genetic mutation in the *IDS* gene causes MPS II.[1] The *IDS* gene regulates production of the iduronate 2-sulfatase enzyme which is responsible for breaking down complex sugar molecules called glycosaminoglycans (previously known as mucopolysaccharides).[1] The 2 glycosaminoglycan substrates that have been identified in MPS II are heparan sulfate and dermatan sulfate.[6] When these glycosaminoglycans accumulate inside lysosomes, cellular damage and tissue

destruction occurs in the respiratory, cardiovascular, skeletal, and neurologic systems.[1] Iduronate 2-sulfastase enzyme deficiency may be due to total lack of enzyme, but is more often from decreased enzyme production, decreased catalytic activity, or protein misfolding.[10]

- Prenatal diagnosis is available if the mother is a carrier of the genetic *IDS* mutation.[1] Newborn screening for MPS II was added to the Recommended Uniform Screening Panel (RUSP) in 2022. A definitive diagnosis of MPS II is established by demonstrating reduced or absent iduronate 2-sulfatase enzyme activity in leukocytes, fibroblasts, serum, or plasma; or molecular genetic testing for mutations in the *IDS* gene.[1] A determination of urinary glycosaminoglycan levels assists in screening potential positive patients; however, this assay is not very sensitive with many false-negative results.[1]
- Mucopolysaccharidosis type II almost always occurs in males but has been reported in a few symptomatic females, through skewing of X-chromosome inactivation.[10,11] The reported global prevalence of MPS II is 1 in 170,000 live births.[11] Signs and symptoms begin to appear in children between the ages of 2 years and 4 years.[2]
- In the Oregon Health Plan (OHP) population, 10 patients had a diagnosis of MPS II from 1/1/25 to 1/1/26. Nine of those patients are enrolled in a Coordinated Care Organization (CCO) and the tenth was enrolled was Fee-for-Service (FFS) but is no longer eligible for OHP.
- Common presenting features of MPS II include facial dysmorphism, enlarged tongue, hoarse voice, organomegaly, joint stiffness and contractures, pulmonary dysfunction secondary to skeletal deformities, myocardial enlargement and valvular dysfunction, hearing loss, and short stature.[11] Complications of MPS II can include congestive heart failure, chronic otitis media, joint and bone abnormalities, declining brain function, obstructive apnea, carpal tunnel syndrome, hernias, seizures, and behavioral problems.[11]
- MPS II has a variable age of onset and variable rate of progression, depending upon the phenotype.[11] Two MPS II phenotypes have been identified: a severe, neuronopathic phenotype (nMPS II) and a mild/attenuated, non-neuronopathic phenotype (nnMPS II).[6]
- Approximately 60% of patients with MPS II have the severe, neuronopathic form (nMPS II) and are likely to experience neuronopathic symptoms at about 3–4 years of age, including behavioral changes, attention difficulties, speech delay, cognitive decline, and poor performance at school.[12] Neurodegeneration is theorized to be related to excess heparan sulfate.[6] In patients with neuronopathic involvement, death usually occurs in the second decade of life due to progressive neurocognitive deterioration and cardiorespiratory failure.[6]
- Patients with minimal or no neuronopathic involvement (nnMPS II) may survive into the fifth or sixth decade of life with normal intellectual development.[11] Symptoms of MPS II may not present until adolescence or adulthood in people with this attenuated MPS II phenotype.[6] Death in patients with nnMPS II is usually due complications associated with obstructive airway disease and/or cardiac failure.[6]
- Goals of treatment include slowing progression of the disease, minimizing complications related to MPS II, and improving quality of life.[10] Surgery to replace defective cardiac valves, repair inguinal hernias, and remove tonsils and/or adenoids is often needed.[10] Hematopoietic stem cell transplantation has not demonstrated clear neurological benefit to date and is not recommended for patients with MPS II due to the high rate of morbidity and mortality associated with this therapy.[10]
- A clinical practice resource was published by the American College of Medical Genetics and Genomics (ACMGG) in 2020.[10] Most rare diseases, even those with approved therapies, lack enough high-quality data to be able to create an evidence-based guideline to assist clinicians in the care of people with these conditions.[10] A previous systematic review[13] of treatment for MPS II demonstrated insufficient strength in all data analyzed to create a definitive practice guideline based solely on published evidence.[10] Due to insufficient high-quality evidence, this practice resource was developed by the ACMGG based on consensus of the 10 committee members with experience in managing MPS II.[10] Only one enzyme replacement therapy, idursulfase, was available in 2020, when this resource was published. No guidance has been issued that includes recommendations for prescribing tividenofusp alfa-eknm. The ACMGG practice resource suggests the following criteria for the use of the enzyme replacement therapy, idursulfase:
    - All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting enzyme replacement therapy, prior to showing signs or symptoms.[10]

- Individuals with signs or symptoms with either attenuated or severe MPS II warrant enzyme replacement therapy.[10]
- Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant enzyme replacement therapy.[10]
- Individuals receiving enzyme replacement therapy who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have enzyme replacement therapy discontinued.[10]
- Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment (idursulfase), with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. Pulmonary function tests are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6MWT. Lab studies of glycosaminoglycans are recommended, as well as antibodies to enzyme replacement therapy to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress.[10]

Drug Information

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

I. ELAPRASE (idursulfase) for Intravenous infusion:

FDA-approved indication:

- Idursulfase has been shown to improve walking capacity in patients 5 years and older.[3]
- In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long-term clinical outcome.[3] In 2 open-label studies (n=38 total enrollment) treatment with idursulfase reduced spleen volume in adults and children aged 5 years and older with MPS II.[3-5]
- The safety and efficacy of idursulfase have not been established in pediatric patients less than 16 months of age.[3]
- Of note: Idursulfase cannot cross the blood brain barrier, and intravenous (IV) administration does not mitigate neurologic manifestations of MPS II.[6] An implantable CSF reservoir containing idursulfase is approved in Japan to mitigate CNS symptoms of MPS II.[6]

The phase 2/3 RCT used to support FDA approval of idursulfase is described in **Table 1.** Noteworthy trial design and patient characteristics include:

- Trial duration: 53 weeks
- Number of participants: 96 males with MPS II
- Study arms: idursulfase 0.5 mg/kg IV once a week, idursulfase 0.5 mg/kg IV every other week, or placebo
- Key inclusion criteria:
  - Aged 5-31 years
  - At least one clinical sign of MPS II: hepatosplenomegaly, valvular heart disease, evidence of obstructive pulmonary disease, or radiographic evidence of skeletal abnormalities (dysostosis multiplex)
  - Documented iduronate 2-sulfatase enzyme deficiency $\leq$ 10% of the lower limit of normal in plasma, fibroblasts, or leukocytes
  - Baseline FVC < 80% of predicted normal value
  - Ambulatory: able to stand 6 minutes and walk at least 5 meters
- Key exclusion criteria:
  - Unable to follow directions to complete pulmonary function testing or 6MWT
  - History of tracheostomy, cord blood transplant, or bone marrow transplant

- Baseline disease severity and population characteristics:
  - Mean age: 14.2 years
  - 82% were White
  - Male gender: 100%
  - Mean baseline walking distance on the 6MWT: 395 meters (range: 49 to 565 meters)
  - Mean Predicted FVC: 55% (range 16% to 79%)
  - Mean Weight: 36 kg
- Setting: Weekly visits to an infusion center for IV administration of placebo or idursulfase over 3 hours. Patients assigned to the idursulfase arm every other week received placebo infusions in the off week.
- Magnitude of benefit and clinical relevance of results:
  - Change in 6MWT: For idursulfase weekly versus placebo, the idursulfase group averaged 37 meters greater gain in the 6MWT over the course of the year (95% CI, not reported; p=0.013).[1] The minimal clinically MCID for the 6MWT depends on the condition being evaluated.[14] One study determined that a change of 14 to 30.5 meters may be clinically important across a variety of disease states.[14] An established MCID for the 6MWT in patients with MPS II has not been formally defined in the clinical literature; however, the idursulfase investigators determined that a walking distance improvement of 30 to 44 meters represented meaningful clinical benefit.[2] There was no statistical difference between placebo and idursulfase every other week (difference 23 meters, 95% CI -2.31 to 49.91; p=0.73).[1]
  - Change in predicted percent of FVC: not statistically significant for any of the comparisons.[1] A 10% relative improvement over baseline in the percent FVC is considered by the American Thoracic Society to be a clinically significant change.[1] According to the FDA review, It is difficult to connect changes in FVC with changes in organomegaly in patients with MPS II, as predicted percent of FVC is expressed as a percentage of normal value an individual of comparable age and height.[1] However, measuring height is difficult in patients with MPS II as not all patients can stand erect due to joint contractures and joint disease for an accurate measurement.[1] Therefore, predicted lung function values based on height is of unclear reliability in this patient population.[1] In MPS II, the primary potential pulmonary effects of the disease process are on structures external to the lung, most notably the upper airway, skeleton, and possibly liver and spleen; the FVC and other pulmonary function tests are measures that combine potential effects on the lung itself and structures external to it, not just on the lung alone.[1]
- Safety signals:
  - Idursulfase prescribing information contains a boxed warning for life-threatening anaphylaxis.[3] In 2 clinical trials with idursulfase, 16 of 108 (15%) patients experienced hypersensitivity reactions involving 3 body systems: cutaneous, respiratory or cardiovascular.[3] Of these 16 patients, 11 (69%) experienced anaphylactic reactions with symptoms of bronchospasm, cyanosis, dyspnea, erythema, edema (facial and peripheral), flushing, rash, respiratory distress, urticaria, vomiting, and wheezing.[3] In postmarketing reports, patients receiving idursulfase experienced anaphylactic reactions up to several years after initiating treatment.[3] Some patients had repeated anaphylactic events over 2 to 4 months.[3]
  - Most commonly reported adverse events with idursulfase in the phase 2/3 RCT of 96 patients were: headache (28%), pruritus (25%), urticaria (16%), musculoskeletal pain (13%), diarrhea (9%) and cough (9%).[3] If infusion reactions occurred, management included use of antihistamines and/or corticosteroids prior or during infusions, a slower rate of infusion, and/or early discontinuation of infusion if serious symptoms developed.[2]

See **Table 1** for major evidence limitations including:

- Risk of selection bias.
- Applicability concerns related to appropriate populations for treatment with idursulfase. Patients who were non-ambulatory, who had severe MPS II with neurocognitive impairment, or who were under 5 years of age were excluded from the study.

Table 1. Comparative Evidence Table for Idursulfase

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints (change from baseline to Week 53)	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Muenzer, J., et al.[1,2] Phase 2/3, DB, PC, MC, RCT	1. Idursulfase 0.5 mg/kg IV once a week 2. Idursulfase 0.5 mg/kg IV once every other week 3. Placebo IV once a week Duration: 52 weeks	Demographics: -Mean age: 14.2 yo -Race White: 82% Asian: 3% Black: 4% Other: 11% -Mean baseline 6MWT walk distance: 395 meters (range: 49 to 565 meters) -Mean Predicted FVC: 55% (range 16% to 79%) -Mean Weight: 36 kg -Gender: 100% male -Mean age at symptom onset: 28 months -Mean disease duration: 9.4 years Key Inclusion Criteria: - aged 5-31 yo - MPS II based on clinical signs and biochemical criteria* -Abnormal FVC < 80% predicted -Able to stand 6 minutes and walk 5 meters Key Exclusion Criteria: -Prior bone marrow or cord blood transplant -Tracheostomy -Unable to complete 6MWT or pulmonary function testing	ITT: 1. 32 2. 32 3. 32 PP: 1. 31 2. 32 3. 31 Attrition: 1. 1 (3%) 2. 0 3. 1 (3%)	Co-Primary Endpoints: ***Adjusted LSM change in 6MWT*** Weekly IDS vs. Placebo 1. 44.3 ± 12.3 meters (SEM) 3. 7.3 ± 9.5 meters (SEM) Difference: 37 meters 95% CI, NR; P=0.0131 EOW IDS vs. Placebo 2. 30.3 ± 10.3 (SEM) 3. 7.3 ± 9.5 (SEM) Difference: 23 meters 95% CI: NR; P=0.0732 ***Adjusted LSM change in predicted FVC%*** Weekly IDS vs. Placebo 1. 3.45 ± 1.77 (SEM) 3. 0.75 ± 1.71 (SEM) Difference: 2.7 95% CI, NR; P=0.0650 EOW IDS vs. Placebo 2. 0.004 ± 1.32 (SEM) 3. 0.75 ± 1.71 (SEM) Difference: -0.746 95% CI, NR; P=0.9531 Secondary Endpoint: ***Mean percent change in urinary GAG levels*** 1. -52.5 ± 5.3 (SEM) 2. -44.7 ± 4.0 (SEM) 3. 21.4 ± 11.6 (SEM) p<0.0001 vs. placebo; 95% CI NR ***Mean percent change in liver volume*** 1. -25.3 ± 1.6 (SEM) 2. -24.0 ± 1.7 (SEM) 3. -0.8 ± 1.6 (SEM) p<0.0001 vs. placebo; 95% CI NR	NA NS NS NS	Headache: 1. 19 (59%) 2. 21 (66%) 3. 14 (44% Nasopharyngitis 1. 17 (53%) 2. 19 (59%) 3. 15 (47%) Abdominal Pain 1. 13 (41%) 2. 19 (59%) 3. 16 (50%) Infusion Site Swelling 1. 1 (3%) 2. 4 (13%) 3. 4 (13%) Infusion-related adverse effect 1. 22 (69%) 2. 22 (69%) 3. 21 (66%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not reported. Patients were stratified by age (5-11 yo, 12-18 yo, 19-31 yo) and baseline disease score (combined 6MWT and % FVC scores). Baseline demographics were balanced across the 3 treatment groups, although placebo-treated patients were younger and smaller than the active comparator, there was overlap between groups for age at onset of MPS II and baseline disease score. Performance Bias: Low. Investigators and participants were blinded to treatment assignment. Detection Bias: Low. Primary outcome assessment was conducted by a clinician not involved with the study. Infusion reactions may have resulted in unblinding of investigators, patients, or caregivers. Attrition Bias: Low. 2 patients died during the study, otherwise all patients completed the 52-week trial. Reporting Bias: Low. All outcomes reported as prespecified in the protocol. Other Bias: Unclear. Study conducted by the manufacturer. Three investigators report payments from the manufacturer for consulting, speaking, travel, and research. **Applicability**: Patient: Children less than 5 years of age were not included in the RCT. Enrollment does not fully depict the full disease severity spectrum as those who could not complete testing due to being bed-bound, severely debilitated or with an intellectual disability were excluded. Intervention: An initial phase 1/2 RCT in 12 patients with MPS II showed that idursulfase decreased urinary GAG excretion and decreased liver/spleen sizes. The phase 2/3 study had a phase 2 component to determine if weekly or every other weekly infusions were effective. Weekly infusions showed the most significant benefit for an improved ability to walk longer distances over 6 minutes. Comparator: Placebo is an appropriate comparator to evaluate efficacy.

				Mean percent change in spleen volume 1. -25.1 ± 2.4 (SEM) 2. -19.8 ± 3.2 (SEM) 3. 7.2 ± 4.2 (SEM) p<0.0001 vs. placebo; 95% CI NR				Outcomes: Changes in 6MWT and FVC were used for FDA approval of other enzyme replacement therapies, although their clinical meaningfulness in MPS II is uncertain. Secondary endpoints for urinary GAG excretion and liver and spleen volumes have uncertain clinical meaningfulness. Setting: 9 study sites: 4 in the United States, 3 in the United Kingdom, 1 site each in Brazil and Germany
Abbreviations: 6MWT = 6 minute walk test; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; EOW = every other week; FDA = Food and Drug Administration; FVC = forced vital capacity; GAGs = glycosaminoglycans; I2S = iduraonate-2-sulfatase; IDS = idursulfase; IV = intravenous; kg = kilograms; ITT = intention to treat; LSM = least squares mean; mITT = modified intention to treat; MPS II = Mucopolysaccharidosis type II; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SEM = standard error of the mean; yo = years old * Clinical signs of MPS II included at least one of the following: hepatosplenomegaly, obstructive airway disease, or radiographic evidence of skeletal abnormalities; Biochemical evidence included documented plasma, fibroblast, or leukocyte I2S enzyme deficiency ≤ 10% normal range								

II. AVLAYAH (tividenofusp alfa-eknm) for IV infusion

Mechanism of action and FDA-approved indication:

- Tividenofusp alfa-eknm provides an exogenous source of iduronate 2-sulfatase enzyme fused to an enzyme transport vehicle to enhance delivery into the CNS.[7]
- Tividenofusp alfa-eknm is indicated for neurologic manifestations of MPS II in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.[7]
- Tividenofusp alfa-eknm is not recommended for use in combination with other enzyme replacement therapies as combination therapy has not been studied and could increase the risk of severe hypersensitivity reactions.[7]

The clinical trial used to support FDA approval is described and evaluated below in **Table 2.** Noteworthy trial design and patient characteristics include:

- Trial design and duration: Phase 1/2, single-arm, open-label trial over 24 weeks with an 80-week safety extension, and 157-week open-label extension
- Number of participants: 47 males
- Study Arms: 5 dosing regimens of tividenofusp alfa - weekly IV infusions of 3, 7.5, or 15 mg per kilogram of body weight, with or without dose escalation (up to 30 mg per kilogram for cohort A), followed by a weekly infusion of 15 mg per kilogram for all 5 dosing cohorts.[8]
- Participants subdivided by age and phenotype into 5 cohorts:
    - Cohort A: Participants aged ≥5 to ≤10 years with nMPS II (n=5)
    - Cohort B: Participants aged ≥1 to ≤18 years with nnMPS II, nMPS II, or unknown phenotype (n=18)
    - Cohort C: Participants aged <4 years with nMPS II (this cohort could include participants ≥4 to ≤18 years of age if participant is a blood relative of a participant <4 years of age) (n=8)
    - Cohort D: Participants aged ≤18 years with nnMPS II or nMPS II with preexisting hepatomegaly who have never taken standard-of-care enzyme replacement therapy (n=5)
    - Cohort E: nMPS II participants aged ≥6 years at screening, nnMPS II participants <6 or ≥17 years at screening, and nMPS II participants ≥1 to ≤18 years at screening with a history of prior hematopoietic stem cell transplant (n=10)
- Key inclusion criteria:

- Confirmed MPS II based upon reduced iduronate 2-sulfatase enzyme activity in plasma, fibroblasts, or leukocytes and documented mutation in *IDS* gene
- For participants with nMPS II: Cognitive standard score or development quotient of 85 or less at screening or a documented decline of at least 7.5 points in the standard score in the previous 6 to 18 months. The developmental quotient was calculated as developmental age divided by chronologic age multiplied by 100; a score of 100 indicates age-expected development.[8]
- If receiving idursulfase, must have tolerated a minimum of 4 months of treatment prior to study enrollment. (If patients had received idursulfase, no mandated washout period was initiated before starting tividenofusp alfa).[8]

- Key exclusion criteria:
  - Use of any CNS-targeted enzyme replacement therapy within 3 months of screening for participants aged 5 years and older or within 6 months for those less than 5 years of age.
  - Use of gene therapy or stem cell therapy at any time (except for participants in Cohort E)
  - Clinically significant thrombocytopenia or other coagulation abnormality. Note: anemia is a risk factor due to the ability of the fragment crystallizable component of tividenofusp alfa to bind to human transferrin receptor, which plays a role in iron homeostatis.[6]
  - Contraindication for lumbar punctures
  - Clinically significant history of stroke, epilepsy, head trauma with loss consciousness, or any CNS disease not MPS II-related within 1 year of screening
  - Placement of a ventriculoperitoneal (VP) shunt or any other brain surgery within 30 days of screening
- Baseline disease severity and population characteristics:
  - Median age: 5 years (range: 3 months to 13 years); 30% were less than 4 years old
  - Phenotype: nMPS II: 44 (94%); nnMPS II phenotype: 3 (6%)
  - Previously received enzyme replacement therapy: 32 (68%)
  - Type of genetic variant:
    - Missense or synonymous: 22 (47%)
    - Large deletion, rearrangement, stop, frameshift, or splice: 25 (53%)
- Magnitude of benefit and clinical relevance of results:
  - The primary objective was safety in the dose-finding Phase 1/2 study. Safety endpoints included adverse events, infusion-related reactions, and anemia.[8] All 47 participants had at least one adverse event; the maximum severity was moderate in 68% and severe in 28%.[8] A total of 18 participants (38%) had at least one serious adverse event.[8] Of these, 3 had at least one serious adverse event that was considered by the investigator to be related to treatment (2 had infusion-related reactions and 1 had anemia); all continued to receive tividenofusp alfa in the study.[8] One participant (2%) discontinued the study owing to a treatment-related adverse event (infusion-related reaction).[8]
  - Another primary objective was change in total urinary glycosaminoglycan levels over 24 weeks, as accumulation of glycosaminoglycans leads to lysosomal dysfunction in multiple organs and tissues.[6,8] Mean baseline urine glycosaminoglycan level was 44.1 mg/mmol creatinine (n=47) and at Week 24 the mean level was 13 mg/mmol creatinine (n=38) for a 57% mean reduction at week 24 (95% CI, 49 to 65).[6] While data from this phase 1/2 study appears to suggest that tividenofusp alfa has favorable effects on biomarkers of somatic disease (e.g., urine glycosaminoglycan and liver volume) in selected subjects with MPS II, there are significant limitations including small number of treatment-naïve subjects, confounding effects of idursulfase use at baseline, limited number of subjects with hepatomegaly/splenomegaly at baseline, changes in imaging modalities during the study and novel methods of interpretation that leads to uncertainty in the effect of tividenofusp alfa on these outcomes.[6]

- The main secondary endpoint was the change in CSF levels of heparan sulfate over 24 weeks.[8] With tividenofusp alfa treatment, levels were reduced from 837.5 ng/mL at baseline to 69 ng/mL at Week 24, reflecting a mean percent reduction of 91.4% (95% CI: 90 to 92).[6] Levels of CSF heparan sulfate observed at 24 weeks are levels observed in healthy individuals, which range from 50 to 70 ng/mL, and are almost always below 200 ng/mL.[6,9] The treatment effect appears sustained beyond Week 24, although there was incomplete follow-up of subjects beyond that time point.[6]
- Heparan sulfate is theorized to be the toxic substrate responsible for neurodegeneration in MPS II.[6] A key review issue for the FDA was whether reduction in CSF levels of heparan sulfate could reasonably predict clinical benefit in patients with severe MPS II.[6] Nonclinical, clinical and literature data were submitted to the FDA to support reduction in CSF levels of heparan sulfate can predict clinical benefit in the neurologic manifestations of Hunter syndrome.[6] The nature of the benefit (e.g., preventing neurocognitive decline vs. delaying the rate of decline in neurocognition) is not yet known.[6] It is hypothesized that once irreversible CNS damage has occurred, initiating an intervention to replace the deficient enzyme may not benefit patients.[6] It also remains uncertain whether (or how to define) a cognitive function threshold and/or age threshold beyond which initiating treatment with tividenofusp alfa will or will not result in benefit.[6] At the present time, there are key residual uncertainties including the MPS II population (e.g., patients who initiate treatment with minimal/no neurodegeneration vs advanced neurodegenerative disease, younger MPS II patients vs older MPS II patients, etc.) in whom reductions in CSF heparan sulfate are reasonably likely to predict clinical benefit on the neuronopathic manifestations of the disease.[6] Another uncertainty is what is the nature of the benefit (e.g., preventing neurocognitive decline versus slowing the rate of decline in neurocognition) of treatment with tividenofusp alfa.[6]
- An ongoing phase 2/3, multicenter, double-blind, randomized trial of tividenofusp alfa as compared with standard-of-care enzyme replacement therapy (idursulfase) (ClinicalTrials.gov number, NCT05371613) will evaluate the relative effects on safety, cognitive, and behavioral outcomes in patients with MPS II.[8]

- Safety signals:
  - Tividenofusp alfa has a boxed warning for risk of hypersensitivity reactions including anaphylaxis.[7]
  - In the phase 1/2 trial, a total of 41 participants (87%) had at least one infusion-related reaction, with moderate symptoms in 55% of participants and severe symptoms in 6% of participants.[8] Infusion-related reactions were generally clinically manageable with premedication, by slowing the infusion rate, reducing the dose, or both. A small number of participants required a slower dose-escalation phase.[8] The incidence of infusion-related reactions declined over time and the use of premedication, including glucocorticoids, also appeared to decrease as the study progressed.[8] One participant with previous idursulfase exposure had severe infusion-related reactions in weeks 3 and 4 that met the Sampson criteria for anaphylaxis.[8] The dose in this participant was escalated slowly to the target of 15 mg per kilogram at week 30, and he continued treatment.[8]
  - Other common adverse events included upper respiratory tract infection (60%), pyrexia (55%), cough (47%), vomiting (43%), diarrhea (40%), rash (40%), anemia (38%), coronavirus disease 2019 (38%), and rhinorrhea (38%).[8]
  - Administration of tividenofusp may cause anemia and/or membranous nephropathy.[7] The manufacturer recommends obtaining hemoglobin levels before treatment and monitoring serum creatinine levels and urine-to-protein creatinine ratio during therapy.[7]

See **Table 2** for major evidence limitations including:

- Risk of selection, performance, and detection bias.
- Applicability concerns related to appropriate populations for treatment (i.e., primarily children with severe MPS II).

Table 2. Comparative Evidence Table for Tividenofusp alfa-eknm

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Muenzer, J., et al[6,8] Phase 1/2, OL, MC single-arm study	4 different dosing regimens in 5 cohorts: Cohort A: Tividenofusp alfa 3 mg/kg/wk x 2 wks, 7.5 mg/kg/wk x 2 wks, 15 mg/kg/wk x 4 weeks, then 30 mg/kg via IV infusion once a week for 18 wks Cohort B1: Tividenofusp alfa 3 mg/kg/wk x 12 weeks then 3, 7.5, or 15 mg/kg/wk x 12 weeks via IV infusion Cohort B2: Tividenofusp alfa 7.5 mg/kg via IV infusion once a week x 24 wks Cohorts B3, C, D and E: Tividenofusp alfa 15 mg/kg via IV infusion once a week x 24 wks Trial Duration: 24 weeks followed by 80-week safety extension (30 mg/kg and 15 mg/kg dosing regimens) and 157-week OL extension (15 mg/kg for all participants)	Demographics: -Median age: 5 yo (range: 3 months to 13 yo) - nMPS II: 44 (94%) - nnMPS II: 3 (6%) - Previous ERT: 32 (68%) - Male: 100% - Race White: 27 (57%) Asian: 4 (9%) Black: 4 (9%) Not Reported: 8 (17%) Other: 1 (2%) More than 1 race: 3 (6%) Key Inclusion Criteria: -Males with MPS II -aged ≤ 18 yo Key Exclusion Criteria: -Use of any CNS-targeted enzyme replacement therapy within 3 months of screening for participants aged 5 years and older or within 6 months for those less than 5 years of age. -Use of gene therapy or stem cell therapy at any time (except for participants in Cohort E) -Clinically significant thrombocytopenia or other coagulation abnormality -Contraindication for lumbar punctures -Clinically significant history of stroke, epilepsy, head trauma with loss consciousness, or any CNS disease not MPS II-related within 1 year of screening -Placement of a VP shunt or any other brain surgery within 30 days of screening	ITT: Total = 47 Dose-finding cohorts (A, B1, B2): n=20 Standard 15 mg/kg dosing cohorts (B3, C, D, E): n=27 PP: 1. 46 Attrition: 1. 1 (2%)	Primary Endpoints: Change from baseline in urinary GAG concentrations Baseline: 44.1 mg/mmol creatinine Week 24: 13 mg/mmol creatinine 57% reduction 95% CI: 49 to 65 Secondary Endpoints Mean change in CSF heparan sulfate level from baseline to Week 24 Baseline: 837.5 ng/mL Week 24: 69 ng/mL 91% reduction 95% CI: 90 to 92 Mean change in urinary heparan sulfate level from baseline to Week 24 Baseline: 97.2 ng/mL Week 24: 8.1 ng/mL 86% reduction 95% CI 83 to 89	NA for all	TEAEs: Mild: 8 (17%) Moderate: 35 (74%) Severe: 4 (9%) Infusion-related reactions: 27 (57%) Anemia: 11 (23%) AE leading to dose interruption: 34 (72%) Upper respiratory tract infection 11 (23%) Pyrexia 11 (235) Cough 8 (17%) Vomiting 14 (30%) Diarrhea 9 (19%) Rash 10 (21%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Not randomized, no comparator group. Performance Bias: High. Single arm; OL study. Detection Bias: High. Single arm; OL design. Attrition Bias: Low. 1 patient discontinued the study due to an adverse event. Reporting Bias: Low. All outcomes reported as prespecified in the protocol. Other Bias: Unclear. Trial design, execution, and data analysis completed by the manufacturer. **Applicability**: Patient: Children less than 18 yo with MPS II were included in this study. 94% had nMPS II. Intervention: Primarily a dose finding safety study. Dosing started at 3 mg/kg once a week and titrated up to 15 mg/kg once a week. Comparator: No comparator, OL study design. Outcomes: Safety was the primary outcome. Impact on biomarkers of substrate accumulation in CNS and urine were surrogate, secondary endpoints. Clinical impact of reducing GAG and heparan sulfate levels has not been determined in MPS II population. Setting: 7 sites in North America and Europe 4 sites in the United States; 1 site each in Canada, United Kingdom, and Netherlands

Abbreviations: AE = adverse event; RR = absolute risk reduction; CI = confidence interval; CSF = cerebrospinal fluid; DB = double-blind; ERT = enzyme replacement therapy; GAGs = glycosaminoglycans; ITT = intention to treat; kg = kilograms; IV= intravenous; MPS II = Type II mucopolysaccharidosis; MC = multi-center; mg = milligrams; N = number of subjects; NA = not applicable; nMPS II = Neuronopathic MPS II; nnMPS II = non-neuronopathic MPS II; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; RCT = randomized controlled trial; TEAEs = treatment-emergent adverse events; VP = ventriculoperitoneal; wks = weeks; yo = years old

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVLAYAH™ safely and effectively. See full prescribing information for AVLAYAH.

AVLAYAH (tividenofusp alfa-eknm) for injection, for intravenous use
Initial U.S. Approval: 2026

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

See full prescribing information for complete boxed warning.

- **Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. (5.1)**
- **Initiate AVLAYAH in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (5.1)**
- **If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue AVLAYAH and immediately initiate appropriate medical treatment, including use of epinephrine. (5.1)**

----------INDICATIONS AND USAGE----------

AVLAYAH is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment. (1)

This indication is approved under accelerated approval based on reduction of cerebrospinal fluid heparan sulfate observed in patients treated with AVLAYAH. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial(s). (1)

Limitations of Use
AVLAYAH is not recommended for use in combination with other enzyme replacement therapies. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administration of AVLAYAH should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
- Obtain a baseline hemoglobin value in all patients. (2.1)
- Recommended AVLAYAH maintenance dosage for pediatric patients who weigh at least 5 kg is 15 mg/kg administered once weekly as an intravenous infusion over approximately 4 hours. (2.2, 2.6)
- Initiate AVLAYAH treatment with a dose escalation regimen. (2.2)
- See the full prescribing information for dosage and administration modifications and monitoring. (2.3)
- See the full prescribing information for preparation and administration instructions. (2.4, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 150 mg of tividenofusp alfa-eknm as a lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- *Infusion-Associated Reactions (IARs)*: If a severe IAR occurs, discontinue AVLAYAH and initiate appropriate medical treatment. (5.2)
- *Anemia*: Obtain baseline hemoglobin levels in all patients and monitor 3 months after initiation, and as clinically indicated. Administer appropriate supportive measures for anemia based on clinical judgment. (5.3)
- *Membranous Nephropathy:* Monitor serum creatinine and urinary protein to creatinine ratio. If membranous nephropathy is suspected, conduct diagnostic evaluation and initiate appropriate treatment. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20%) were IAR, upper respiratory tract infection, ear infection, pyrexia, anemia, cough, vomiting, diarrhea, rash, COVID-19, rhinorrhea, nasal congestion, fall, headache, skin abrasion, and urticaria. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Denali Therapeutics toll-free at 1-833-ONE-DNLI (1-833-663-3654) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2026

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELAPRASE safely and effectively. See full prescribing information for ELAPRASE.

ELAPRASE® (idursulfase) injection, for intravenous use
Initial U.S. Approval: 2006

WARNING: RISK OF ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Life-threatening anaphylactic reactions, presenting as respiratory distress, hypoxia, hypotension, urticaria and/or angioedema of throat or tongue have occurred in some patients during and up to 24 hours after ELAPRASE infusions. Closely observe patients during and after ELAPRASE administration and be prepared to manage anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions and require additional monitoring. (5.1, 5.3, 6)

----------INDICATIONS AND USAGE----------

ELAPRASE is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age (1).

----------DOSAGE AND ADMINISTRATION----------

The recommended dosage is 0.5 mg per kg of body weight administered once every week as an intravenous infusion (2).

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 6 mg/3 mL (2 mg/mL) in single-use vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions Including Anaphylaxis: Ensure that personnel administering product are adequately trained in cardio-pulmonary resuscitative measures and have ready access to emergency medical services (EMS) (5.1).
- Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations: Hunter syndrome patients aged 7 years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions, and anti-idursulfase antibody development (5.2).
- Risk of Acute Respiratory Complications: Patients with compromised respiratory function or acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of ELAPRASE and consider delaying the ELAPRASE infusion (5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions occurring in at least three patients (≥9%) aged five years and older were headache, pruritus, musculoskeletal pain, urticaria, diarrhea, and cough. The most common adverse reactions occurring in at least three patients (≥10%) aged seven years and younger were pyrexia, rash, vomiting, and urticaria. In all clinical trials, the most common adverse reactions requiring medical intervention were hypersensitivity reactions, and included rash, urticaria, pruritus, flushing, pyrexia, and headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2025

Enzyme Replacement Therapy for Hunter syndrome

Goal(s):

- Ensure medically appropriate use of enzyme replacement therapies that are FDA-approved for management of Hunter syndrome (also known as mucopolysaccharidosis [MPS] type II).

Length of Authorization:

- Up to 12 months

Requires PA:

- Elaprase® (idursulfase) and Avlayah™ (tividenofusp alfa-eknm) for provider administered claims.

Covered Populations: FFS and CCO patients beginning 1/1/26 for idursulfase and 5/1/2026 for tividenofusp alfa

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved age and indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug prescribed by or in consultation with a provider with expertise in managing lysosomal storage disorders (i.e., metabolic disorder specialist, endocrinologist, geneticist).	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient prescribed any other enzyme replacement therapies for Hunter syndrome? Note: Use of dual enzyme replacement therapy in Hunter syndrome has not been evaluated.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5

Approval Criteria		
5. Has the diagnosis of Hunter syndrome (or MPS type II) been confirmed by either: • genetic testing OR • an enzyme assay showing deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma?	**Yes:** Go to #6 Document date and test results_____	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for idursulfase?	**Yes:** Go to #7	**No:** Go to #10
7. Is the patient aged 16 months or older? Note: The safety and efficacy of idursulfase in patients aged less than 16 months has not been established.	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there documentation of one of the following symptoms of MPS type II: • Hepatosplenomegaly or • Skeletal deformities or • Neurocognitive decline or • Cardiovascular disorders or • Impaired respiratory function?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Have one of the following tests to document baseline disease severity been documented: • Spleen volume or • Liver volume or • Forced vital capacity (FVC) or • 6-minute walk test (6MWT)?	**Yes**: Pass to RPh. Pend; Refer to DMAP for secondary review.	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for tividenofusp alfa-eknm?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Is there documentation of neurologic manifestations consistent with Hunter syndrome (e.g., cognitive impairment, developmental delay, seizures, or structural brain abnormalities on MRI)?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Have baseline hemoglobin, serum creatinine and urinary protein to creatinine levels been obtained? Note: Due to risk of anemia, baseline hemoglobin should be obtained before starting therapy and reassessed 3 months afterwards. Because of the risk of membranous nephropathy, creatinine and urinary protein to creatinine ration should be monitored if membranous nephropathy is suspected.	**Yes:** Pass to RPh. Pend; Refer to DMAP for secondary review.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/2026 (DM)
Implementation: TBD

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: Monoclonal Antibodies for Lupus

Date of Review: August 2026

Date of Last Review: February 2022
Dates of Literature Search:
01/01/2021 – 05/29/2026 belimumab and Anifrolumab-fnia
01/01/1946 – 05/29/2026 obinutuzumab

Generic Name: Obinutuzumab

Brand Name (Manufacturer): Gazyva (Genentech)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

Evaluate new comparative evidence for efficacy and safety of monoclonal antibodies indicated for the treatment of systemic lupus erythematosus (SLE) or lupus nephritis (LN), and evaluate place in therapy for belimumab, anifrolumab-fnia, and obinutuzumab. Obinutuzumab has been used for various oncology indications since initial Food and Drug Administration (FDA) approval in November 2013. In October 2025, it gained an expanded FDA indication for treatment of adult patients with active LN who are receiving standard therapy.

Plain Language Summary:

- Systemic lupus erythematosus is an autoimmune disorder which affects connective tissue in the body. An autoimmune disorder is a condition where a person's immune system attacks the body itself, instead of an outside invader, such as a virus. Symptoms of SLE include severe fatigue, joint pain, fever, hair loss and a rash across the cheeks and nose.
- Many people with SLE develop kidney disease which is a complication of the disease called lupus nephritis.
- A person with SLE or LN will often take more than one oral medicine to treat the condition and prevent flares.
- Some people may also need medicines that are infused into the veins (intravenously) or injected through the skin (subcutaneously).
- Guidelines recommend multiple combinations of medicines when first treating LN for most patients. These may include mycophenolate mofetil, steroids, cyclosporine, cyclophosphamide, injectable medications like obinutuzumab or belimumab, or others. Different patients may need different combinations of medicines. In addition, hydroxychloroquine is recommended to treat SLE.
- One medicine, called obinutuzumab, was recently approved by the FDA to treat LN. It has been approved for many years to treat certain types of cancers. It is infused through the vein every few weeks at first, then once every 6 months thereafter. Compared to a placebo (saline infusion), obinutuzumab increased the chances of having a remission or improvement in kidney function in people with LN. For one person to have this response, eight people would need to be treated.

Author: Sara Fletcher, PharmD, MPH, BCPS

- Obinutuzumab can increase a person's risk of having an infection. This is a side effect that is associated with most medicines used to treat SLE or LN.
- We recommend that providers send in additional information before the Oregon Health Authority pays for obinutuzumab. This process is called prior authorization (PA).

Research Questions:

1. Is there new comparative evidence that monoclonal antibodies indicated for SLE differ in efficacy or effectiveness?
2. Is there new comparative evidence that monoclonal antibodies indicated for SLE differ in safety?
3. What is the evidence for obinutuzumab in LN?
4. Are there specific subpopulations (age, race, ethnicity, gender, diagnosis, disease severity, and comorbidity) for which some monoclonal antibodies indicated for SLE have different effectiveness or safety than other immunosuppressants?

Conclusions:

This evidence review includes 2 high-quality international guidelines, one new published pivotal randomized controlled trial (RCT) for a lupus related indication, one new formulation, and 2 medications with expanded indications. Current FDA approved biologic agents for SLE, LN, or both SLE and LN are listed in **Appendix 1.**

- There is no head-to-head comparative evidence of monoclonal antibodies approved for SLE or LN.
- The European Alliance of Associates of Rheumatology (EULAR) updated guidelines in 2025 for management of SLE with kidney involvement.[1] For patients with active LN, especially those with poor prognostic factors, recommended options include:
    - For initial treatment, mycophenolate or low-dose intravenous cyclophosphamide with belimumab (Level of Evidence [LoE] 1b/Recommendation grade A), mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus) (LoE 1b/Grade A), or mycophenolate with obinutuzumab (LoE 1b/Grade A)[1]
    - After renal response, defined here as a reduction of urine protein-to-creatinine ratio (UPCR) of < 500 mg/g, treatment should continue for at least 3 years (LoE 2b/Grade B)
        - Patients initially treated with mycophenolate alone (LoE 1a/ Grade A) or in combination with (1) belimumab (LoE 1b/Grade A), (2) a calcineurin inhibitor (LoE 1b/Grade A), or (3) obinutuzumab should remain on these drugs (noting courses beyond 12 months for obinutuzumab await further research evaluation);
        - Patients initially treated with cyclophosphamide, alone or in combination with belimumab, should replace cyclophosphamide with mycophenolate (LoE 1a/Grade A) or azathioprine (LoE 1a/Grade A).[1]
- Kidney Disease Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guidelines for the Management of Lupus Nephritis include recommendations that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any one of the following:
    - mycophenolic acid analogs (1B); or
    - low-dose intravenous cyclophosphamide (1B); or
    - belimumab and either mycophenolic acid analogs or low-dose intravenous cyclophosphamide (1B); or
    - mycophenolic acid analog and a calcineurin inhibitor when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] </=45 ml/min per 1.73 m^2)(1B).[2]
    - a triple immunosuppressive regimen of belimumab, glucocorticoids, and either mycophenolic acid analogs or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or patients at high-risk for progression to kidney failure due to severe chronic kidney disease. This triple immunosuppressive regimen can be continued as maintenance therapy.[2]

- In adults with lupus nephritis (LN), there is moderate-quality evidence from one high-quality, phase 3, double-blind, placebo-controlled, multinational, trial (n=271) that obinutuzumab improves the number of people who achieve complete renal response (CRR) at week 76 compared to placebo (obinutuzumab 46.4% vs. placebo 33.1%; adjusted difference 13.4%, 95% confidence interval [CI] 2.0 to 24.8; p=0.02; number needed to treat [NNT] 8).[3] A CRR was considered to be urine protein-to-creatinine ratio (UPCR) less than 0.5 mg/mg based on a timed 24-hour urine collection, an estimated glomerular filtration rate (eGFR) of at least 85% of the baseline value (calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation), and no occurrence of an intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal).[3]
- There were more serious adverse events (SAEs) reported in the obinutuzumab group (32.4%) compared to placebo (18.2%), with a low rate of discontinuations due to adverse events in both groups (7 patients [5.1%] discontinuations due to adverse events compared to 2 patients [1.5%) in the placebo treated group.[3] The most frequent SAEs observed among the obinutuzumab-treated patients were infections, including coronavirus disease 2019 (Covid-19)–related events, urinary tract infection, pneumonia, and gastroenteritis.[3]
- There is insufficient evidence to evaluate differences in efficacy or safety for specific populations based on race and ethnicity. Men are underrepresented in the study. While men develop SLE at lower rates than women, those with SLE have a higher propensity to develop LN. Safety in pregnancy and pediatric patients is unclear.
- SAPHNELO (anifrolumab-fnia) was FDA-approved in April 2026 for a weekly 120 mg/0.8 mL dose via subcutaneous self-administration with use of an autoinjector pen or prefilled syringe for adults with moderate to severe SLE.[4]
- BENLYSTA (belimumab) has received expanded indications including children age 5 years and older with active LN or active SLE who are receiving standard therapy.[5] Belimumab is available as a prefilled syringe and autoinjector for subcutaneous use for adults and pediatrics age 5 years and older.[5]

Recommendations:
- Move obinutuzumab (GAZYVA) to "Monoclonal Antibodies for Lupus" Class and apply PA with clear pathway to the oncology policy for oncology indications.
- Update anifrolumab-fnia and belimumab to allow longer approval duration.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- BENLYSTA (belimumab) was initially reviewed in May 2018 for treatment of patients aged 5 years and older with active, autoantibody-positive SLE and again in August 2021 when it was approved by the FDA for adults with active LN.
- In February 2022, the newly approved medications, LUKYNIS (voclosporin) and SAPHNELO (anifrolumab-fnia), were reviewed with BENLYSTA (belimumab). Voclosporin is non-preferred and PA is required in the immunosuppressants class. Anifrolumab-fnia and belimumab are both non-preferred and PA is required with drug specific PAs **(Appendix 7)**. They are included in the "Monoclonal Antibodies for Lupus" class. Literature was reviewed through Sept 2021 for that class update.
    a. There was low-quality evidence that *low dose* voclosporin 23.7 mg twice daily is superior to placebo at achieving CRR at 24 to 52 weeks based on 2 RCTs with background therapy of mycophenolate mofetil (MMF) (corticosteroid use varied by protocol) in patients with Class III, certain Class IV or Class V alone or in combination with Class III or IV LN.[6]
    b. There was insufficient evidence from 3 RCTs (one phase 2b, two phase 3) that anifrolumab-fnia 300 mg intravenously (IV) reduces SLE disease activity at 24 to 52 weeks in patients with moderate to severe SLE.[7-9] Evidence was downgraded due to risk of bias, imprecision, and indirectness.
    c. There was low-quality evidence that belimumab is more likely to achieve CRR or primary efficacy renal response (PERR) than placebo at week 104 in patients with Class III, Class IV, or Class V (in combination with Class III or IV) LN based on 2 randomized controlled trials (RCTs)[6]

Background:

Systemic lupus erythematosus is a chronic multisystem autoimmune disorder of the connective tissue which causes significant morbidity and mortality in the United States (U.S.) and worldwide. Estimates on prevalence vary based on changing detection methods and case definitions over time. Estimates may also vary based on genetic and environmental differences between countries.[10] Research studies conducted within the past 2 decades have described prevalence estimates of 9 to 241 per 100,000 person-years and an incidence of 0.3 to 23.2 per 100,000 person-years.[10] Data from studies conducted within the U.S. population with better designs involving strict case definitions, broad case-finding methodology, and correcting for possible case under-ascertainment show an SLE incidence of 4.6 to 6.4 per 100,000 person years and prevalence of 62.2 to 84.8 per 100,000 person years.[10] The Centers for Disease Control and Prevention estimates a U.S. prevalence of 322,000 probable or definite SLE cases.[11] Rates are generally higher among non-Whites, including both Hispanic and Arab ethnicities and those with American Indian, Alaska native, South/East Asian, and African descent.[10] Hispanic and South/East Asian individuals may have more severe disease and organ damage.[6,10] People of African descent are three times more likely to be afflicted with SLE, and have higher rates of renal involvement and mortality than Whites.[10,11] European ancestry is associated with a lower risk of LN.[10] While some of these differences may have genetic components, it has been shown that lower socioeconomic status, educational level, and poverty are associated with the health disparities of higher disease activity, organ damage, and mortality.[10]

Females in their reproductive years are most commonly afflicted with SLE.[6,10] The female-to-male ratio is estimated at 7 to 15:1 in adults and 3 to 5:1 in children. Disease onset in women is usually the 3rd to 5th decade of life; it generally presents later in men in the 5th to 7th decade. While representing about 1 in 10 SLE diagnoses, men tend to develop more severe disease and are 66% more likely to be diagnosed with LN than women based on U.S. Medicaid data.[6]

Smoking, endometriosis, alcohol consumption, and inhalational silica exposure have been strongly associated with SLE.[10] Additionally, psychological stress and environmental triggers such as ultraviolent light, certain drugs (echinacea, trimethoprim/sulfamethoxazole), infections, and mercury have been implicated.[11] The possible role of the gut microbiome is also under investigation.[10]

Systemic lupus erythematosus results from disruption of both the innate and adaptive arms of the immune system.[11] SLE patients have variable presentation, prognosis, and experience remissions and flares over the course of disease.[12] Many different organs are attacked by autoantibodies produced by the body, and this results in variety of complications.[6] Cutaneous lupus presents in nearly 90% of patients, and may manifest in an acute, subacute, or chronic fashion.[11] Non-lupus specific manifestations such as alopecia, vasculitis, (net-like pattern of skin discoloration), periungual telangiectasias, and Raynaud's phenomenon may be present.[11] Musculoskeletal involvement is very common, and arthralgia and true synovitis occur for almost 90% of patients. Renal disease and central nervous system disease are both associated with significant complications.[11] Renal disease, present in 50% of patients, is a major cause of morbidity and mortality. The delayed diagnosis of LN is a major risk factor for end-stage-renal disease (ESRD).[11] Prevalence of LN varies within US; among Medicaid beneficiaries LN is two times more common in the South.[6] Childhood-onset of SLE is associated with higher incidence and more severe LN than adult-onset disease.[13] Cognitive impairment is present is nearly 80% of SLE patients.[11] Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state are associated with SLE and may assist with diagnosis once other causes are excluded.[11] Patients with SLE are at higher risk of cardiovascular disease, and 10-15% of SLE cases are complicated by antiphospholipid syndrome. Pregnancy in patients with SLE is associated with higher rates of preterm birth, pre-eclampsia, and caesarean section. Prenatal planning and antenatal care are necessary to reduce the risk of complications to both parent and child.[11] Malignant disorders are more common in SLE patients.[10,13] Hospitalization rates due to infection, most commonly pneumonia, are twelve times higher in patient with SLE than those without, though the specific drug classes used for treatment of SLE are further risk factors for infectious complications.[10] Long-term use of steroids can also increase bone loss and fractures in patients with SLE.[13]

Diagnosis of SLE is made using clinical manifestations and positive serologies.[11,12,14] The EULAR/American College of Rheumatology (ACR) 2019 and Systemic Lupus International Collaborating Clinics (SLICC) 2012 both have classification criteria for SLE.[12,14] The more recent EULAR/ACR criteria are frequently used in practice (**Table 1**). Patients who meet the entry criterion of a positive antinuclear antibody (ANA) proceed to assessment of additive criteria. Patients with at least one clinical criterion without a more likely explanation, and a score of ≥ 10 points meet criteria for SLE diagnosis.[14]

Table 1. European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019 Diagnostic Criteria[14]

Entry criterion Antinuclear antibodies at a titer of ≥ 1:80 on HEp-2 cells or an equivalent positive test ever in lifetime			
↓			
If absent, do not classify as systemic lupus erythematosus If present, apply additive criteria			
↓			
Additive criteria Do not count a criterion if there is a more likely explanation than systemic lupus erythematosus Occurrence of a criterion on a least one occasion is sufficient SLE classification requires at least one clinical criterion and ≥ 10 points Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total scores.*			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional • Fever	2	***Antiphospholipid antibodies*** • Anti-cardiolipin antibodies OR • Anti-beta2GP1 antibodies OR • Lupus anticoagulant	2
Hematologic • Leukopenia • Thrombocytopenia • Autoimmune hemolysis	3 4 4	***Complement proteins*** • Low C3 OR low C4 • Low C3 AND low C4	3 4
Neuropsychiatric • Delirium • Psychosis • Seizure	2 3 5	***SLE-specific antibodies*** • Anti-dsDNA antibody† OR • Anti-Smith antibody	6
Mucocutaneous • Non-scarring alopecia • Oral ulcers	2 2		

• Subacute cutaneous OR discoid lupus • Acute cutaneous lupus	4 6	
Serosal • Pleural or pericardial effusion • Acute Pericarditis	 5 6	
Musculoskeletal • Joint involvement	 6	
Renal • Proteinuria >0.5g/24 h • Renal biopsy Class II or V lupus nephritis • Renal biopsy Class III or IV lupus nephritis	 4 8 10	
Total Score: If entry criterion fulfilled and score of 10 or greater should be classified as systemic lupus erythematosus		
* Additional criteria within the same domain will not be counted † Using assay with 90% specificity against relevant disease controls		

Diagnois of LN is generally confirmed through kidney biopsy. Serum creatine, urinalysis, spot protein-creatinine ratio, and serology (including anti-dsDNA and complement) are recommended in patients at SLE presentation and times of suspected SLE flare.[13] Evidence of abnormal protein/urine sediment or decreased/decreasing glomerular filtration rate (GFR) should be further evaluated to quantify proteinuria or accuracy of GFR results. Patients with 24-hour proteinuria ≥ 0.5 g/24h or abnormal eGFR with no attributable cause other than SLE should be considered for kidney biopsy.[13]

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system is most commonly used for LN (**Table 2**).[15] Disease classes are based on glomerular pathology ranging from class I, demonstrating minimal mesangial LN, to Class VI, demonstrating advanced sclerosis LN with ≥ 90% of glomeruli globally sclerosed without residual activity. Class III focal lupus nephritis and class IV diffuse lupus nephritis include additional subcategories for the presence of lesions which are active, active and chronic, or inactive and chronic. Additionally, classifications can differentiate segmental versus global lesions. Tubular atrophy, interstitial inflammation and fibrosis, and severity of arteriosclerosis or other vascular lesions should also be graded as mild, moderate, or severe.[12]

Table 2. ISN/RPS Lupus Nephritis Classifications[15]

Status	Description
Class I	Minimal mesangial lupus nephritis: earliest and mildest form of glomerular involvement
Class II	Mesangial proliferative lupus nephritis: excellent prognosis and no specific therapy is indicated
Class III	Focal lupus nephritis: patients present with hematuria and proteinuria, possibly to also have hypertension, decreased renal function and/or nephrotic syndrome. Light microscopy reveals less than 50 percent of glomeruli are affected.
Class IV	Diffuse lupus nephritis: patients present with hematuria and proteinuria and frequently seen with hypertension, decreased renal function and nephrotic syndrome. Light microscopy reveals more than 50 percent of glomeruli are affected.
Class V	Lupus membranous nephropathy: patients present with signs of nephrotic syndrome
Class VI	Advanced sclerosing lupus nephritis: patients present with slowly progressive kidney dysfunction associated with proteinuria

The goal of SLE treatment is to achieve remission or low disease activity.[16] Treatment of SLE for most patients involves use of hydroxychloroquine (HCQ), unless contraindicated, with the addition of GC at the lowest dose needed to enable remission or prevention of flares. Remission is characterized by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 0 (range 0 to 105, higher scores indicate more active disease)[10] on HCQ and without need for glucocorticoid (GC).[16] Administration of GC ranges from chronic therapy to high dose pulses for severe flares, and GC should be withdrawn whenever possible for stable disease. Immunosuppressive agents such as methotrexate, azathioprine, and MMF can be added in patients unresponsive to other therapies and those unable to achieve low daily GC doses (e.g. ≤ 7.5 mg/day). Intravenous cyclophosphamide can be considered as a rescue treatment in severe or life-threatening situations when disease is unresponsive to other therapies.[17] The biologic agent rituximab has been considered in certain situations; use of rituximab for SLE is off-label, and there have been negative results in certain SLE RCTs.[16,17] Treatment for specific organ complications is dependent on the organ system involved.[16] Treatment goals for LN usually rely on a renal response, which may have varied definitions of improvement of eGFR and UPCR from baseline.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 16 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Several reviews were duplicated amongst the different literature searches.

New Guidelines:
High Quality Guidelines:
<u>European Alliance of Associates of Rheumatology (EULAR)/European Renal Association/European Dialysis Transplantation Association (ERA-EDTA) Recommendations for the Management of Systemic Lupus Erythematosus with Kidney Involvement: 2025 update[1]</u>

EULAR updated the previous 2019 guidelines in 2025. The task force included experts outside of Europe, including the Americas and Asia, and generally followed the same standard methodology as the previous guideline iteration.[1] A new EULAR standard operating procedure suggested a maximum of 15 bullet pointed statements, resulting in a streamlining of existing recommendations.

The systematic literature search was updated to include January 2019 through March 2024, with final recommendations delayed until publication and evaluation of the phase 3 obinutuzumab RCT for inclusion in recommendations.[1] Level of evidence ratings ranged from 1 (highest) to 5 (lowest, expert opinion) using the

Oxford Centre for Evidence-based Medicine definitions, while grading of recommendation strength ranged from A (highest) to D (lowest).[1] Recommendations including monoclonal antibodies for SLE are shaded for emphasis in **Table 3**.

Overarching principles of management include:

- In patients with SLE, regular monitoring for signs and symptoms of kidney involvement, input from experts, and timely biopsy are essential to ensure optimal outcomes.[1]
- The management of patients with SLE with kidney involvement should align with the general recommendations for SLE, including treatment with hydroxychloroquine.[1]
- Kidney involvement in SLE carries the risk of progressive chronic kidney disease and is best managed with shared, informed patient-physician decisions by rheumatology-nephrology interdisciplinary care teams, with regular assessment of risk factors for chronic kidney disease progression.[1]
- Management aims to prevent progression of chronic kidney disease and flares, address comorbidities, and improve health-related quality of life; both immunosuppressive therapy and nonimmune therapy, including kidney protection, are essential.[1]

Table 3. Recommendations for management of patients with SLE and kidney involvement (Level of Evidence/GRADE)[1]

Recommendation
1. Kidney biopsy is recommended in every patient with evidence of kidney involvement, especially in those with persistent proteinuria (≥0.5 g/24 h or urine protein-creatinine ratio [UPCR] ≥500 mg/g) **(2b/B)**, glomerular hematuria **(2b/C)**, and/or unexplained decrease in glomerular filtration rate **(2b/C)**.
2. Treatment should aim for optimization (preservation or improvement) of kidney function within 3 months, accompanied by a reduction in proteinuria of at least 25% by 3 months **(2b/C)**, 50% by 6 months **(2a/B)**, and a UPCR target <700 mg/g by 12 months **(1b/B)**, and as low as possible afterwards.
3. For patients with active lupus nephritis, intravenous pulse methylprednisolone is recommended **(2b/C)**, followed by oral glucocorticoids gradually tapered to ≤5 mg/d prednisone-equivalent by 4-6 months **(2b/C)**, and slowly withdrawn in patients with sustained complete renal response.
4. For patients with active lupus nephritis, especially those with poor prognostic factors, we recommend combination therapy of (a) mycophenolate or low-dose intravenous cyclophosphamide with belimumab **(1b/A)**, (b) mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus) **(1b/A)**, or (c) mycophenolate with obinutuzumab **(1b/A)**. Alternative regimens include single-agent therapy with either mycophenolate **(1a/A)** or low-dose intravenous cyclophosphamide **(1a/A)**.
5. In patients with rapidly progressive glomerulonephritis, a short course (6-7 monthly pulses) of high-dose intravenous cyclophosphamide can also be considered **(1a/A)**.
6. Following renal response, treatment should continue for at least 3 years **(2b/B)**; patients initially treated with mycophenolate alone **(1a/A)** or in combination with (1) belimumab **(1b/A)**, (2) a calcineurin inhibitor **(1b/A)**, or (3) obinutuzumab should remain on these drugs; mycophenolate **(1a/A)** or azathioprine **(1a/A)** should replace cyclophosphamide for those initially treated with cyclophosphamide, alone or in combination with belimumab. *Note: Obinutuzumab was used for a maximum of 1 year (52 weeks) in the REGENCY trial; longer courses await further evaluation.*

7. In patients with sustained complete renal response, gradual withdrawal of immunosuppressive and/or biologic therapy should be considered after 3 years of therapy following response, taking into consideration the risk for flare **(2a/B)**.
8. For patients with persistently active or relapsing disease, switching among the aforementioned immunosuppressive **(2b/B)** and/or biologic drugs **(2b/B)** and referral to experts is recommended.
9. Repeat kidney biopsy should be considered, especially in cases of clinical uncertainty, to evaluate (1) response to treatment, (2) worsening of kidney-specific laboratory tests, or (3) contemplated withdrawal of immunosuppressive treatment **(2b/B)**.
10. Recommended nonimmune treatment includes renin-angiotensin-aldosterone blockade (for patients with persistent proteinuria or arterial hypertension) **(5/D)**, sodium glucose transporter 2 inhibitors (for stable patients with persistent proteinuria or estimated glomerular filtration rate <60 ml/min/m2, or other risk factors for progressive chronic kidney disease) **(5/D)**, statins (based on cardiovascular risk levels) **(5/D)**, and/or bone protective agents **(5/D)**.
11. In patients with features of thrombotic microangiopathy (antiphospholipid syndrome nephropathy, thrombotic thrombocytopenic purpura-like, or complement-mediated hemolytic uremic syndrome), glucocorticoids (IV pulse methylprednisolone) **(4/C)**, complement inhibitors **(4/C)**, B-cell depleting agents **(4/C)**, caplacizumab **(4/C)**, plasma exchange **(4/C)**, and/or anticoagulation **(2b/C)** should be considered.
12. In patients with inactive nephritis and adequately controlled extrarenal manifestations, pregnancy may be planned after preconception counselling, initiation of pregnancy-compatible medications, and regular multidisciplinary assessments **(1b/A)**.
13. All methods of kidney replacement therapy can be used in patients with SLE; in those with clinically inactive extrarenal disease for at least 6 months, transplantation (including living donor and pre-emptive transplantation) should be considered **(2b/C)**.

Belimumab and obinutuzumab are both recommended for use with other immunosuppressants for the treatment of active LN, particularly in patients with poor prognostic factors.[1] The authors noted that the phase 3 REGENCY trial of obinutuzumab did not include patients with pure class V LN, however they felt it was still a potential option given its efficacy in mixed proliferative and membranous nephritis.[1]

Complete renal response was defined in this document as a UPCR of less than 500 mg/g at any time point.[1] Factors leading to higher risk of suboptimal response and development of chronic kidney disease include reduced baseline GFR (<60 mL/min/m^2), previous flare, nephrotic range proteinuria at baseline, hypertension at baseline, male sex, increased chronicity index (>3, in the presence of activity), histological evidence of crescents, or severe tubulointerstitial inflammation.[1] Prognostic factors leading to increased risk of kidney flares include nonadherence to treatment, shorter duration of treatment (e.g., less than 3 years), incomplete response following initial therapy, ongoing extrarenal and serologic activity, no use of hydroxychloroquine, young age (e.g., less than 30 years), male sex, and residual histologic activity at repeat biopsy (National Institutes of Health Activity Index of 2 or greater).[1]

<u>Kidney Disease Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guidelines for the Management of Lupus Nephritis[2]</u>

KDIGO updated LN guidelines in 2024 based on a literature search conducted in July 2022 and updated in April 2023.[2] Previous guidelines on the Management of Glomerular Diseases was published in 2021. This update focuses on guidance for patients with SLE and kidney involvement. Strength of recommendations were given grades of Level 1 (Strong, “we recommend”) and Level 2 (Weak, “we suggest”). Quality of supporting evidence is shown as Grade A (High), Grade B (Moderate), Grade C (Low), and Grade D (Very Low).[2] A summary of recommendations related to monoclonal antibodies for lupus is included in **Table 4**.

Table 4. KDIGO recommendation for monoclonal antibody use for LN[2]

For initial therapy for active Class III/IV lupus nephritis	We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus any one of the following: i. mycophenolic acid analogs (MPAA) (1B); or ii. low-dose intravenous cyclophosphamide **(1B)**; or iii. belimumab and either MPAA or low-dose intravenous cyclophosphamide **(1B)**; or iv. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] </=45 ml/min per 1.73 m^2)**(1B)**.
	A triple immunosuppressive regimen of belimumab, glucocorticoids, and either MPAA or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or patients at high-risk for progression to kidney failure due to severe chronic kidney disease.
	Newer biologic and non-biologic therapies are under development and may offer future options for the treatment of active lupus nephritis. Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.
Maintenance therapy for Class III and Class IV lupus nephritis	Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with a triple immunosuppressive regimen as maintenance therapy.
Class V lupus nephritis Management of unsatisfactory response to treatment	Consider the following in patients refractory: Addition of rituximab or other biologic therapies, extended course of intravenous pulse cyclophosphamide, and enrollment in clinical trials if eligible

New Formulations or Indications:

SAPHNELO (anifrolumab-fnia) was FDA-approved in April 2026 for a weekly 120 mg/0.8 mL dose via subcutaneous self-administration with use of an autoinjector pen or prefilled syringe for adults with moderate to severe SLE.[18] The drug was previously available as a monthly 300 mg/2mL intravenous infusion in a healthcare setting. Approval was based on results of the TULIP-SC trial, evaluating safety and efficacy of subcutaneous anifrolumab in adults with moderate to severe SLE compared to placebo with those on standard therapy.[4] A 52-week interim analysis has been published, showing a statistically significant BICLA (British Isles Lupus Assessment Groups Index [BILAG]-based Combined Lupus Assessment) response for anifrolumab compared to placebo (anifrolumab vs. placebo: 59.4% vs. 43.9%; difference 15.5%, 95% CI 2.3–28.6; p = 0.0211).[4] Partial improvement in multiple affected systems may achieve BICLA response.

BENLYSTA (belimumab) has received expanded indications since previous review.

- July 2022-Expanded indication for children age 5 years to 17 years with active LN who are receiving standard therapy[5]
- May 2024-Approval of subcutaneous administration for pediatrics age 5 years and older with SLE[5]
- June 2025-Approval of use of autoinjector use for pediatric patients age 5 years and older with LN[5]

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Belimumab[5]	BENLYSTA	Feb 2023	Warnings and Precautions	Addition of new section for "concomitant use with other biologic therapies" *"Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies."*

Randomized Controlled Trials:
A total of 5 citations were manually reviewed from the initial literature search. After further review and exclusion of duplicates, all 4 remaining citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 5**.

Clinical Efficacy:
Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody. B-cell lysis is mediated through several pathways after binding with pre-B and mature B lymphocytes.[19] It has been approved for use on the U.S. market for more than a decade with indications related to chronic lymphocytic leukemia and follicular lymphoma. It was FDA approved in October 2025 for the treatment of adult patients with active LN who are receiving standard therapy.[19] Dosing for active LN is 1000 mg on day 0 then repeated on week 2, 24, 26, and every 6 months thereafter.[19] Approval for use in active LN was based on the results of the phase 3 REGENCY trial (**Table 6**).

This double-blind, placebo-controlled, multicenter, multinational, RCT included adults age 18 to 75 years who met the American College of Rheumatology (ACR) criteria for SLE with International Society of Nephrology and the Renal Pathology Society active class III or IV LN, with or without concomitant class V disease.[3] Those with an eGFR of less than 30 ml/min/1.73m^2 were excluded.[3] Additional inclusion/exclusion criteria are listed in **Table 6**. Patients were randomized 1:1 to placebo (n=136) or one of two treatment groups.[3] The active drug treatment groups were pooled (n=135) for outcome assessment and differed only with the inclusion or exclusion of a dose at Week 50 which was intended to evaluate pharmacokinetic and pharmacodynamic data and exploring dose-related efficacy for long-term treatment beyond 76 weeks.[3] Treatment groups were similar in demographics and baseline disease severity.[3]

The primary endpoint was CRR at Week 76.[3] This was defined as UPCR less than 0.5 mg/mg based on a timed 24-hour urine collection, an eGFR of at least 85% of the baseline value (calculated with the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration equation), and no occurrence of an intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal).[3] Treatment failure was considered ESRD or the use of long-term dialysis or renal transplantation, receipt of rescue therapy (except for glucocorticoid-only rescue), or clinically significant and sustained worsening of the UPCR or eGFR beyond week 24 that led the center investigator to conclude that the assigned regimen had failed. The obinutuzumab group achieved CRR at week 76 (46.4%) at a statistically significantly higher rate than placebo treated patients (33.1%)(adjusted difference 13.4%, 95% CI 2.0 to 24.8, p=0.02).

Multiple secondary endpoints were also assessed. These include CRR at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 (obinutuzumab 42.7% versus placebo 30.9%; adjusted difference 11.9, 95% CI 0.6 to 23.2; p=0.04); a UPCR less than 0.8 at week 76 with no intercurrent event (obinutuzumab 55.5% versus placebo 41.9%; adjusted difference 13.7, 95% CI 2.0 to 25.4; p=0.02); a change in the eGFR from baseline to week 76 (no significant difference); death or a renal-related event through week 76 (obinutuzumab 18.9% versus placebo 35.6%; adjusted difference -16.8%, 95% CI -27.4 to -6.2; p not reported); an overall renal response at week 50, which was defined as a complete renal response or a partial renal response (no significant difference); and a change in score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) from baseline to week 76 (no significant difference). [3] The lack of statistical significance at week 50, compared to achieving the primary endpoint at week 76, may indicate clinical response to treatment is not rapid.

Clinical Safety:
The safety population included all the patients who received any infusion of obinutuzumab or placebo in a blinded manner.[3] The patients in the safety population were grouped according to the infusion that was actually administered, regardless of the randomly assigned trial group.

Serious adverse events occurred more frequently in the obinutuzumab group (32.4%) compared to placebo (18.2%), with 7 discontinuations due to adverse event compared to 2 in the placebo treated group. The most frequent SAEs observed among the obinutuzumab-treated patients were infections, including Covid-19–related events, urinary tract infection, pneumonia, and gastroenteritis.

FDA labeling includes warnings and precautions related to both lupus and oncology indications. It has a black box warning for hepatitis B reactivation and all patients should be screened prior to treatment.[19] Labeling carries a second black box warning for potential for progressive multifocal leukoencephalopathy (PML), which can be fatal.[19] Patients require premedication with glucocorticoids, acetaminophen, and antihistamines to prevent and mitigate infusion-related reactions.[19] Hypersensitivity reactions, including serum sickness, can also occur.[19] Live vaccines should be administered prior to start of therapy or held until b-cell recovery, and females of childbearing potential must use effective contraception due to embryo-fetal toxicity.[19] Given the similar mechanism of action to rituximab, the medications should not be used concomitantly.

Look-alike / Sound-alike Error Risk Potential: none

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reduction in disease activity
2) Clinical response or remission
3) Quality of Life

Primary Study Endpoint:
1) Complete renal response at week 76

4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 6. Comparative Evidence Table.[3]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. REGENCY trial[3] Phase 3, DB, PC, RCT	1. Obinutuzumab IV 1000 mg day 1, weeks 2, 24, 26, 50, 52 + standard therapy 2. Obinutuzumab IV 1000 mg day 1, weeks 2, 24, 26, 52 + standard therapy 3. Placebo + standard therapy 1:1 randomization Standard therapy beginning at screening if not already receiving: mycophenolate mofetil and glucocorticoids (goal prednisone 7.5 mg daily by week 12 and 5 mg daily by week 24).	Demographics: -Mean Age ~33 years -Female 84.5% -White 47.6% -Black 14.8% -American Indian/Alaska Native 18.9% -Asian 5.9% -Hispanic or Latino 57.6% -Median eGFR ~108 ml/min/1.73m^2 -Median UPCR 2.13-2.73 mg/mg -Previously diagnosed Lupus Nephritis 57.9% Key Inclusion Criteria: -18-75 years old -ACR criteria for SLE with active class III or IV Lupus Nephritis -Biopsy-proven active Lupus Nephritis (w/ or w/o class V disease) -UPCR ratio of at least 1 using 24 hr urine collection -ANA positive Key Exclusion Criteria:	ITT: 1+2: 135 3: 136 Safety: 1+2: 136 3: 132 Completed week 76: 1+2: 13 (9.6%) 3: 16 (11.8%) Discontinued treatment: 1+2: 29 (21.3%) 3: 38 (28.8%)	Primary Endpoint: Complete Renal Response at week 76 1+2: 46.4% 3: 33.1% Adjusted Difference: 13.4% (95% CI, 2.0 to 24.8) P=0.02 Secondary Endpoints: Complete Renal response at week 76 with a prednisone dose of 7.5 mg/day or lower between weeks 64 and 76 1+2: 42.7% 3: 30.9% Adjusted Difference: 11.9% (95% CI, 0.6 to 23.2) P=0.04 Death or renal related event through week 76 1+2: 18.9% 3: 35.6% Adjusted Difference: -16.8% (95% CI, -27.4 to -6.2)	13.4/ 8 11.9/ 9 16.8/ 6	Total AE: 1+2: 748 3: 665 Any AE: 1+2: 126 (92.6%) 3: 117 (88.6%) SAE: 1+2: 44 (32.4%) 3: 24 (18.2%) AE with fatal outcome: 1+2: 3 (2.2%) 3: 2 (1.5%) Discontinuation due to AE: 1+2: 7 (5.1%) 3: 2 (1.5%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomization using central interactive voice- and web-based response system with permuted block design. Stratified by geographic region (US or Canada, Latin America or Caribbean, or other) and race (Black or other). Baseline characteristics balanced. Performance Bias: (low) Blinding maintained until all patients completed week 76 assessment. For investigators and patients with adequate response, blinding was maintained 1 year beyond week 76 and data analysis through that point completed. Detection Bias: (low) Slightly higher rate of discontinuation due to inadequate response in placebo group (22 placebo vs. 6 obinutuzumab), but overall low. Objective outcomes decrease risk of bias. Attrition Bias: (unclear) More than 20% of patients discontinued treatment. Missing data imputed using a multiple-imputation method that used fully conditional specification with predicted mean matching (100 imputed data sets) with the use of data for patients who did not have intercurrent events. Patients who had intercurrent events were imputed as no response. Reporting Bias: (Low) Protocol published with prespecified outcomes. Other Bias: (unclear) Sponsor (F.Hoffmann-La Roche) designed and participated in data collection, analysis, interpretation, manuscript preparation and submission. **Applicability**: Patient: Applicable primarily to those with Class III or IV LN, with or without class V. Excluded medications (cyclophosphamide, tacrolimus,

		-eGFR < 30mL/min/1.73 m^2 or ESKD on dialysis or s/p transplantation -Evidence of infection -Anti-CD20 medication within 9 months -Cyclophosphamide, tacrolimus, cyclosporine, voclosporin within 2 months						cyclosporin, etc.) more likely to select for less refractory patients on first-line treatment and those with less risk for additional drug induced renal toxicity. Intervention: Appropriate based on phase 2 study, more appropriate to dose intervention the same for all patients or assess separately rather than pooled. Comparator: Placebo comparison appropriate for initial approval, comparative data vs. belimumab or a calcineurin inhibitor would be helpful for place in therapy. Outcomes: Appropriate, though complete renal response defined slightly differently than belimumab pivotal study and optimization goals in EULAR guidelines, further reinforcing need for direct comparative evidence. Setting: 15 countries
Abbreviations: ACR = American College of Rheumatology; AE = adverse event; ANA = antinuclear antibody; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; ITT = intention to treat; hr = hour; ITT = modified intention to treat; IV = intravenous; LN = lupus nephritis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse event; SLE = systemic lupus erythematosus; s/p = status post; UPCR = urinary protein-to-creatinine ratio (in mg/mg); US = United States; w/o = without; w/ = with.								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
anifrolumab-fnia	SAPHNELO	INTRAVEN	VIAL	N
anifrolumab-fnia	SAPHNELO PEN	SUBCUT	AUTO INJCT	
belimumab	BENLYSTA	INTRAVEN	VIAL	N
belimumab	BENLYSTA	SUBCUT	AUTO INJCT	N
belimumab	BENLYSTA	SUBCUT	SYRINGE	N
obinutuzumab*	GAZYVA	INTRAVEN	VIAL	

*Currently in the “Antineoplastics, newer” drug class

Appendix 2: Abstracts of Comparative Clinical Trials

None

Appendix 3: Medline Search Strategy

Ovid medline 1946 to 5/29/26 and 2021 to 5/29/26

☐	1	obinutuzumab.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	1379
☐	2	Lupus Erythematosus, Systemic/ or Lupus Nephritis/	72287
☐	3	1 and 2	50
☐	4	limit 3 to (english language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or network meta-analysis or practice guideline or randomized controlled trial or "systematic review"))	16
☐	5	anifrolumab.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	439
☐	6	4 and 5	3
☐	7	belimumab.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	1488
☐	8	4 and 7	7

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GAZYVA safely and effectively. See full prescribing information for GAZYVA.

GAZYVA® (obinutuzumab) injection, for intravenous use
Initial U.S. Approval: 2013

WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)**
- **Progressive Multifocal Leukoencephalopathy (PML) resulting in death. (5.2)**

----------RECENT MAJOR CHANGES----------
Indication and Usage, Lupus Nephritis (1.3) ----------10/2025
Dosage and Administration (2.4)----------10/2025
Warnings and Precautions (5)---------- ----------10/2025

---------- INDICATIONS AND USAGE----------
GAZYVA is a CD20-directed cytolytic antibody indicated:

- in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). (1.1, 14)
- in combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma (FL)who relapsed after, or are refractory to, a rituximab-containing regimen. (1.2, 14)
- in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma. (1.2, 14)
- for the treatment of adult patients with active lupus nephritis (LN) who are receiving standard therapy (1.3, 14)

----------DOSAGE AND ADMINISTRATION----------

- Premedicate for infusion-related reactions and tumor lysis syndrome. (2.1, 5.3, 5.4)
- Administer only as intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
- The recommended dosage for chronic lymphocytic leukemia is 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1,000 mg on day 8 and 15 of Cycle 1, and 1,000 mg on day 1 of Cycles 2–6. (2.2)
- The recommended dosage for follicular lymphoma is 1,000 mg on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years. (2.3)
- The recommended dosage for active lupus nephritis is 1,000 mg at the initial infusion, on Week 2, 24, 26, and every 6 months thereafter. (2.4)

---------- DOSAGE FORMS AND STRENGTHS----------
Injection: 1,000 mg/40 mL (25 mg/mL) single-dose vial. (3)

---------- CONTRAINDICATIONS ----------
GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Infusion-Related Reactions: Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt, reduce rate, or discontinue for infusion-related reactions based on severity. (2.1, 5.3)
- Hypersensitivity Reactions Including Serum Sickness: Discontinue GAZYVA permanently. (5.4)
- Tumor Lysis Syndrome: In CLL and FL, premedicate with anti-hyperuricemics and adequate hydration, especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance. (5.5)
- Serious, Including Fatal, Infections: Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection. (5.6)
- Neutropenia: In patients with Grade 3 to 4 neutropenia, monitor laboratory tests until resolution and for infection. Consider dose delays and infection prophylaxis, as appropriate. (5.7)
- Thrombocytopenia: Monitor for decreased platelet counts and bleeding. Transfusion may be necessary. (5.8)
- Disseminated Intravascular Coagulation: Evaluate cause and monitor for bleeding, thrombosis, and need for supportive care. (5.9)
- Immunization: Avoid administration of live virus vaccines during GAZYVA treatment and until B-cell recovery. (5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use effective contraception. (5.11)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (incidence ≥ 20% and ≥ 2% greater in the GAZYVA treated arm in CLL and NHL, and incidence ≥ 5% in the GAZYVA treated arm in LN) were:

- Previously untreated CLL: infusion-related reactions and neutropenia. (6)
- Relapsed or refractory non-Hodgkin lymphoma (NHL): infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain. (6)
- Previously untreated NHL: infusion-related reactions, neutropenia, upper respiratory tract infections, cough, constipation, and diarrhea. (6)
- Lupus Nephritis: upper respiratory tract infection, COVID-19, urinary tract infection, bronchitis, pneumonia, infusion-related reactions, and neutropenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2025

Appendix 5. Pharmacology and Pharmacokinetic Properties[19]

Parameter	
Mechanism of Action	-Monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. -Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.
Oral Bioavailability	n/a
Distribution and Protein Binding	Not reported
Elimination	Clearance of 0.13 L/day via two parallel pathways, a linear clearance pathway and a non-linear clearance pathway, which changes as a function of time. The time-varying clearance decreases with time with an exponential decay coefficient, likely related to CD20 target reduction and proteinuria improvement over time, and a time-independent clearance related to the endogenous catabolic processes of IgG.
Half-Life	22.4 days
Metabolism	Not reported

Abbreviations: IgG = immune globulin G; L = liter; n/a = not applicable

Appendix 6: Key Inclusion Criteria

Population	Patients with SLE and/or LN
Intervention	Appendix 1
Comparator	Appendix 1, standard therapy (e.g., corticosteroids, cyclophosphamide, mycophenolate products, cyclosporin, voclosporin, etc.)
Outcomes	Renal response, disease activity scores, hospitalizations, need for dialysis, quality of life, adverse events
Timing	Not applicable
Setting	Outpatient

Anifrolumab-fnia

Goal(s):
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12~~6~~ months

Requires PA:
- Anifrolumab-fnia provider administered and pharmacy claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have severe active central nervous system lupus or severe, active lupus nephritis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6

Approval Criteria		
6. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Go to #8 Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the patient currently taking ALL of the following or have a documented contraindication: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone) • Methotrexate OR Azathioprine OR Mycophenolate	**Yes:** Approve for 12~~6~~ months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Approve for ~~6~~ 12 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 8/26 (SF); 2/22 (SF)
Implementation: TBD; 4/1/22

Belimumab (Benlysta®)

Goal(s):
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:
- Up to 24 ~~6~~ months

Requires PA:
- Benlysta® (belimumab) pharmacy or provider administered claims.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

~~Table 1: FDA approved ages~~

~~Indication~~	~~Approved formulation~~	
	~~Intravenous (IV) powder for solution~~	~~Subcutaneous (SC) Injection~~
~~Systemic Lupus Erythematosus (SLE)~~	~~5 years and older~~	~~5 years and older~~
~~Lupus Nephritis~~	~~5 years and older~~	~~5 years and older~~
~~IV (usual adult dosage): SLE or Lupus Nephritis: 10 mg/kg IV infusion over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter~~ ~~SC (usual adult dosage): SLE: 200 mg SC once weekly~~ ~~Lupus Nephritis:400 mg (two 200-mg injections) SC once weekly into abdomen or thigh for 4 doses, then 200 mg SC once weekly thereafter~~		

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #3
3. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient diagnosed with lupus nephritis or systemic lupus erythematosus (SLE)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is belimumab dosed according to FDA label for age and formulation? ~~appropriately and with an approved formulation for patient's age as outlined in Table 1?~~	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient currently on other targeted immune modulators?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other targeted immune modulators	**No:** Go to #7
7. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE or lupus nephritis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have active autoantibody-positive SLE or lupus nephritis and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to #9 Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the patient currently taking or have a contraindication to BOTH of the following: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone) PLUS one of the follow if treating lupus nephritis: mycophenolate acid analog OR azathioprine OR cyclophosphamide	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness. ~~Belimumab has not been studied as monotherapy in patients with SLE.~~
10. Does the patient have lupus nephritis AND a urine protein: creatinine ratio of >500 mg/g?	**Yes:** Go to #11	**No:** Approve for 12~~6~~ months
11. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Approve for 12~~6~~ months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on another ~~therapeutic immune modulator~~biologic agent? Note: Belimumab has not been studied in combination with other ~~therapeutic immune modulators~~biologic agents.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for ~~6~~24 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *08/26 (SF); 02/22 (SF); 8/21 (DM) 2/20, 5/18*
Implementation: *TBD; 4/1/22; 3/1/2020; 7/1/18*

Obinutuzumab (GAZYVA®)

Goal(s):
- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:
- 12 months

Requires PA:
- Gazyva® (obinutuzumab) pharmacy or provider administered claims.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the ICD-10 for an oncology indication?	**Yes:** Use "Oncology Agents" prior authorization document to adjudicate request.	**No:** Go to #3
3. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult diagnosed with active lupus nephritis class III, IV, or V?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently on another biologic agent without a documented plan to switch therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating lupus nephritis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a baseline assessment of renal function with both of the following tools within 6 months: • Urinary protein-to-creatinine ratio (UPCR) • estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to #9 Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the patient currently taking or have a contraindication to all of the following: • Hydroxychloroquine • Mycophenolate • Glucocorticoids (e.g. prednisone)	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Does the patient have a urine protein-to-creatinine ratio of >/= 1 mg/mg?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the patient of childbearing potential?	**Yes:** Go to #13	**No:** Approve for 12 months
13. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14
14. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on another biologic agent?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's renal function improved or stabilized as assessed by one of the following: • UPCR • eGFR	**Yes:** Approve for 12 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *08/26 (SF)*
Implementation: *TBD*

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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update with New Drug Evaluation: C-Type Natriuretic Peptides

Date of Review: August 2026

Generic Name: Navepegritide

Date of Last Review: April 2022
Dates of Literature Search: 01/01/1946 – 05/13/2026
Brand Name (Manufacturer): YUVIWEL (Ascendis Pharma)
Dossier Received: no

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Assess the evidence for efficacy and safety of YUVIWEL (navepegritide), a C-type natriuretic peptide (CNP) pro-drug recently approved by the Food and Drug Administration (FDA) to increase linear growth in children aged 2 years and older with achondroplasia and open epiphyses. In addition, new evidence for VOXZOGO (vosoritide), a CNP analog indicated for the management of bone growth in children with achondroplasia will be evaluated.

Plain Language Summary:

- Achondroplasia is a rare condition that affects the growth of bones in childhood. It is caused by a mutation, or change, in a gene that is responsible for bone development. The bones in the arms and legs are mostly affected, which causes short-limbed dwarfism or short stature.
- Other features of the achondroplasia include enlarged head, short fingers, spinal curvature, and bowed legs. Complications of this condition are frequent ear infections which can affect hearing development, brief periods of stopped breathing while sleeping (apnea), back pain, numbness, leg weakness, and slowed development of motor skills such as sitting and walking.
- YUVIWEL (navepegritide) is a new medicine approved by the FDA to stimulate bone growth in children aged 2 years and older with achondroplasia. A similar medicine, VOXZOGO (vosoritide), was approved in 2021 to also stimulate bone growth in children with achondroplasia. Vosoritide must be given once a day by an injection under the skin (subcutaneously), while navepegritide is given once a week by a subcutaneous injection. The two medicines have not been studied together so it is not known if one medicine is safer or more effective than the other medicine.
- A clinical study conducted over one year found that navepegritide added an additional 0.6 inches of height in children who received the medicine instead of placebo. However, the final effect on final adult height measurements has not yet been determined.
- The most common side effects with navepegritide injections are redness, swelling or rash at the site where the medicine was given (injection site reactions).
- The Oregon Health Plan should offer coverage of navepegritide similar to vosoritide in children enrolled in the plan who have achondroplasia after the prescriber documents medical need through a process called prior authorization.

Author: Deanna Moretz, PharmD, BCPS

Research Questions:

1. What is the efficacy and effectiveness of navepegritide in reducing symptoms, avoiding complications, and improving functional outcomes in patients with achondroplasia?
2. What are the harms of navepegritide in the treatment of patients with achondroplasia?
3. Are there populations based on demographic characteristics, such as age, gender, ethnicity, comorbidities, who would benefit from or be harmed by navepegritide?

Conclusions:

- No new high-quality systematic reviews or clinical guidelines were identified for this drug class update.
- The FDA approved an expanded indication for vosoritide for all pediatric patients with achondroplasia and open epiphyses in October 2023.[1] Prior to the expanded indication, vosoritide was only approved in children aged 5 years and older.[1] The expanded approval is based on results from a 52-week, double-blind, placebo-controlled, phase 2 randomized controlled trial (RCT) evaluating the efficacy and safety of vosoritide in 64 children younger than 5 years (range: 4.4 months to 59.8 months).[2] The study was not powered to detect significant changes in primary endpoints. The least-squares mean difference (LSMD) from baseline to 52 weeks in height Z-score between the vosoritide (-0.06) and placebo (-0.31) was 0.25 (95% CI -0.02 to 0.53; low-quality evidence).[2] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]
- In February 2026, a new CNP pro-drug, navepegritide, received FDA approval to increase linear growth in pediatric patients 2 years or older with achondroplasia with open epiphyses.[3] This indication was approved under accelerated approval based on an improvement in annualized growth velocity observed in clinical trials.[4] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[3]
- The phase 2b APPROACH trial evaluated the safety and efficacy of navepegritide in children (n=84) with genetically confirmed achondroplasia.[4] Compared to placebo, once weekly navepegritide resulted in a LSMD in annualized growth velocity of 1.49 centimeters (cm)/year (4.41 vs.5.89 cm/year; 95% confidence interval [CI] 1.05 to 1.93; P<0.0001; moderate-quality evidence) over 52 weeks.[4] Although this difference was statistically significant, the clinical significance of this change is not clear. Evidence to support navepegritide to reduce symptoms, avoid complications, and improve functional outcomes in patients with achondroplasia is insufficient.
    - The most frequently reported adverse events in the trial and subsequent open-label extension study were vomiting, injection site reactions, pain in the extremity, and nausea (see **Table 2**).[3]
    - Evidence specific to demographic characteristics such as race, ethnicity, and comorbidities are insufficient due to underrepresentation in the studies. Study results are most applicable to white patients with achondroplasia ages 2 to 11 years which may limit broader applicability.

Recommendations:

- Create a new drug class on Oregon's Practitioner-Managed Prescription Drug Plan (PMPDP) called "C-Type Natriuretic Peptides" and include vosoritide and navepegritide in this class.
- Designate vosoritide and navepegritide as non-preferred and require prior authorization (PA) to ensure appropriate use (see **Appendix 6**).

Summary of Prior Reviews and Current Policy:
The first drug approved for management bone development in children with achondroplasia was vosoritide, which was reviewed by the Pharmacy and Therapeutic Committee at the April 2022 meeting. The Committee approved the recommendation to implement PA criteria for vosoritide to ensure appropriate use in FDA-approved populations. The PA criteria are presented in **Appendix 6**.

Background:
Achondroplasia, the most common form of short-stature skeletal dysplasia, is caused by a recurrent pathogenic variant in the gene encoding the fibroblast growth factor receptor 3 (FGFR3) protein, which results in impaired conversion of cartilage to bone (ossification).[5,6] Features associated with achondroplasia are short fingers, shortened proximal limb bones, macrocephaly, midface hypoplasia, and a long trunk.[6] The estimated prevalence of achondroplasia is 3.72–4.6 per 100,000 births.[7] About 20% of individuals inherit the disorder in an autosomal dominant pattern.[8] About 75% of individuals with achondroplasia are born to average-stature parents due to a de novo genetic mutation.[8] Advanced paternal age (over 35 years) is a risk factor for de novo genetic mutations, as the mutation is thought to occur during spermatogenesis.[8] There is no recognized ethnic or sex predisposition for this condition.[8] In 2025, there were 55 Oregon Health Plan members with the diagnosis of achondroplasia (ICD 10: Q77.4), of whom 10% were enrolled in the fee-for-service (FFS) program.

Achondroplasia can be diagnosed before birth by fetal ultrasound to identify shortened fetal long bones during late second-trimester or third-trimester imaging.[8] DNA testing is also available before birth to confirm fetal ultrasound findings for parents who are at increased risk of having a child with achondroplasia.[8] After birth, the diagnosis can usually be made on the basis of clinical characteristics and specific features on radiographs, including a square-shaped pelvis with a small sacrosciatic notch, short pedicles of the vertebrae with interpedicular narrowing from the lower thoracic through lumbar region, proximal shortening of the long bones, proximal femoral radiolucency, and a characteristic chevron shape of the distal femoral epiphyses.[8]

Potential medical complications of achondroplasia include kyphosis, hydrocephalus, middle ear dysfunction, sleep apnea, spinal stenosis, and genu varum (bowlegs).[6] The most common complication, occurring in adulthood, is related to lumbosacral spinal stenosis with compression of the spinal cord.[9] Lumbosacral spinal stenosis is usually treatable by surgical decompression, with better outcomes if treated at an early stage.[9] Children diagnosed with achondroplasia commonly have delayed motor milestones, chronic otitis media which can impair hearing, and bowing of the lower legs, which can cause tripping and frequent falls.[9] Less commonly, infants and children may have serious health consequences related to craniocervical junction compression because of a relatively small foramen magnum (the bony hole at the base of the skull through which the brainstem and spinal cord exit the skull), which can result in numbness, weakness, increased irritability, poor feeding, difficulty walking, and loss of bowel and bladder control.[9] Most individuals with achondroplasia have average intelligence and are able to lead independent and productive lives.[9] The mean lifespan in this condition is about 10 years shorter than the general population.[10] The average height of an adult with achondroplasia is about 4 feet.[10]

There is no universally accepted standard of care for the management of patients with achondroplasia, and there is limited evidence-based guidance to assist providers and caregivers. There is no known cure for achondroplasia. The 2020 practice guideline from the American Academy of Pediatrics (AAP) focuses on identification of patients at high risk of developing complications.[8] Monitoring recommendations are stratified by age and include recommendations for diagnostic procedures, genetic counseling, and type of medical evaluation.[8] Most of the AAP recommendations are based on expert opinion. The guideline does not meet criteria for high quality and therefore is not discussed in detail here. There is insufficient comparative evidence to guide recommendations on first-line medical therapy.

Clinical trials in patients with achondroplasia often evaluate outcomes such as improvements in final height, weight, and proportionality.[11] To monitor growth, specialized charts have been created for children with achondroplasia since their height advances considerably below the normal curve area.[12] Deficits in growth in terms of annualized growth velocity from infancy to adolescence are often tracked and compared to population norms.[12] Some studies have used these values and converted measurements to an age- and sex-appropriate score known as a height Z-score which allows a comparison with normal references.[11,12] A negative Z-score value such as -2 is interpreted as 2 standard deviations lower than the mean height for a particular age and sex.[12] Clinically relevant outcomes in patients with achondroplasia include final height, functional improvement, and avoidance of long-term disease complications but no minimal clinically important difference has been established for these outcomes in this population. Research investigating whether there may be a correlation between height Z-score and negative outcomes such as spinal cord compression or stenosis in patients with achondroplasia is ongoing.[13]

All children with achondroplasia should receive regular follow-up by a multidisciplinary team, guided by a health-care provider with expertise in achondroplasia.[14] Close monitoring in the first 2 years of life is important.[14] Treatment for spinal stenosis might include decompression and fusion. Treatment for lower extremity misalignment may include surgery to correct the limbs. Growth hormone therapy has not been shown to be effective in improving final adult height in patients with achondroplasia.[9]

Medical treatments enhancing C-type natriuretic peptide (CNP) activity have recently been approved to promote bone growth in children with achondroplasia. Vosoritide is a recombinant CNP analog that is FDA-approved to promote linear growth in children with achondroplasia and open epiphyses.[1] Approval was based on data demonstrating the efficacy of vosoritide in improving annualized growth velocity and changes in height Z-scores.[1] The effects of vosoritide on final height, proportional growth, or other areas of clinical significance such as reduced symptoms, avoidance of medical complications, or improvements in functionality of people with achondroplasia are unknown. Navepegritide is a prodrug of CNP that is converted in the bloodstream to its active form.[3] Navepegritide recently received accelerated approval by the FDA to promote linear growth in children with achondroplasia aged 2 years and older whose epiphyses have not fused.[3] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[3] Additional details on the safety and efficacy of this medication are provided in the New Drug Evaluation section of this report.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No new high-quality systematic reviews were identified. Three systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or endpoints studied (e.g., non-clinical).[15-17]

Clinical Practice Guidelines:
No new high-quality guidelines were identified. Current published recommendations are based on expert opinion and consensus of practitioners experienced in managing this condition. Two guidelines were excluded due to poor quality.[18,19]

New Formulations or Indications:
10/2023: The FDA approved the expanded use of vosoritide for all children with achondroplasia and open epiphyses.[1] Prior to this approval, vosoritide was only approved in children aged 5 years and older.[1] The expanded indication was based on results from a 52-week, double-blind, placebo-controlled, phase 2 RCT evaluating the efficacy and safety of vosoritide in 64 children younger than 5 years (range: 4.4 months to 59.8 months).[2] The study was not powered for the efficacy endpoints.[2] The first primary endpoint was safety and tolerability of vosoritide, administered subcutaneously once daily, assessed in all participants who received at least one study dose.[2] The most common adverse events were injection-site reactions (86%) and rash (28%).[1] The second primary endpoint was change in height Z- score from baseline to week 52.[2] The LSMD at 52 weeks in height Z-score between the vosoritide (-0.06) and placebo (-0.31) was 0.25 (95% CI -0.02 to 0.53; low-quality evidence).[2] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[1]

New FDA Safety Alerts:
No new FDA Safety Alerts identified.

Randomized Controlled Trials:
A total of 10 citations were manually reviewed from the initial literature search. None of the trials were included because of either wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or endpoints studied (e.g., non-clinical).

NEW DRUG EVALUATION:
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 4**.

Clinical Efficacy:

The APPROACH trial contributed the efficacy and safety data used for the approval of navepegritide in children with achondroplasia, which is described and evaluated below in **Table 2**. This was a multi-center, double-blind, placebo-controlled, 52-week, Phase 2b RCT, followed by a single-arm 52-week open-label study period.[4] The trial enrolled 84 pediatric participants aged 2 years and older with genetically confirmed achondroplasia who had never received treatment. Fifty-seven participants received navepegritide 100 mcg/kg administered subcutaneously (SC) once weekly and 27 participants received placebo SC once weekly.[4] Mean age at enrollment was 5.7 years (range, 2–11 years).[4] Forty-five participants (54%) were male and 39 (46%) were female.[4] Participants had a mean baseline Centers for Disease Control and Prevention (CDC)–based height Z-score of −5.0 and mean baseline height of 89 cm (range, 64–120 cm).[4]

The primary efficacy endpoint was annualized growth velocity at week 52.[4] Height Z-scores were calculated using reference data from untreated children with achondroplasia (achondroplasia-specific height Z-score) and using reference data from the general population (CDC–based height Z-score).[4] Compared to placebo, treatment with navepegritide resulted in a LSMD in annualized growth velocity of 1.49 cm/year (5.89 vs. 4.41 cm/yr; 95% CI 1.05 to 1.93; P<0.0001) and

a LSMD increase in achondroplasia-specific height Z-score of 0.3 (95% CI 0.2 to 0.4; P<0.0001) at 52 weeks (see **Table 3**).[4] The clinical significance of these relatively modest differences in height-related outcomes is unclear.

All 57 patients in the phase 2 trial entered a single-arm, open-label follow-up study with navepegritide for another 52 weeks.[4] Annualized growth velocity was maintained among those who had received 2 years of treatment with navepegritide 100 mcg/kg once weekly.[3]

Trial Limitations:

The trial used annualized growth velocity and changes in height Z-scores as primary and secondary endpoints, which are intermediate clinical endpoints. It is unclear if a change of 1.49 cm in annualized growth velocity is clinically significant and whether treatment with navepegritide leads to sustained growth velocity improvements throughout a child's natural growth period. It is also unknown if the study results apply to those with more severe disease as participants were required to be able to stand without assistance and not have a prior bone fracture. The trial did not evaluate the long-term effects of navepegritide on adult height nor how efficacy may differ based on longer treatment duration.[4] The analyses also do not directly evaluate functional improvements, medical complications, or the need for surgical interventions.[4] Investigations are underway to assess the long-term effects of navepegritide, the efficacy and safety in additional age groups (<2 years and 12-18 years), and additional outcomes, including orthopedic outcomes and health-related quality of life.[4]

Clinical Safety:

The most frequently reported adverse events in the navepegritide phase 2B RCT and open-label extension study were vomiting, injection site reactions, pain in the extremity and nausea (**Table 1**).[3]

Table 1. Adverse Events Reported in Clinical Studies of Navepegritide.[3]

Adverse Event	**Navepegritide 0.1 mg/kg/week** (n=68)	**Placebo** (n=42)
Vomiting	21%	14%
Injection-Site Reactions	19%	14%
Pain in Extremity	12%	7%
Nausea	6%	0

Hypotension was not reported with navepegritide, but the manufacturer recommends that providers advise their patients to contact them if they experience symptoms of low blood pressure (dizziness, fatigue, and/or nausea) while being treated with navepegritide.[3] Navepegritide is not recommended for patients with moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min).[3]

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Final adult height
2) Disease progression and complications (cervicomedullary compression, spinal stenosis, etc.)

Primary Study Endpoint:
1) Annualized growth velocity at 52 weeks

3) Health-related quality of life and function
4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Savarirayan, et al.[4] Phase 2B, R, DB, PC, MC	1. Navepegritide 100 mcg/kg SC once a week 2. Placebo SC once a week 52 weeks	Demographics: -Mean age: 5.5 y (range: 2 to 11 y) -Age < 5 y: 37% -Age ≥ 5 y: 63% -Male: 54% -Race: Asian: 9.5% Black: 0% White: 88.1% Other: 24% -Mean Height: 89 cm (range 64 to 120 cm) -Mean baseline AGV: 3.9 cm/y -Mean baseline CDC-based height Z score: -5.0 -Mean baseline ACH-specific height Z score: 0.1 Key Inclusion Criteria: -Aged 2-11 y -Genetically confirmed ACH -Able to stand without assistance Key Exclusion Criteria: -Closed epiphysis -Planned or history of bone surgery -Untreated sleep apnea -Treatment with growth hormone therapies -Bone fracture within 6 months of screening	ITT: 1. 57 2. 27 PP: 1. 55 2. 27 Attrition: 1. 2 (4%) 2. 0	Primary Endpoint: AGV at week 52 1. 5.89 cm/yr 2. 4.41 cm/yr LSMD: 1.49 cm/y (95% CI 1.05 to 1.93; p<0.0001) Secondary Endpoints: Change from baseline in achondroplasia-specific height Z-score at week 52 1. 0.3 2. 0.0 LSMD: 0.3 (95% CI 0.2 to 0.4; p<0.0001) Change from baseline in CDC height Z-score at week 52 1. 0.1 2. -0.2 LSMD: 0.3 (95% CI 0.1 to 0.5; p-value NR, endpoint analyzed outside of prespecified testing strategy)	NA NA NA	TEAEs 1. 52 (91.2%) 2. 26 (96.3%) Serious AEs 1. 3 (5.3%) 2. 3 (11.1%) Pyrexia 1. 20 (35.1%) 2. 6 (22.2%) Vomiting 1. 11 (19.3%) 2. 3 (11.1%) Injection Site Reactions 1. 11 (19.3%) 2. 4 (14.8%) p-values and CIs NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to active treatment or placebo and stratified by age and gender (< 5 y, ≥ 5 y and male, ≥ 5 y and female) via interactive web response system. Baseline characteristics are similar between groups. Performance Bias: Low. Participants, investigators, and caregivers blinded to treatment assignments. Placebo visually identical to active treatment. Injection site reactions with active treatment may have risked unblinding. Detection Bias: Low. Data assessors blinded to treatment assignment. Attrition Bias: Low. Attrition was less than 5%. Reporting Bias: Low. Protocol published online and all prespecified endpoints were reported per protocol. Other Bias: High. Study funded by manufacturer. Investigators received personal fees and grants from manufacturer. **Applicability**: Patient: Recruitment limited by the rare condition. Results most applicable to children with aged 2 to 11 y with achondroplasia. Most participants were white (88%). Intervention: Only the 100 mcg/kg weekly dose improved AGV compared to placebo. Comparator: Placebo is an appropriate comparator to determine efficacy. Comparative trials with vosoritide needed. Outcomes: AGV is a surrogate marker to demonstrate drug efficacy in treatment of disproportional short stature at 52 weeks. The impact on long-term growth velocity, final height upon closed epiphyses, physical symptoms or daily functioning improvement is unknown. Setting: 10 sites in 7 countries: Australia, Canada, Denmark, Ireland, New Zealand, Spain, United States.

Abbreviations: ACH = achondroplasia; AE = adverse events; AGV = annualized growth velocity; ARR = absolute risk reduction; CDC = Centers for Disease Control and Prevention; cm = centimeters; DB = double-blind; CI = confidence interval; ITT = intention to treat; kg = kilograms; LSMD = least-squares mean difference; MC = multi-center; mcg = micrograms; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PP = per protocol; R = randomized; SC = subcutaneous; TEAEs = treatment-emergent adverse effects; y = year(s).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
vosoritide	VOXZOGO	SUBCUT	VIAL	
navepegritide	YUVIWEL	SUBCUT	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to May 13, 2026>

1	exp Achondroplasia/th [Therapy]	110
2	vosoritide.mp. or Natriuretic Peptide, C-Type/	1558
3	navepegritide.mp.	5
4	2 or 3	1560
5	1 and 4	10

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUVIWEL safely and effectively. See full prescribing information for YUVIWEL.

YUVIWEL® (navepegritide) for injection, for subcutaneous use
Initial U.S. Approval: 2026

----------INDICATIONS AND USAGE----------
YUVIWEL is a C-type natriuretic peptide (CNP) analog indicated to increase linear growth in pediatric patients 2 years of age and older with achondroplasia with open epiphyses. (1)

This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer once-weekly by subcutaneous injection. Dosage is based on body weight. (2.1)
- Periodically monitor growth and adjust dose according to body weight. Discontinue when no further growth potential, as indicated by epiphyseal closure. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.3, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 1.3 mg, 2.8 mg, and 5.5 mg as a lyophilized powder in single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Risk of Low Blood Pressure: Transient decreases in blood pressure have been reported with a once daily CNP analog. Advise patients to contact their healthcare provider if they experience symptoms of decreased blood pressure while being treated with YUVIWEL. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 5%): vomiting, injection-site reaction, pain in extremity, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ascendis Pharma at 1-844-442-7236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: Not recommended for patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73 m^2). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2026

Appendix 4. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Prodrug of C-type natriuretic peptide, which stimulates skeletal bone growth
Oral Bioavailability	Not Applicable
Distribution and Protein Binding	Volume of Distribution: 1.8 Liters Protein Binding: Not Described
Elimination	Clearance = 0.052 Liters/day
Half-Life	6.7 days
Metabolism	Natural degradation pathways for peptides

Appendix 5: Key Inclusion Criteria.

Population	Children with achondroplasia aged 2 years and older
Intervention	100 mcg/kg administered subcutaneously once a week
Comparator	Placebo
Outcomes	Annualized growth velocity, Height Z-Scores
Timing	52 weeks
Setting	Outpatient

C-type Natriuretic Peptides

Goal:
- Ensure medically appropriate use of approved agents for the treatment of achondroplasia in pediatric patients

Length of Authorization:
- Up to 12 months

Requires PA:
- Vosoritide and navepegritide (pharmacy claims)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Vosoritide Weight-Based Dosing

Actual Body Weight*	Dose	Injection Volume	Vial Strength for Reconstitution**
3 kg	0.096 mg	0.12 mL	0.4 mg
4 kg	0.12 mg	0.15 mL	0.4 mg
5 kg	0.16 mg	0.2 mL	0.4 mg
6 to 7 kg	0.2 mg	0.25 mL	0.4 mg
8 to 11 kg	0.24 mg	0.3 mL	0.4 mg
12-16 kg	0.28 mg	0.35 mL	0.56 mg
17-21 kg	0.32 mg	0.4 mL	0.56 mg
22-32 kg	0.4 mg	0.5 mL	0.56 mg
33-43 kg	0.5 mg	0.25 mL	1.2 mg

Actual Body Weight*	Dose	Injection Volume	Vial Strength for Reconstitution**
44-59 kg	0.6 mg	0.3 mL	1.2 mg
60-89 kg	0.7 mg	0.35 mL	1.2 mg
≥90 kg	0.8 mg	0.4 mL	1.2 mg

*Intermediate body weights that fall within these weight bands should be rounded to the nearest whole number.
**The concentration of vosoritide in reconstituted 0.4 mg vial and 0.56 mg vial is 0.8 mg/mL.
The concentration of vosoritide in reconstituted 1.2 mg vial is 2 mg/mL.

Table 2. Navepegritide Weight-Based Dosing

Patient Body Weight	Weekly Dose	Injection Volume	Vial Strength for Reconstitution*
8 to 9.9 kg	0.88 mg	0.4 mL	1.3 mg
10 to 13.4 kg	1.2 mg	0.55 mL	
13.5 to 17.5 kg	1.6 mg	0.35 mL	2.8 mg
17.6 to 23 kg	2.1 mg	0.45 mL	
23.1 to 30.5 kg	2.8 mg	0.6 mL	
30.6 to 41.2 kg	3.6 mg	0.65 mL	5.5 mg
41.3 to 55.9 kg	5 mg	0.9 mL	
56 to 73.5 kg	6.6 mg	1.2 mL (use 2 kits; administer 0.6 mL from each kit)	
73.6 to 90 kg	8.8 mg	1.6 mL (use 2 kits; administer 0.8 mL from each kit)	

*The concentration of navepegritide is 2.2 mg/mL in a reconstituted 1.3 mg vial; 4.6 mg/mL in a 2.8 mg vial; and 5.5 mg/mL in a 5.5 mg vial

Approval Criteria	
1. What diagnosis is being treated?	Record ICD-10 code.

Approval Criteria		
2. Is this an FDA-approved indication based on diagnosis and current age restrictions? *Vosoritide is approved for all pediatric patients and navepegritide is approved for pediatric patients aged 2 years and older	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
~~2.~~3. Is the prescribed agent being dosed according to actual body weight (ABW) as outlined in Tables 1 and 2?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
~~3.~~4. Is the request for continuation of therapy in a patient previously approved under fee-for-service (FFS) criteria?	**Yes:** Go to Renewal Criteria	**No:** Go to #5
~~4.~~5. Is the agent prescribed by, or in consultation with, a pediatric endocrinologist, neurologist, or other prescriber specialized in the care of patients with achondroplasia or skeletal dysplasia?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~6. Is there documented evidence of a baseline measurement of annualized growth velocity (AGV) within the last 90 days AND (for males ≥15 years or females ≥13 years old) documented non-closure of epiphyseal plates?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
~~6.~~7. Does the patient have a history of bone-related surgery or fracture of long bone or spine within the previous 6 months or planned bone surgery?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months ~~Go to #8~~
~~7. Does the patient have a diagnosis of recurrent symptomatic hypotension with or without orthostasis?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Approve for 6 months~~

Renewal Criteria		
1. Is this FDA-approved for the diagnosis and current age restrictions?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
~~2. Is there documented evidence that the regimen is well tolerated with no adverse effects or drug toxicity?~~	~~**Yes:** Go to #3~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~6.~~2. Is there documented evidence of ≥ 85% adherence to therapy regimen (verified through claims history and/or provider assessment) OR < 85% adherence with documented temporary interruption due to surgery or infection?	**Yes:** Go to #3~~4~~	**No:** Pass to RPh. Deny; medical appropriateness
~~7.~~3. Is this the first renewal request?	**Yes:** Approve for 6 months	**No:** Go to #4~~5~~
~~8.~~4. Is there documented evidence of an improvement in annualized growth velocity (AGV) ≥ 1.0 cm/year from baseline AND, if male ≥15 years or female ≥13 years old, evidence of non-closure of epiphyseal plates?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/26 (DM); 4/22 (DE)
Implementation: TBD; 5/1/22