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, July 26, 2018 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302
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 as required by 414.325(9).

	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	T. Klein (Chair)
	D. Department Update	T. Douglass (OHA)
	E. Legislative Update	T. Douglass (OHA)
	F. Mental Health Clinical Advisory Group Discussion	K. Shirley (MHCAG)
1:40 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
	A. P&T Methods	
	B. CMS and State Annual Reports	
	C. Quarterly Utilization Reports	
	1. Public Comment	
	III. DUR ACTIVITIES	
1:45 PM	A. ProDUR Report	R. Holsapple (DXC)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Reviews	K. Sentena (OSU)
	1. A Review of Implications of FDA Expedited Approval Pathways, Including the Breakthrough Therapy Designation	
	IV. PREFERRED DRUG LIST NEW BUSINESS	
2:00 PM	A. Oral Cystic Fibrosis Modulators Class Update	M. Herink (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Symdeko™ (tezacaftor/ivacaftor) New Drug Evaluation	
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	

2:30 PM	B. Newer Diabetes Treatments Class Update 1. Class Update/Prior Authorization Criteria 2. Steglatro™ (ertugliflozin) New Drug Evaluation 3. Ozempic® (semaglutide) New Drug Evaluation 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:00 PM	BREAK	
3:10 PM	C. Asthma Biologics DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:30 PM	D. Radicava® (edaravone) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:45 PM	E. Neuropathic Pain DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
	V. DUR OLD BUSINESS	
4:05 PM	A. Sedatives 1. Updated Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Page (OSU)
4:10 PM	B. New Drug Policy 1. Updated Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
4:15 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2020
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2020
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2020
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2020
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 24, 2018, 1:00-5:00 PM
DXC Building
Salem, OR 97301

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 as required by 414.325(9).

Members Present: Tracy Klein, PhD, FNP; Phil Levine, PhD; Walter Hardin, DO, MBA; Jim Slater, PharmD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; Cathy Zehrung, RPh; Kelley Burnett, DO

Members Present by Phone:

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Lindsay Newton; Dee Weston; Renae Wentz, MD; Julia Page, PharmD; Jonnaliz Corbett; Deanna Moretz, PharmD; Tiffany Tsai, PharmD; Pearce Engelder, PharmD; Megan Herink, PharmD; David Engen, PharmD

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Leo Yasinski; Rick Frees, Vertex; Vivian Chau, SMC; Bobbi Jo Drum, BMS; Teresa Blair, Ipsen; Brittany Duffy-Goche, National Psoriasis Foundation; Troy Larsen, Sage; Laura Jeffcoat, AbbVie; Maragaret Olmon, AbbVie; Kelly Nguyn, OHSU; Larry Curtis, Allergant; Julie Haynes; Mary Kemhus, Novartis; Diann Matthews; Rashid Kazerooni, Merz; Amy Burns, AllCare; Bing Bing Liany, Care Oregon; Lisa Boyle, WVP Health; Raulo Frear, Merck.

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:02 pm. Introductions were made by Committee members and staff. No new conflict of interests were declared.
B. Dr. Douglass provided a department update and legislative update.

ACTION: Motion to approve, 2nd, All in Favor.

II. CONSENT AGENDA TOPICS

A. Approval of agenda and March minutes presented by Mr. Citron. (pages 5-8)

ACTION: Motion to approve, 2nd, All in Favor.

B. Topical Antibiotics Class Update with Xepi™ (ozenoxacin) New Drug Evaluation (pages 9-19)
    1. Review in executive session.
C. Glaucoma Class Update with Rhopressa™ (netarsudil) and Vyzulta™ (latanoprostene) New Drug Evaluations (pages 20-40)
    1. Review in executive session.

ACTION: Motion to approve, 2nd, All in Favor.

III. DUR Old Business

A. Exclusion List
Dee Weston presented the exclusion list and the recommendation to remove it from the current PA guide.

ACTION: Motion to approve, 2nd, All in Favor.

IV. DUR Activities

A. Quarterly Utilization Reports (pages 41-46) – Mr. Citron presented the quarterly report
B. ProDUR Report (pages 47-50) – Mr. Holsapple presented the ProDUR report
C. RetroDUR Report (pages 51-54) – Dr. Engen presented the RetroDUR report
D. Oregon State Drug Reviews
    1. Recently published reviews:
        i. What's New with Biologic Agents for Inflammatory Disease? (pages 55-56)
        ii. Second Generation Antipsychotic Use in Major Depressive Disorder (pages 57-58)
    2. Future Topic Recommendations

Dr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters.

V. PREFERRED DRUG LIST NEW BUSINESS

A. Benlysta ® (belimumab) New Drug Evaluation (pages 59 - 72)

Dr. Moretz presented the new drug evaluation, proposed PA criteria and recommended:

1. Designate belimumab as a non-preferred agent with PA criteria.

ACTION: The Committee amended the proposed PA criteria to require documentation of baseline disease severity and objective documentation of improvement in disease activity to the renewal criteria; to require treatment with current standard of care medications for systemic lupus erythematosus prior to approval of belimumab; and to require prescription by or in consultation with a specialist. Motion to approve, 2nd, All in Favor.

B. Fluoroquinolone Class Update (pages 73-88)
Dr. Herink presented the class update and recommended:

1. Continue to maintain at least one FQ with broad coverage of gram-negative bacteria and at least one 'respiratory' FQ as preferred options.
2. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

C. *Clostridium Difficile* Drugs Class Update (pages 89-106)
Dr. Moretz presented the class update and proposed PA criteria to:

1. Designate bezlotoxumab as non-preferred and subject to PA.
2. Modify fidaxomicin PA criteria to remove metronidazole as a prerequisite to fidaxomicin in patients with recurrent CDI.
3. Evaluate comparative costs in executive session.

ACTION: The Committee amended the proposed PA criteria to also remove metronidazole as a prerequisite for bezlotoxumab, and to remove the question which asks if the provider will switch to a preferred agent in the fidaxomicin PA criteria. Motion to approve, 2nd. All in favor. Approved.

D. Botulinum Toxins Class Update (pages 107-132)
Dr. Page presented the class update with the following recommendations:

1. Update current clinical prior authorization criteria to reflect current coverage and guidelines in the OHA Prioritized List of Health Services.

ACTION: Motion to approve, 2nd. All in favor. Approved.

VI. DUR NEW BUSINESS

A. Methadone Drug Use Evaluation (pages 133-145)
Dr. Tsai presented the drug use evaluation with the following recommendations:

1. Maintain status of methadone as non-preferred on the PDL.

ACTION: The Committee agreed with the recommendation to maintain methadone as non-preferred on the PMPDP.

B. Gabapentin Drug Use Evaluation (pages 146-161)

Dr. Engelder presented the drug use evaluation with the following recommendations:

1. No changes are recommended.

ACTION: The Committee agreed with the recommendation that no changes were needed.

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VII. EXECUTIVE SESSION

VIII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Topical Antibiotics Class Update (pages 9-19)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

B. Glaucoma Class Update (pages 20-40)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

C. Fluoroquinolone Class Update (pages 73-88)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

D. Clostridium Difficile Drugs Class Update (pages 89-106)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

IX. A. Short Acting Opioid PA criteria classification (pages 162-168)
***ACTION: Update PA criteria to include language regarding taper plans for patients on chronic therapy.**

Motion, 2nd, Majority in Favor, One Opposed. Approved.

X. ADJOURN

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Pharmacy Utilization Summary Report: January 2017 - December 2017

Eligibility	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Total Members (FFS & Encounter)	956,495	953,093	978,100	991,147	991,908	994,823	982,276	963,901	959,096	961,528	962,260	963,814	971,537
FFS Members	144,554	140,575	146,756	144,374	130,857	135,409	143,784	127,100	130,304	128,336	118,961	126,786	134,816
OHP Basic with Medicare	32,850	32,815	33,065	33,156	33,179	33,308	33,513	33,453	33,651	33,710	33,679	33,770	33,346
OHP Basic without Medicare	12,851	12,507	12,526	12,803	12,559	12,546	12,903	12,546	12,333	12,541	11,983	12,096	12,516
ACA	98,853	95,253	101,165	98,415	85,119	89,555	97,368	81,101	84,320	82,085	73,299	80,920	88,954
Encounter Members	811,941	812,518	831,344	846,773	861,051	859,414	838,492	836,801	828,792	833,192	843,299	837,028	836,720
OHP Basic with Medicare	40,501	40,586	40,562	40,614	40,798	40,843	40,894	40,986	41,036	41,080	41,162	41,174	40,853
OHP Basic without Medicare	67,089	67,386	67,328	67,031	67,125	66,631	63,104	62,676	62,828	63,025	63,731	63,827	65,148
ACA	704,351	704,546	723,454	739,128	753,128	751,940	734,494	733,139	724,928	729,087	738,406	732,027	730,719

Gross Cost Figures for Drugs	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	YTD Sum
Total Amount Paid (FFS & Encounter)	$72,993,802	$69,215,377	$77,258,158	$69,366,556	$76,955,136	$75,829,592	$71,904,669	$75,119,813	$69,674,162	$73,319,364	$72,833,675	$69,621,682	$874,091,986
Mental Health Carve-Out Drugs	$8,131,413	$7,725,767	$8,473,030	$7,748,396	$8,416,208	$8,188,295	$8,013,540	$8,133,945	$7,117,776	$7,580,574	$7,277,252	$7,031,984	$93,838,181
OHP Basic with Medicare	$1,485	$1,159	$3,173	$954	$912	$37	$52	$117	$28	$282	$61	$36	$8,295
OHP Basic without Medicare	$3,427,353	$3,256,865	$3,538,763	$3,171,809	$3,441,968	$3,335,909	$3,269,113	$3,297,186	$2,949,828	$3,120,770	$3,033,710	$3,000,334	$38,843,608
ACA	$4,640,032	$4,404,849	$4,852,045	$4,504,018	$4,892,311	$4,778,025	$4,666,558	$4,755,174	$4,112,076	$4,401,698	$4,181,314	$3,973,388	$54,161,489
FFS Physical Health Drugs	$3,790,543	$3,460,817	$3,746,079	$3,273,403	$3,497,983	$3,157,461	$2,860,585	$2,976,106	$2,968,513	$2,840,215	$2,630,842	$2,698,869	$37,901,418
OHP Basic with Medicare	$302,413	$290,118	$264,823	$238,677	$243,315	$230,766	$221,915	$230,457	$227,731	$235,567	$232,087	$202,727	$2,920,598
OHP Basic without Medicare	$1,009,211	$927,664	$1,275,728	$1,054,099	$1,121,385	$954,074	$859,909	$1,008,346	$1,051,278	$956,070	$857,815	$887,997	$11,963,576
ACA	$2,361,409	$2,135,150	$2,084,717	$1,825,247	$2,006,381	$1,815,103	$1,657,401	$1,606,758	$1,566,833	$1,535,078	$1,405,911	$1,494,947	$21,494,935
FFS Physician Administered Drugs	$2,891,053	$2,739,625	$2,615,450	$1,873,499	$2,905,075	$2,907,720	$2,056,042	$2,532,612	$1,748,682	$1,334,525	$1,788,224	$1,316,528	$26,709,034
OHP Basic with Medicare	$375,003	$364,941	$443,632	$437,585	$428,030	$348,478	$543,560	$472,475	$337,974	$381,482	$539,617	$462,122	$5,134,898
OHP Basic without Medicare	$325,987	$391,446	$391,838	$251,044	$1,250,811	$1,251,274	$456,812	$314,225	$244,427	$322,659	$499,569	$243,928	$5,944,020
ACA	$1,728,631	$1,321,655	$1,334,526	$774,666	$917,231	$921,794	$801,970	$848,217	$932,900	$423,355	$500,152	$424,065	$10,929,161
Encounter Physical Health Drugs	$47,327,962	$44,654,508	$51,035,567	$46,038,732	$50,300,729	$49,486,563	$47,733,937	$49,787,132	$46,883,994	$50,013,072	$49,446,222	$48,070,452	$580,778,870
OHP Basic with Medicare	$122,203	$116,525	$122,188	$115,126	$116,709	$109,884	$111,192	$116,116	$106,470	$124,213	$118,188	$101,114	$1,379,927
OHP Basic without Medicare	$13,139,428	$12,464,113	$13,722,579	$12,405,539	$13,568,071	$13,259,246	$13,237,199	$13,892,735	$12,753,347	$13,403,131	$13,332,638	$12,465,412	$157,643,438
ACA	$33,525,129	$31,483,518	$36,564,641	$32,928,292	$35,913,514	$35,439,035	$33,712,561	$35,034,737	$33,247,581	$35,772,671	$35,290,333	$34,803,839	$413,715,851
Encounter Physician Administered Drugs	$10,852,830	$10,634,660	$11,388,031	$10,432,526	$11,835,141	$12,089,553	$11,240,565	$11,690,018	$10,955,196	$11,550,979	$11,691,135	$10,503,849	$134,864,482
OHP Basic with Medicare	$236,694	$227,590	$274,503	$205,868	$264,797	$210,724	$224,067	$213,726	$182,791	$199,314	$180,754	$184,103	$2,604,929
OHP Basic without Medicare	$2,611,784	$2,372,310	$2,267,151	$2,409,139	$2,606,688	$2,375,954	$2,674,953	$2,646,417	$2,227,920	$2,213,425	$2,579,853	$2,228,502	$29,214,097
ACA	$7,810,986	$7,787,388	$8,665,794	$7,648,140	$8,694,903	$9,326,422	$8,210,793	$8,625,399	$8,365,523	$8,830,963	$8,664,783	$7,921,818	$100,552,913

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: July 18, 2018

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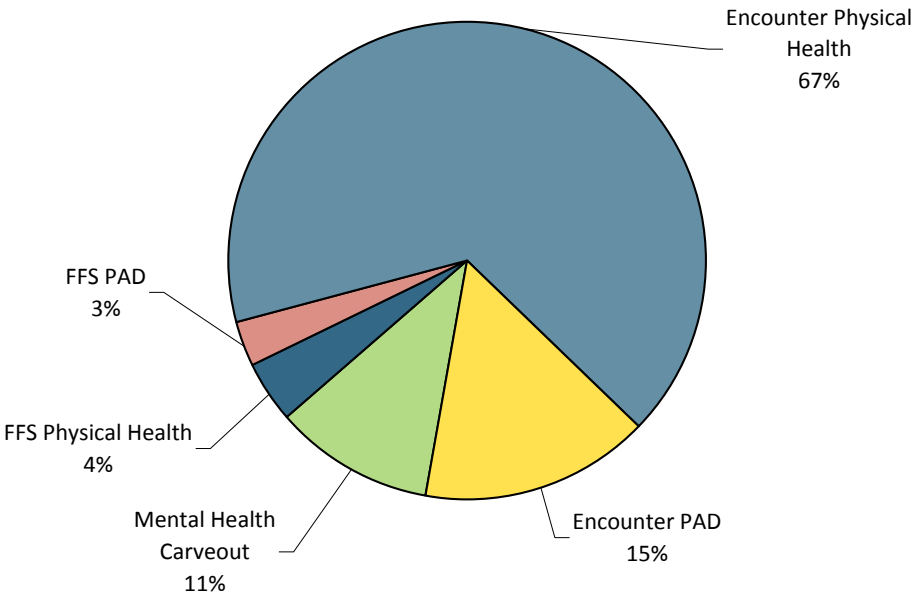
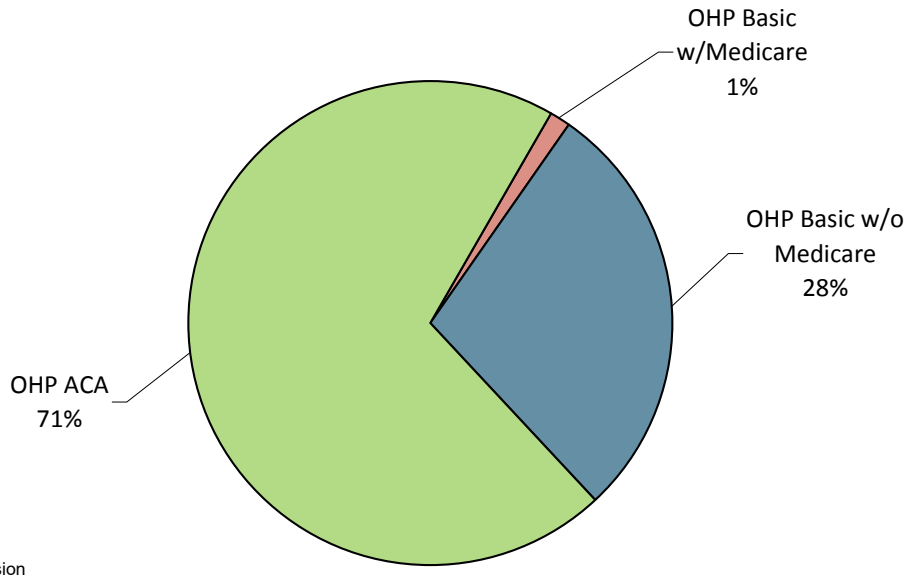
YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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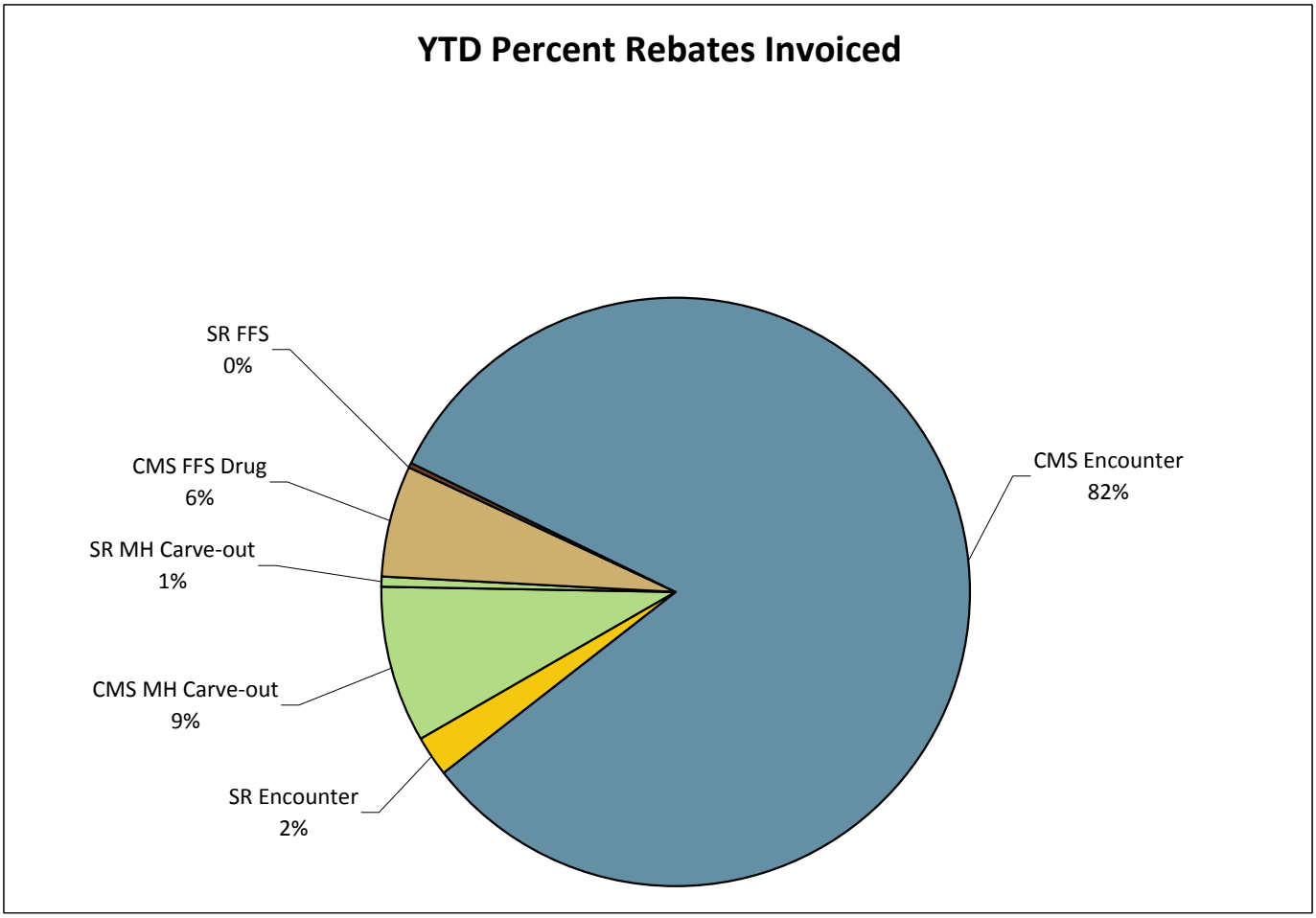
Pharmacy Utilization Summary Report: January 2017 - December 2017

Quarterly Rebates Invoiced	2017-Q1	2017-Q2	2017-Q3	2017-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$105,628,941	$145,800,639	$100,072,738	$100,629,849	$452,132,167
CMS MH Carve-out	$10,791,366	$10,291,651	$9,380,517	$8,966,396	$39,429,930
SR MH Carve-out	$634,141	$594,672	$609,003	$655,360	$2,493,177
CMS FFS Drug	$7,918,443	$7,569,296	$6,500,523	$5,786,728	$27,774,990
SR FFS	$207,986	$218,470	$178,105	$180,363	$784,925
CMS Encounter	$83,896,232	$123,813,433	$81,250,389	$82,198,306	$371,158,361
SR Encounter	$2,180,772	$3,313,116	$2,154,201	$2,842,696	$10,490,784

Quaterly Net Drug Costs	2017-Q1	2017-Q2	2017-Q3	2017-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$113,838,397	$76,350,644	$116,625,905	$115,144,873	$421,959,819
Mental Health Carve-Out Drugs	$12,904,703	$13,466,575	$13,275,741	$12,268,055	$51,915,074
FFS Phys Health + PAD	$11,117,139	$9,827,375	$8,463,912	$6,642,112	$36,050,538
Encounter Phys Health + PAD	$89,816,555	$53,056,694	$94,886,252	$96,234,706	$333,994,207



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

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Pharmacy Utilization Summary Report: January 2017 - December 2017

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$76.31	$72.62	$78.99	$69.99	$77.58	$76.22	$73.20	$77.93	$72.65	$76.25	$75.69	$72.24	$74.97
Mental Health Carve-Out Drugs	$8.50	$8.11	$8.66	$7.82	$8.48	$8.23	$8.16	$8.44	$7.42	$7.88	$7.56	$7.30	$8.05
FFS Physical Health Drugs	$26.22	$24.62	$25.53	$22.67	$26.73	$23.32	$19.90	$23.42	$22.78	$22.13	$22.12	$21.29	$23.39
FFS Physician Administered Drugs	$20.00	$19.49	$17.82	$12.98	$22.20	$21.47	$14.30	$19.93	$13.42	$10.40	$15.03	$10.38	$16.45
Encounter Physical Health Drugs	$58.29	$54.96	$61.39	$54.37	$58.42	$57.58	$56.93	$59.50	$56.57	$60.03	$58.63	$57.43	$57.84
Encounter Physician Administered Drugs	$13.37	$13.09	$13.70	$12.32	$13.74	$14.07	$13.41	$13.97	$13.22	$13.86	$13.86	$12.55	$13.43

Claim Counts	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Total Claim Count (FFS & Encounter)	1,035,308	975,701	1,097,717	1,015,191	1,086,362	1,036,446	986,695	1,028,081	982,082	1,046,037	1,015,022	1,000,091	1,025,394
Mental Health Carve-Out Drugs	149,055	138,687	156,365	146,934	159,209	152,473	147,393	153,499	144,563	153,763	149,710	145,639	149,774
FFS Physical Health Drugs	72,072	67,953	72,433	63,983	67,366	64,301	61,600	63,035	59,035	60,683	56,834	56,311	63,801
FFS Physician Administered Drugs	25,173	22,282	22,808	17,209	17,650	17,194	17,700	18,290	17,208	16,696	15,815	15,580	18,634
Encounter Physical Health Drugs	684,225	644,939	734,518	680,795	733,545	698,798	655,212	683,153	653,995	701,352	682,094	675,274	685,658
Encounter Physician Administered Drugs	104,783	101,840	111,593	106,270	108,592	103,680	104,790	110,104	107,281	113,543	110,569	107,287	107,528

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$70.50	$70.94	$70.38	$68.33	$70.84	$73.16	$72.87	$73.07	$70.95	$70.09	$71.76	$69.62	$71.04
Mental Health Carve-Out Drugs	$54.55	$55.71	$54.19	$52.73	$52.86	$53.70	$54.37	$52.99	$49.24	$49.30	$48.61	$48.28	$52.21
FFS Physical Health Drugs	$52.59	$50.93	$51.72	$51.16	$51.93	$49.10	$46.44	$47.21	$50.28	$46.80	$46.29	$47.93	$49.37
FFS Physician Administered Drugs	$114.85	$122.95	$114.67	$108.87	$164.59	$169.11	$116.16	$138.47	$101.62	$79.93	$113.07	$84.50	$119.07
Encounter Physical Health Drugs	$69.17	$69.24	$69.48	$67.62	$68.57	$70.82	$72.85	$72.88	$71.69	$71.31	$72.49	$71.19	$70.61
Encounter Physician Administered Drugs	$103.57	$104.43	$102.05	$98.17	$108.99	$116.60	$107.27	$106.17	$102.12	$101.73	$105.74	$97.90	$104.56

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$27.71	$27.76	$27.36	$26.65	$26.77	$27.11	$27.15	$27.27	$26.86	$26.08	$26.15	$26.20	$26.92
Mental Health Carve-Out Drugs	$34.26	$34.28	$33.26	$30.99	$30.25	$30.08	$30.36	$29.02	$24.77	$24.51	$23.57	$23.24	$29.05
FFS Physical Health Drugs	$24.26	$23.65	$23.07	$21.28	$21.55	$21.17	$21.55	$21.53	$22.74	$21.42	$20.75	$21.65	$22.05
Encounter Physical Health Drugs	$26.58	$26.73	$26.47	$26.17	$26.46	$26.98	$26.92	$27.38	$27.72	$26.85	$27.19	$27.25	$26.89

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$641.18	$652.70	$666.70	$665.85	$679.06	$693.47	$723.23	$697.11	$626.36	$618.93	$680.65	$689.80	$669.59
Mental Health Carve-Out Drugs	$814.64	$819.62	$821.59	$852.76	$871.61	$882.88	$893.16	$897.48	$895.92	$922.01	$924.68	$953.68	$879.17
FFS Physical Health Drugs	$425.56	$426.32	$448.65	$464.20	$475.68	$443.30	$406.90	$406.05	$397.69	$356.68	$384.64	$391.73	$418.95
Encounter Physical Health Drugs	$650.28	$662.22	$675.33	$669.13	$681.02	$699.28	$736.48	$705.32	$624.23	$617.38	$684.18	$693.34	$674.85

Multi-Source Drug Use Percentage	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Multi-Source Drug Use Percentage	93.8%	93.9%	94.0%	94.2%	94.2%	94.1%	94.2%	94.0%	93.4%	93.3%	93.8%	94.0%	93.9%
Mental Health Carve-Out Drugs	97.4%	97.3%	97.3%	97.4%	97.3%	97.2%	97.2%	97.2%	97.2%	97.2%	97.2%	97.3%	97.3%
FFS Physical Health Drugs	92.9%	93.2%	93.3%	93.3%	93.3%	93.4%	93.5%	93.3%	92.7%	92.4%	93.0%	92.9%	93.1%
Encounter Physical Health Drugs	93.2%	93.3%	93.4%	93.6%	93.6%	93.5%	93.5%	93.3%	92.6%	92.5%	93.1%	93.4%	93.2%

Preferred Drug Use Percentage	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Avg Monthly
Preferred Drug Use Percentage	86.67%	86.67%	86.64%	86.57%	86.43%	86.30%	86.42%	86.18%	87.07%	86.89%	86.70%	86.66%	86.6%
Mental Health Carve-Out Drugs	75.89%	75.78%	75.66%	75.64%	75.29%	75.09%	74.83%	74.80%	74.72%	74.64%	74.47%	74.52%	75.1%
FFS Physical Health Drugs	95.41%	95.35%	95.31%	95.16%	95.27%	95.24%	95.42%	95.40%	95.55%	95.48%	95.61%	95.57%	95.4%
Encounter Physical Health Drugs	88.09%	88.10%	88.12%	88.14%	88.01%	87.89%	88.14%	87.87%	89.03%	88.84%	88.64%	88.54%	88.3%

Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,373,082	15.2%	4,502	$1,193	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,192,603	6.2%	1,239	$1,770	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,085,231	3.1%	587	$1,849	Y
4	REXULTI	Antipsychotics, 2nd Gen	$949,376	2.7%	927	$1,024	V
5	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$670,180	1.9%	1,712	$391	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	$615,391	1.7%	109	$5,646	V
7	FLUOXETINE HCL	Antidepressants	$602,231	1.7%	31,863	$19	Y
8	VRAYLAR	Antipsychotics, 2nd Gen	$597,101	1.7%	553	$1,080	V
9	SAPHRIS	Antipsychotics, 2nd Gen	$560,348	1.6%	820	$683	Y
10	DULOXETINE HCL	Antidepressants	$545,173	1.5%	29,010	$19	V
11	SERTRALINE HCL	Antidepressants	$492,972	1.4%	41,805	$12	Y
12	ATOMOXETINE HCL*	ADHD Drugs	$472,415	1.3%	5,145	$92	Y
13	TRAZODONE HCL	Antidepressants	$418,979	1.2%	37,300	$11	
14	BUPROPION XL	Antidepressants	$402,162	1.1%	22,130	$18	V
15	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$396,797	1.1%	461	$861	Y
16	VIIBRYD	Antidepressants	$351,265	1.0%	1,343	$262	V
17	MAKENA*	Progestational Agents	$350,170	1.0%	132	$2,653	Y
18	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$350,117	1.0%	2,031	$172	
19	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$345,115	1.0%	14,056	$25	V
20	Factor Viia	Physican Administered Drug	$334,590	0.9%	2	$167,295	
21	TRINTELLIX	Antidepressants	$332,957	0.9%	912	$365	V
22	VENLAFAXINE HCL ER	Antidepressants	$326,312	0.9%	1,727	$189	V
23	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$323,915	0.9%	1,700	$191	V
24	ESCITALOPRAM OXALATE	Antidepressants	$269,340	0.8%	23,439	$11	Y
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	$265,134	0.7%	22,625	$12	Y
26	SPINRAZA*	Oligonucleotides for Muscular Disorders	$250,000	0.7%	2	$125,000	
27	AMITRIPTYLINE HCL	Antidepressants	$248,932	0.7%	15,330	$16	Y
28	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$243,309	0.7%	61	$3,989	Y
29	CITALOPRAM HBR	Antidepressants	$237,626	0.7%	23,598	$10	Y
30	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$236,327	0.7%	17,208	$14	
31	ARISTADA	Antipsychotics, Parenteral	$234,587	0.7%	138	$1,700	Y
32	HUMIRA PEN*	Biologics for Autoimmune Conditions	$207,126	0.6%	70	$2,959	Y
33	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$199,589	0.6%	14,998	$13	Y
34	VENLAFAXINE HCL ER	Antidepressants	$198,221	0.6%	14,981	$13	Y
35	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$198,203	0.6%	672	$295	V
36	Infliximab Not Biosimil 10mg	Physican Administered Drug	$168,662	0.5%	114	$1,479	
37	FETZIMA	Antidepressants	$163,658	0.5%	429	$381	V
38	CLOZAPINE	Antipsychotics, 2nd Gen	$159,041	0.4%	2,883	$55	Y
39	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$157,509	0.4%	1	$157,509	
40	BUPROPION HCL SR	Antidepressants	$156,148	0.4%	10,655	$15	Y
		Top 40 Aggregate:	**$21,681,894**		**347,270**	**$11,982**	
		All FFS Drugs Totals:	**$35,440,182**		**670,123**	**$648**	

*** 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 (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2018

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	MAKENA*	Progestational Agents	$350,170	2.9%	132	$2,653	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$350,117	2.9%	2,031	$172	
3	Factor Viia	Physican Administered Drug	$334,590	2.8%	2	$167,295	
4	SPINRAZA*	Oligonucleotides for Muscular Disorders	$250,000	2.1%	2	$125,000	
5	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$243,309	2.0%	61	$3,989	Y
6	HUMIRA PEN*	Biologics for Autoimmune Conditions	$207,126	1.7%	70	$2,959	Y
7	Infliximab Not Biosimil 10mg	Physican Administered Drug	$168,662	1.4%	114	$1,479	
8	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$157,509	1.3%	1	$157,509	
9	Inj Pembrolizumab	Physican Administered Drug	$153,860	1.3%	48	$3,205	
10	METHYLPHENIDATE ER*	ADHD Drugs	$144,348	1.2%	1,066	$135	N
11	ORKAMBI*	Cystic Fibrosis	$125,924	1.0%	13	$9,686	N
12	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$122,165	1.0%	426	$287	Y
13	LANTUS	Diabetes, Insulins	$121,496	1.0%	362	$336	Y
14	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$120,825	1.0%	1,973	$61	Y
15	LANTUS SOLOSTAR*	Diabetes, Insulins	$116,809	1.0%	357	$327	Y
16	Rituximab Injection	Physican Administered Drug	$113,264	0.9%	48	$2,360	
17	GENVOYA	HIV	$110,029	0.9%	50	$2,201	Y
18	NOVOLOG FLEXPEN	Diabetes, Insulins	$108,766	0.9%	227	$479	Y
19	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$108,558	0.9%	2,030	$53	Y
20	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$106,205	0.9%	9	$11,801	Y
21	VYVANSE*	ADHD Drugs	$100,223	0.8%	715	$140	Y
22	NUVARING	STC 63 - Oral Contraceptives	$98,789	0.8%	422	$234	
23	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$97,423	0.8%	6	$16,237	Y
24	ADVATE	Antihemophilia Factors	$95,313	0.8%	6	$15,886	
25	FLOVENT HFA	Corticosteroids, Inhaled	$94,224	0.8%	605	$156	Y
26	Aflibercept Injection	Physican Administered Drug	$93,329	0.8%	184	$507	
27	Drugs Unclassified Injection	Physican Administered Drug	$91,457	0.8%	5,745	$16	
28	PULMOZYME	Cystic Fibrosis	$91,446	0.8%	59	$1,550	Y
29	Etonogestrel Implant System	Physican Administered Drug	$86,971	0.7%	159	$547	
30	Factor Viii Recombinant Nos	Physican Administered Drug	$84,086	0.7%	6	$14,014	
31	Injection, Nivolumab	Physican Administered Drug	$82,749	0.7%	55	$1,505	
32	TRUVADA	HIV	$78,340	0.6%	68	$1,152	Y
33	Xyntha Inj	Physican Administered Drug	$77,791	0.6%	2	$38,896	
34	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$77,611	0.6%	312	$249	Y
35	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$77,099	0.6%	40	$1,927	
36	ENBREL*	Biologics for Autoimmune Conditions	$77,004	0.6%	16	$4,813	Y
37	HUMIRA*	Biologics for Autoimmune Conditions	$74,973	0.6%	26	$2,884	Y
38	SPIRIVA	Anticholinergics, Inhaled	$74,924	0.6%	209	$358	Y
39	Mirena, 52 Mg	Physican Administered Drug	$73,430	0.6%	138	$532	
40	HUMALOG	Diabetes, Insulins	$72,858	0.6%	219	$333	Y
		Top 40 Aggregate:	**$5,213,772**		**18,014**	**$14,848**	
		All FFS Drugs Totals:	**$12,133,762**		**204,567**	**$671**	

*** Drug requires Prior Authorization**

Notes
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- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last updated: July 18, 2018

ProDUR Report for April through June 2018
High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Set alert/Pay claim	5	0	0	5	0.01%	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,559	332	0	1,226	1.40%	21.30%
DD (Drug/Drug Interaction)	Set alert/Pay claim	135	24	0	111	0.05%	17.78%
ER (Early Refill)	Set alert/Deny claim	74,741	14,059	124	60,543	68.57%	18.81%
ID (Ingredient Duplication)	Set alert/Pay claim	22,977	5,920	9	17,034	20.97%	25.76%
LD (Low Dose)	Set alert/Pay claim	672	116	0	556	0.57%	17.26%
LR (Late Refill/Underutilization)	Set alert/Pay claim	5	5	0	0	0.00%	100.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	911	272	4	606	0.80%	29.86%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	654	136	1	516	0.57%	20.80%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	36	24	0	12	0.02%	66.67%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,385	2,155	2	5,217	6.73%	29.18%
	Totals	**109,080**	**23,043**	**140**	**85,826**	**99.68%**	**21.12%**

ProDUR Report for April through June 2018

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,202	182	1,020	10,850	11.1%	15.1%
ER	Hydrocodone/APAP	59	26	33	3,446	1.7%	44.1%
ER	Oxycodone	72	33	39	2,075	3.5%	45.8%
ER	Oxycodone/APAP	19	4	15	1,013	1.9%	21.1%
ER	Tramadol	12	4	8	946	1.3%	33.3%
ER	Buspirone (Buspar)	2,213	331	1,882	21,998	10.1%	15.0%
ER	Lorazepam	572	129	443	14,380	4.0%	22.6%
ER	Alprazolam	409	68	341	10,431	3.9%	16.6%
ER	Diazepam	248	58	190	5,764	4.3%	23.4%
ER	Lamictal (Lamotrigine)	4,202	835	3,366	34,355	12.2%	19.9%
ER	Abilify (Aripiprazole)	2,519	425	2,094	19,995	12.6%	16.9%
ER	Seroquel (Quetiapine)	3,409	689	2,720	24,736	13.8%	20.2%
ER	Risperdal (Risperidone)	1,898	366	1,532	13,655	13.9%	19.3%
ER	Wellbutrin (Bupropion)	4,241	659	3,578	47,590	8.9%	15.5%
ER	Zoloft (Sertraline)	5,215	909	4,306	51,807	10.1%	17.4%
ER	Prozac (Fluoxetine)	3,753	590	3,163	40,812	9.2%	15.7%
ER	Celexa (Citalopram)	2,359	308	2,051	28,330	8.3%	13.1%

ProDUR Report for April through June 2018

Early Refill Reason Codes

DUR Alert	2Q2018	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Totals =	10,530	479	659	2,864	11	6,514	3

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Duloxetine 40mg caps to 2x20mg	Unique Prescribers Identified			125	
		Unique Patients Identified			148	
		Prescriptions Changed to Recommended Within 6 Months of Intervention			35	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention			$2,976	
	Fluoxetine Tabs to Caps	Unique Prescribers Identified			740	
		Unique Patients Identified			1100	
		Prescriptions Changed to Recommended Within 6 Months of Intervention			328	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention			$15,353	
	Lamotrigine ER to IR	Unique Prescribers Identified	324			
		Unique Patients Identified	645			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	142			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$91,290			
	QVAR to fluticasone	Unique Prescribers Identified	400			
		Unique Patients Identified	463			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	64			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	($4,767)			

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	Venlafaxine Tabs to Caps	Unique Prescribers Identified		585		
		Unique Patients Identified		807		
		Prescriptions Changed to Recommended Within 6 Months of Intervention		335		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$225,978		

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	189	120	89	8
		Total Faxes Successfully Sent	75	46	52	1
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	34	47	17	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	27	16	7	
		Prescriptions Unchanged after 3 Months of Fax Sent	96	37	1	
		Safety Monitoring Profiles Identified	14	18	15	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$108,673	$142,692	$24,094	

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	49	25	33	24
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	1	5	5
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	49	27	21	28
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	4	2	6
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed	6	15		2
	Lock-In	RetroDUR_Profiles Reviewed	26	37	26	
		RetroDUR_Letters Sent To Providers	1	5	2	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	1	5	2	
	Polypharmacy	RetroDUR_Profiles Reviewed	33	53	157	
		RetroDUR_Letters Sent To Providers	5	7	26	
		Provider Responses	0	0	4	
		Provider Agreed / Found Info Useful	0	0	2	

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Retro-DUR Intervention History by Quarter FFY 2017 - 2018

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	25	23	26	4
		Disqualified - Erroneous denial	25	23	26	4
		Faxes Sent	5	3	6	3
		Fax Sent - Combination Inhaler			1	
		Fax Sent - Controller	2	2		
		Fax Sent - SABA	3	1	4	
		No Subsequent Pulmonary Claims			1	3

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2017 - 2018

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,039	2,184	48%									
Five or more concurrent psychotropics	127	10,200	1%									
Three or more concurrent psychotropics	1,611	10,200	16%									
Two or More Concurrent Antipsychotics	88	10,200	1%									
Under 18 years old on any antipsychotic	2,197	10,200	22%									
Youth five years and younger on psychotropics	149	10,200	1%									

7/11/2018

Important: Totals for each quarter are generated three months after the end of the quarter to allow for delays in claim submission. Therefore, totals in this report may differ from dashboard reports, which do not account for these delays.

Note: The metric "Under 18 years old on any antipsychotic" counts children with or without diabetes receiving antipsychotics. The metric "Children on antipsychotics without diabetes screening" excluded children with pre-existing diabetes.

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Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2017 - 2018

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	217	335	65%									
Five or more concurrent psychotropics	15	1,866	1%									
Three or more concurrent psychotropics	230	1,866	12%									
Two or More Concurrent Antipsychotics	12	1,866	1%									
Under 18 years old on any antipsychotic	326	1,866	17%									
Youth five years and younger on psychotropics	33	1,866	2%									

7/11/2018

Important: Totals for each quarter are generated three months after the end of the quarter to allow for delays in claim submission. Therefore, totals in this report may differ from dashboard reports, which do not account for these delays.

Note: The metric "Under 18 years old on any antipsychotic" counts children with or without diabetes receiving antipsychotics. The metric "Children on antipsychotics without diabetes screening" excluded children with pre-existing diabetes.

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A Review of Implications of FDA Expedited Approval Pathways, Including the Breakthrough Therapy Designation

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Since 1962, the United States (U.S.) Food and Drug Administration (FDA) has required that manufacturers demonstrate drugs are effective and safe prior to patient exposure.[1] This review and approval process is intended to ensure sufficient evidence demonstrates the benefits of therapy outweigh the risks. However, one major criticism has been the delay of getting new medications to market, particularly for medical conditions with few treatment options. To expedite the drug development process and facilitate approval of drugs indicated for serious or life-threatening conditions, the FDA has created expedited approval programs to allow faster approval of drugs and address unmet medical needs in the treatment of serious conditions. The purpose of this newsletter is to review the different accelerated approval pathways and designations with a focus on the latest breakthrough therapy designation (BTD), discuss the strengths and limitations associated with these pathways, and evaluate the evidence concerns behind some of the specific non-oncology drug approvals.

Accelerated Approval Pathways

The FDA created four accelerated approval pathways and designations **(Table 1**). Although each pathway has different qualifying and approval features, the drugs approved via these routes must address an unmet clinical need in the treatment of a serious condition.[2] The FDA defines a serious disease or condition as one that is associated with morbidity that has substantial impact on day-to-day functioning, leaving much of it up for interpretation and clinical judgement.[3] A recent study identified drugs approved through these expedited pathways and documented a significant increase in the number of drugs qualifying for one of these approvals, with an increase of 2.4% each year from 1987 to 2014.[2] Additionally, the authors found an increasing number of drug approvals that are less likely to be innovative or clinically transformative.[2]

Table 1: FDA Expedited Approval Pathways[3]

Pathway and Designation	Qualifying Features	Approval Features
Fast-track designation	Nonclinical or clinical data demonstrate the potential to address an unmet clinical need	Increased communication to facilitate development and incorporates a rolling review
Accelerated approval pathway	Meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit	Allows approval based on a surrogate or intermediate endpoint
Priority review designation	If approved would provide a significant improvement in safety or effectiveness	Shorter clock for review of application (6 months vs. 10 months with standard)
Breakthrough therapy designation	Preliminary clinical evidence indicates it may demonstrate substantial improvement over available therapies on a clinically significant endpoint	Provides all features associated with the fast track designation, intensive guidance on efficient drug development and organizational commitment from senior agency officials

The passage of the FDA Safety and Innovation Act of 2012 provided the most recent expedited approval pathway, the "breakthrough therapy designation" (BTD).[4] Drugs are eligible for the BTD if they treat a serious or life-threatening disease or condition and a surrogate endpoint (e.g., laboratory measurement, radiographic image, or physical sign) suggests an improvement over existing therapy.[3,5] Since approval is based on a surrogate endpoint, the clinical evidence required for approval is considered preliminary and drugs commonly include language in their official labeling stating that the clinical benefit has not been established. FDA requires the manufacturer to conduct post-approval trials to confirm the drug's efficacy.[6] The BTD has become quite widespread since its inception, likely because of the close attention and guidance given by FDA officials, as early as during phase 1 studies. Since introduction of the BTD in July 2012 through the end of 2017, the FDA has approved 91 drugs or new indications through the BTD, and 32 in the year 2017 alone.[7] Approximately two-thirds of these approvals have been for small molecules and non-biologic drugs, and more than 50% are oncology drugs.

Concerns and Limitations

Surrogate Outcomes: The FDA frequently approves new drugs on the basis of trials that use surrogate markers of disease instead of clinical outcomes for primary endpoints. Surrogate endpoints include markers such as laboratory measurements or radiographic images. However, these surrogate endpoints may not translate into a meaningful benefit for the patient. Additionally, the required post-approval trials to confirm clinical efficacy can be significantly delayed. It has been shown that only half of the required post-approval studies are completed within 3 years after drug approval, the quality of the studies varies widely, and even confirmatory trials frequently depend on surrogate endpoints.[8] Furthermore, the ability to secure approval based on unvalidated surrogate endpoints reduces the incentive for pharmaceutical companies to conduct high quality trials that evaluate clinical benefits and risks of a drug therapy.

Table 2 includes examples of drugs approved through the BTD based on a surrogate outcome that has not been proven to impact clinical disease activity and/or does not have a well-defined minimal clinically significant change associated with it.

Table 2: Drugs Approved with a BTD Based on a Surrogate Outcome

Drug or Drug Class	Approved	Primary Outcome	Approximate 30-day cost
CF modulators*	Cystic Fibrosis	Forced expiratory volume in one second (FEV_1)	$25,103 -$28,675
Pimavanserin	Parkinson's disease psychosis	Adapted scale for assessment of positive symptoms (SAPS-PD scale)	$3,334
Direct Acting Antivirals**	Chronic hepatitis C	Sustained Virologic Response	$15,840-$113,400 (per treatment course)
VMAT 2 Inhibitors†	Tardive dyskinesia	Abnormal involuntary movement scale	$3,946 - $7,470

***Cystic Fibrosis Modulators: ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor**
****Direct Acting Antivirals: sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir; dasabuvir, ombitasvir/paritaprevir/ritonavir, grazoprevir/elbasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir**
†Vesicular Monoamine Transporter 2 inhibitors: valbenazine, deutetrabenazine

For approval of both pimavanserin and the vescicular monoamine transporter 2 (VMAT2) inhibitors, observed changes in subjective scales were used as the primary outcome. In the primary approval trial for pimavanserin, efficacy was determined based on a new Parkinson's disease (PD) adapted scale, SAPS-PD, to assess the frequency and severity of hallucinations and delusions associated with PD. This was the first use of this scale in a clinical trial and remains an unvalidated tool to evaluate Parkinson's disease psychosis. Pimavanserin demonstrated a mean 3.06 point reduction in SAPS-PD compared to placebo at 6 weeks.[9] Although further information is needed to establish a minimal clinically important difference in the SAPS-PD, review by the FDA suggested that a 5 to 7 point change may be necessary to demonstrate a clinical improvement.[10]

Likewise, the VMAT2 inhibitors were approved based on changes in the Abnormal Involuntary Movement Scale (AIMS) to assess the severity of tardive dyskinesia symptoms. No minimal clinically important difference has

been established and evidence has not demonstrated that improvement in the AIMS translates into improved function or quality of life for patients.[11] For the cystic fibrosis oral modulators, the primary outcome of forced expiratory volume in one second (FEV_1) does not prove that the drug prolongs survival or prevents complications. Lastly, in chronic hepatitis C, achieving a sustained viral response does not verify the drug prevents progression of liver disease or prevents the need for a transplant.

Safety: A concern with the expedited approval pathways is that minimizing the data collection time prior to FDA approval and exposing drugs to fewer patients in clinical trials could lead to drugs approved with underlying major safety issues identified post approval. A recent study found that drugs approved through expedited pathways had a rate of 0.94 safety-related label changes for each drug per year, compared with 0.68 for drugs approved through the traditional pathway.[6] This concern was further validated with post-approval reports of possible reactivation of hepatitis B and liver injury in patients receiving direct acting antivirals.

Additionally, during FDA review of pimavanserin, the medical reviewer recommended against approval due to an unacceptable rate of serious adverse effects including death.[12] These concerns were confirmed in November 2017 when the Institute of Safe Medical Practices issued a warning based on significant reports of serious adverse effects with pimavanserin including hallucinations (n=487), confusion (258), deaths (n=244), and lack of efficacy (n=333).[13] Almost 75% of these reports came from health professionals. With a controversial approval based on one clinical trial demonstrating a minimal benefit on a surrogate outcome and significant safety concerns, patients and prescribers need to know that long term safety and efficacy remain unproven.

Drugs Approved for Rare Diseases

Table 3 includes drugs approved with the BTD which are the first FDA approved therapies for rare inherited genetic diseases. These drugs clearly provide some benefit over existing therapy and satisfy that specific BTD criteria. Nonetheless, many of the pivotal trials for these drugs suffered from significant methodologic concerns such as small sample sizes, use of a retrospective, historical control as a comparator, and a lack of established surrogate markers to assess clinical efficacy, all of which raise questions about clinical significance and long-term benefits. Several of the indications of these drugs are extremely rare which does make researching them properly incredibly challenging. However, significant questions remain about whether these agents provide meaningful benefits for unfortunate patients with these diseases.[14] Cost is also a significant concern with drugs approved for rare diseases. According to one analyst, the cost of treating a rare disease averaged $140,000 a year in 2016, and all of the treatments included in **Table 3** are over $400,000 per year. Although these treatments offer options for the first time for these rare illnesses, because of the high cost and limited data available demonstrating clinical efficacy, they are unlikely to be cost-effective based on widely accepted thresholds for cost-effectiveness.

Table 3: New Drugs Approved for Rare Diseases

FDA approved drug	Indication	Patients	Comparator	Approximate 30-day cost
Sebelipase alfa	Lysosomal acid lipase deficiency	N=75	Historical control	$49,008*
Asfotase alfa	Hypophosphatasia	N=70	Historical control	$41,184*
Uridine Triacetate	Hereditary orotic aciduria	N=4	Historical control	$54,000*
Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2	N=42	Historical Control	$64,800
***Dosing is weight based causing variability in pricing based on age and weight**				

Conclusion

The intent of the BTD and other FDA expedited approval pathways is to provide quicker access to medications for patients who have rare conditions or conditions with suboptimal therapies available. While some medications approved through these programs will prove to demonstrate a significant advancement in the treatment of a disease, healthcare professionals and patients should be aware of the uncertainties and heterogeneity in the quality of the evidence leading to these approvals. Additionally, the 21st Century Cures Act was signed into law in December 2016 and is designed to help accelerate medical product development and bring drugs to the market even faster. This bill may allow drug approvals based on limited evidence to assess the safety and efficacy of drugs without the need for rigorous clinical trials. It will become even more critical for both patients and providers to evaluate the potential long-term benefits and risks of new drugs approved via an expedited pathway.

Peer Reviewers: Bill Origer, MD, Faculty, Samaritan Family Medicine Residency and James Slater, PharmD, Executive Director of Pharmacy, CareOregon.

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Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators

Date of Review: July 2018
Generic Name: tezacaftor/ivacaftor

End Date of Literature Search: May 2018
Brand Name (Manufacturer): Symdeko™ (Vertex)
Dossier Received: yes

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the safety and effectiveness of oral cystic fibrosis (CF) modulators in reducing respiratory symptoms or pulmonary exacerbations associated with CF and improving quality of life as well as to evaluate the evidence and place in therapy of tezacaftor/ivacaftor (TEZ/IVA).

Research Questions:
1. What is the comparative evidence for oral CF modulators in improving clinically important outcomes such as respiratory symptoms, pulmonary exacerbations, mortality and quality of life in children and adults with CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the effectiveness or efficacy of the CF modulators?
2. What are the comparative harms of oral CF modulators in patients being treated for CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the safety of the CF modulators?
3. Are there subpopulations of patients with CF based on a specific gene mutation, disease severity, race, age, or sex, for which one of the oral CF modulators are more effective or associated with greater harm than other populations?

Conclusions:
Tezacaftor/ivacaftor:
- There is low quality evidence that TEZ/IVA modestly improves ppFEV$_1$ compared to placebo in patients with cystic fibrosis (CF) homozygous for the F508del mutation. Therapy has been shown to increase FEV$_1$ by a mean absolute change from baseline of 3.4% compared to -0.6% with placebo (mean difference of 4.0%).
- There is low quality evidence that TEZ/IVA decreases pulmonary exacerbations over 24 weeks compared to placebo (0.64 vs. 0.99 events per year; rate ratio 0.65; 95% CI 0.48 to 0.88) and improves quality of life with no impact on body mass index (BMI) in patients with CF homozygous for the F508del mutation.
- There is insufficient evidence that TEZ/IVA has a significant effect on clinically important outcomes (pulmonary exacerbations, hospitalizations, body mass index [BMI]) for the treatment of CF in those heterozygous for the F508del mutation and a second allele predicted to have residual function compared to

placebo over IVA monotherapy. Therapy was associated with a small statistical mean difference in $ppFEV_1$ compared to placebo (6.8%; 95% CI 5.7 to 7.8). However, this was estimated by averaging the change at weeks 4 and 8. There is insufficient evidence of a decrease in pulmonary exacerbations in this patient population.

- There is low quality evidence of a small, clinically insignificant improvement in absolute change from baseline in $ppFEV_1$ (mean difference 2.1%; 95% CI 1.2 to 2.9) with TEZ/IVA compared to IVA monotherapy in patients heterozygous for the F508del mutation and a second allele predicted to have residual function.
- TEZ/IVA has not demonstrated a significant effect in patients who are heterozygous for the F508del mutation and a second allele not predicted to be responsive to therapy and should not be used in this patient population.

Ivacaftor:

- There is low quality evidence that IVA improves percent predicted FEV_1 ($ppFEV_1$) compared to placebo (least square mean [LSM] difference 4.7%; 95% CI 3.7 to 5.8) and improves Cystic Fibrosis Questionnaire-revised (CFQ-R) respiratory domain score (0-100 scale) with 58% of patients in the IVA group achieving a 4 point or greater difference compared to 33% in the placebo group (ARR 25%; NNT 4), in patients heterozygous for the F508del mutation and a second allele with a CFTR mutation with residual function. This is based on one phase 3 randomized, 8-week crossover trial.[2] There was no significant difference seen in pulmonary exacerbations.
- There is insufficient evidence that IVA has a clinically relevant impact on outcomes of interest for recently approved CFTR mutations which were approved based on in vitro cell-based data only (E56K, S549R, K1060T, P67L, E193K, A1067T, R74W, L206W, G1069R, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E, S977F, F1074L, F1052V, D1152H).

Evidence limitations:

- Evidence remains insufficient to compare the efficacy/effectiveness or safety of CF modulators against standard of care including dornase alfa and hypertonic saline.
- Evidence remains insufficient to determine the effects of oral CF modulators on long term disease progression or to know if TEZ/IVA is effective in patients with very severe CF ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >90%).
- Evidence remains insufficient to determine appropriate criteria for discontinuing oral CF modulators for lack of effectiveness.
- There is significant involvement from the manufacturer in all clinical trials of IVA, LUM/IVA and TEZ/IVA including but not limited to: funding, study design, data collection analysis and interpretation as well as writing and publication of the manuscript.

Previous Conclusions:

Ivacaftor:

- There is moderate quality evidence that ivacaftor (IVA) monotherapy is effective in patients with the G115D mutation. IVA has been shown to increase forced expiratory volume in one second [FEV_1] by an absolute value of 10.6% compared to placebo within 2 weeks of treatment; decrease number of patients with respiratory exacerbations at 24 weeks (OR 0.54; 95% CI 0.29 to 1.01) and increase weight by 2.7 kg.[1]
- There is insufficient evidence that IVA has a clinically relevant impact on outcomes of interest for other approved CFTR mutations. Studies either did not demonstrate a clinically significant effect (R117H), demonstrated a modest benefit in FEV_1 or sweat chloride only (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) or more recently, additional CFTR mutations were approved based on in vitro cell-based data only (E56K,S549R ,K1060T,

P67L,,E193K,A1067T, R74W , L206W , G1069R, D110E , R347H, D579G , R1070Q D1270N,D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E , S977F, F1074L, F1052V, D1152H).

Lumacaftor/ivacaftor

- There is insufficient evidence that lumacaftor/ivacaftor (LUM/IVA) has a significant effect on clinically important outcomes for the treatment of CF in those homozygous for the F508del mutation on the CFTR gene. It was associated with only an absolute 2.8% improvement in FEV_1 (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo.
- There is insufficient evidence that LUM/IVA improves lung function in children ages 6 to 11 years old with CF homozygous for the F508del mutation. Approval was based on a phase 3 study evaluating nonclinical outcomes.[3]
- LUM/IVA has not demonstrated a significant effect on FEV_1 in patients who are heterozygous for the F508del mutation and therapy should not be used in this patient population.

Recommendations:

- No changes recommended to the PDL.
- Continue to require prior authorization policy (**Appendix 3**) for the approval in appropriate patients.
- Remove the requirement of an FDA-approved CF gene mutation test from PA criteria.

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[4] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[5] CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.[6] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[7] The F508del mutation results in misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR to open channels at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ions. [7] There are three common alleles at the poly-T locus of the R117H gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.[8] Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype. The most common CFTR mutation is the F508del, which accounts for approximately two thirds of the recognized mutations, and carries the most severe prognosis.[9] In the United States, approximately 90% of CF patients carry at least one allele and 50% are homozygous for the F508del mutation. In contrast, approximately 5% of those with CF exhibit residual CFTR ion transport. These residual function mutations cause disease that generally progresses more slowly than more common forms.[2]

Clinically meaningful outcomes of CF treatment include mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used surrogate outcome in clinical trials. A minimal clinically important difference for FEV_1 has not been defined or agreed upon because of the heterogeneous nature of the condition.[10] According to National Institute of Clinical Excellence (NICE), an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important.[10] Changing the FEV_1 rate of decline would be the most meaningful effect, but would require a long study duration. In CF patients, FEV_1 decreases on average by 1-3% per year but varies based on age and baseline lung function.[11] In CF patients with moderate to severe lung disease, inhaled tobramycin and dornase alfa have shown improvement in FEV_1 ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa.[12] There is also fair evidence to suggest that macrolide antibiotics provide benefit for all levels of disease with improvements in FEV_1

from 3.6%-6.2%.[12] The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for the respiratory symptom domain.[13] Weight is also a commonly measured secondary outcome in trials of CF children, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, and increased morbidity and mortality.[13] The nutritional status of patients with CF is strongly associated with pulmonary function, respiratory status and survival. Sweat chloride level is the gold standard for a diagnosis of CF. Normal individuals typically have levels less than40 mmol/L but patients with CF have elevated levels greater than 60 mmol/L.[12] More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.[7] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA.[14] Although initial studies showed a reduction in the sweat chloride levels to values below the diagnostic threshold for CF (60 mmol/L), there is no evidence that sweat chloride is correlated with meaningful clinical benefits, and it has not shown to correlate with improvement in FEV_1. [12] Clinical severity of CF is dependent on other factors in addition to CFTR function, and what aspect of CFTR function is affected depends on the specific combination of mutations in the individual.

IVA (Kalydeco®) and LUM/IVA (Orkambi®) are oral agents intended to enhance mutant CFTR protein function (**Table 1**).[14] Both of these agents are specific to CFTR mutation dysfunction. IVA is a CFTR potentiator indicated for the management of CF in patients in patients at least 2 years of age who have one of 38 CFTR mutations (**Table 1**).*[15]* The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population. [14] In trials of patients with the G115D mutation, IVA increased FEV_1 by an absolute value of 10.6% compared to placebo within 2 weeks of treatment; a 26% absolute decrease in respiratory exacerbations, a reduction in sweat chloride values by 50-60 mmol/L and a weight gain of 2.7 kg was also found.[1] However, while the 2-week endpoint was noted in a post-hoc analysis, the study was designed to look at outcomes at 24 weeks. IVA is proposed to treat the underlying cause of CF by influencing the basic gene defect which can normalize airway surface liquid and help re-establish mucociliary clearance.[16,17] IVA is designed to increase the time that activated CFTR channels at the cell surface remain open.[16,17]

LUM/IVA is a combination drug that contains the molecular entity LUM. The exact mechanism of LUM is unknown, but it may promote more functional folding of the defective F508del CFTR protein, allowing it to get to the cell surface. Previous studies of IVA did not demonstrate a clinical improvement in lung function in patients with an F508del mutation.[6] However, the combination was approved after phase 3 trials demonstrated its efficacy for the management of CF in patients 12 years of age and older homozygous for the F508del mutation in the CFTR gene.[18] Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[19] It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[20] This patient group includes approximately 34% of the U.S. CF population.[14] Studies of LUM/IVA did not demonstrate clinically significant results on meaningful outcomes. It was associated with only an absolute 2.8% improvement in FEV_1 (estimated by averaging the absolute change at weeks 16 and 24) and nominal decrease in pulmonary exacerbations compared to placebo (RR 0.61; 95% CI 0.49 to 0.76). However, this outcome was actually reported as the number of events per 48 weeks which is unreliable since the trial only went through 24 weeks. There is insufficient evidence to make the assumption that a reduction in pulmonary exacerbations is maintained as long as patients stayed on treatment. It remains unclear if the combination provides more benefit than IVA alone which was found to be deleterious in F508del homozygous adults in previous trials.

Tezacaftor is a CFTR corrector designed to improve the cellular processing and trafficking of normal and mutated CFTR protein to increase the amount of functional CFTR at the cell surface. It has been studied in two phase 3 randomized, double-blind trials in patients 12 years of age or older who were heterozygous for the F508del mutation and having a residual-function CFTR mutation as well as in those homozygous for F508del.[2,21]

Table 1: CFTR Modulators: Summary of Studied Mutations

CFTR Modulator	Mutation	Age Group Studied
IVA[15]	E56K, G178R S549R K1060T G1244E P67L E193K G551D A1067T S1251N R74W L206W G551S G1069R S1255P D110E R347H D579G R1070Q D1270N D110H R352Q S945L R1070W G1349D R117C A455E S977F F1074L R117H S549N F1052V D1152H 3849 + 10kbC –T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X	≥ 2 years
LUM/IVA[20]	F508del homozygous	≥ 6 years
Tezacaftor/IVA[2,21]	F508del homozygous F508del heterozygous + CFTR mutation with residual function	≥ 12 years

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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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 identified.

New Guidelines:
No new guidelines identified.

Previous guidance from the National Institute for Health and Clinical Excellence (NICE) published recommendations for LUM-IVA for treating cystic fibrosis homozygous for the F508del mutation.[10] The following recommendation was included:

- *LUM/IVA is not recommended for treating CF in people 12 years and older who are homozygous for the F508del mutation in the CFTR gene.*

This recommendation came from a systematic review of the literature which identified 2 studies evaluating clinical effectiveness and safety of LUM/IVA. The panel concluded that the two trials were generally of good quality and included people with mild to moderate CF, and therefore, the clinical evidence may not be generalizable to people with severe CF ($ppFEV_1$ <40%) or with very mild CF ($ppFEV_1$ >90%). In addition, the absolute change in $ppFEV_1$ was less than 5% which would be considered clinically important, and there was insufficient long-term evidence to support the assumptions that a reduction in pulmonary exacerbations is maintained as long as people stay on treatment.

New Safety Alerts:
None identified.

New Formulations or Indications:

1. In September 2016, the FDA approved LUM/IVA for use in an expanded population of patients, children ages 6 through 11 years, who are homozygous for the F508del mutation.[20] This approval is expected to cover approximately 2,400 additional patients in the U.S. The efficacy in this group was extrapolated from previous studies in patients at least 12 years of age with additional pharmacokinetic analyses showing similar drug exposure levels.[19]

   The decision by the FDA to expand the age indication was also based on data from an open-label phase 3 safety study (n=58) in patients homozygous for the F508del CFTR mutation aged 6 through 11 years.[22] A baseline $ppFEV_1$ greater than 40% was required for inclusion. Efficacy endpoints, including sweat chloride, nutritional status, and quality of life were included as secondary outcomes. This study had many limitations and was not powered to evaluate efficacy outcomes. The study population generally had preserved lung function (mean $ppFEV_1$ 91.4%). A total of 11 patients (19.3%) had elevations in liver transaminases more than 3-times the upper-limit-of-normal (ULN) and 5 patients (8.8%) had elevations more than 5-times ULN.[22]The most common adverse events were cough, nasal congestion, pulmonary exacerbations and headache. There were no significant changes in $ppFEV_1$. There was a statistically significant decrease in sweat chloride from baseline (mean change -24.8 mmol/L; 95% CI -29.1 to -20.5) and 41/51 had a decrease of at least 15 mmol/L.[22] This decline in sweat chloride demonstrates a biochemical response to the drug but has not been associated with clinically meaningful efficacy outcomes.

   A randomized phase 3 trial evaluating nonclinical outcomes was published in July 2017 (**Table 2)**.[3] The primary outcome was mean change in lung clearance index ($LCI_{2.5}$) from baseline. LCI is used in trials with pediatric patients since studies among children with normal lung function with CF using normal spirometry have found LCI to be more sensitive than FEV_1 for detecting a response to treatment. LCI derived from a multiple breath washout provides a global measurement of ventilation inhomogeneity. It reflects abnormalities in ventilation in the respiratory tract compared to normal where changes are not easily detected with traditional pulmonary function techniques.[23] LCI has been shown to discriminate between individuals with CF and healthy, non-CF individuals. However, there is no evidence of a correlation between LCI and clinical outcomes including quality of life, pulmonary exacerbations or disease progression. Studies have demonstrated a significant, but variable correlation between LCI and FEV_1. While the gold standard LCI uses sulfar hexafluoride, more centers are using a nitrogen-based washout which is more readily available.[23] However, the nitrogen washout technique has not yet been fully validated.

   The baseline $LCI_{2.5}$ was 10.3 and baseline $ppFEV_1$ was 90%, demonstrating relatively preserved lung function. There were more patients in the treatment group with FEV_1 of less than 70% at baseline (10%) compared to placebo group (1%). There were also more subjects receiving inhaled antibiotics and

inhaled corticosteroids in the placebo group compared to treatment group. There was a statistically significant difference between absolute improvement in LCI from baseline between the LUM/IVA group (LSM -1.01; 95% CI -1.27 to -0.75) compared to placebo (LSM 0.08; 95% CI -0.18 to 0.34). However, the upper and lower limits of the 2 confidence intervals are fairly close. The magnitude of effect is unclear but is much lower than what was seen with IVA in children with the G551D mutation (-2.07). This is the first study using LCI as the primary clinical outcome.
There was a significant change in baseline sweat chloride in both the LUM/IVA group and placebo group with a decrease from baseline of approximately 20 in both groups. Body mass index (BMI) significantly increased in both groups as well. There was no significant difference in quality of life as measured by the CFQ-R respiratory score and there was numerical improvement in both groups. There was no significant change in ppFEV1 in either group. [3] Infective pulmonary exacerbations were reported as a safety outcome and there was no significant difference between LUM/IVA and placebo (29% vs. 18%).

Vertex pharmaceuticals was involved in funding, study design, data collection analysis and interpretation as well as writing and publication of the manuscript.

There remains insufficient data in those with advanced lung disease. A phase 3b open-label study was conducted in those 12 years of age or older with advanced lung disease but remains unpublished (clinicaltrials.gov NCT02390219) and results are not available.

2. In May 2017, the FDA expanded the approved use of IVA for treating CF.[15] The new approval triples the number of rare gene mutations that IVA is approved for (**Table 1**). This expanded approval was based largely on laboratory data since many of these mutations are so rare. Approval was based on an in vitro cell-based model system designed to predict clinical response to IVA. When mutations responded to the lab test, data was extrapolated from earlier clinical trials in other mutations to support FDA approval. This expanded approval is expected to affect approximately 900 patients or 3% of the CF population. It is unknown how reliable in vitro data is to establish efficacy in these rare mutations. There is no evidence demonstrating efficacy in patients with these mutations.

3. In August 2017, IVA was approved for an additional 5 residual function mutations that result in a splicing defect in the CFTR gene increasing the number of approved mutations in the CFTR gene to 38. This approval was based on the EXPAND double-blind, randomized, crossover trial (**Table 3**) which evaluated the efficacy and safety of TEZ/IVA and IVA monotherapy in patients 12 years of age or older who were heterozygous for the F508del mutation and a second allele with a CFTR mutation with residual function. [2] Patients received two of the treatment arms for 8 weeks with an 8 week washout period between the treatment periods. The criteria for residual function mutation was an average sweat chloride of less than 86 mmol/L and incidence of pancreatic insufficiency of less than 50% or laboratory criteria (presence of mature CFTR and observed chloride transport). Results demonstrated a significant improvement in change in percent predicted FEV_1 with IVA compared to placebo (LSM 4.7%; 95% CI 3.7 to 5.8) and a significant improvement in the CFQ-R respiratory domain score with 58% of patients in the IVA group achieving a 4 point or greater difference compared to 33% in the placebo group (ARR 25%; NNT 4) with a high placebo response. However, there was only an absolute change from baseline in FEV_1 of 0.17 L in the IVA group. There was no significant difference in pulmonary exacerbations between IVA and placebo (rate ratio 0.46; 95% CI 0.21 to 1.01). There was no significant difference in any outcomes between TEZ/IVA and IVA therapy and no clear benefit of the addition of TEZ in this patient population. Extensive exclusion criteria (anemia, abnormal liver function tests, colonization with certain organisms, concomitant CYP3A4 medications) limits generalizability to patients with more severe disease.

Randomized Controlled Trials:
A total of 12 citations were manually reviewed from the literature search. After manual review, 7 trials were excluded because of wrong study design (observational), outcome studied (non-clinical), wrong therapy (topical), or were published prior to November 2016. Two of the trials are included in the new drug evaluation. The remaining 3 trials are included below in **Table 2**.

Two of the trials supported expanded FDA approval of IVA and two trials studied the combination of tezacaftor/IVA. These studies will be further assessed for quality, risk of bias, and clinical significance in the following new drug evaluation.

Table 2: Characteristics of Included RCTs

Study	Comparison	Population	Primary Outcome	Results
Ratjen, et al.[3] Phase 3, RCT, DB	LUM 200mg / IVA 250 mg Q12 hours vs. matched placebo X 24 weeks	6-11 y/o, homozygous for the F508del mutation (n=206)	Lung clearance index 2.5 ($LCI_{2.5}$)	Mean absolute change in $LCI_{2.5}$ up to week 24: LUM/IVA: -1 Placebo: +0.1 P<0.0001
Rowe, et al.[24] Phase 2, DB RCT, PC	LUM/IVA vs. placebo X 56 days	18 years or older heterozygous for the F508del-CFTR mutation (n=126)	Absolute change in $ppFEV_1$ at day 56	Change from baseline in $ppFEV_1$ LUM/IVA: -0.6% Placebo: -1.2% LSM difference 0.6; 95% CI -1.7 to 2.9 >5% reduction $ppFEV_1$ LUM/IVA vs. placebo 22.6% vs. 14.3%; OR 1.7; 95% CI 0.7 to 4.3; p=0.25
Edgeworth, et al.[25] DB, PC, RCT, crossover	IVA vs. placebo	Adult patients with G551D CFTR mutation (n=20) *over 300 subjects did not meet eligibility criteria	Exercise tolerance (percentage change from baseline for maximal oxygen uptake; %VO2max)	There was no significant difference between IVA and placebo in %VO2max
Abbreviations: DB: double blind, FEV_1: forced expiratory volume in one second, IVA: ivacaftor; LUM: lumacaftor; PC: placebo controlled; RCT: randomized controlled trial; y/o = years old				

NEW DRUG EVALUATION: Tezacaftor/Ivacaftor

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.

Clinical Efficacy:
Tezacaftor (TEZ) is a CFTR corrector designed to improve the cellular processing and trafficking of normal and mutated CFTR protein to increase the amount of functional CFTR at the cell surface. [26] IVA is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. The combination of TEZ/IVA is FDA approved for patients with CF 12 years of age and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence.[26] The approval for mutations responsive based on in vitro data were allowed by the FDA for rare mutations that would be difficult to study. The intent of the assay was to determine if TEZ/IVA meets the threshold of increasing chloride transport by at least 10% from baseline. The FDA concluded that this threshold is reasonably likely to predict a clinical benefit with TEZ/IVA. However, this data does not show that TEZ offers additional benefit on top of IVA monotherapy.

TEZ/IVA was approved based on three phase 3 studies in three different CFTR mutation subpopulations (**Table 3**). The primary outcome in all trials was absolute change in percent predicted FEV_1 ($ppFEV_1$). Pulmonary exacerbations was a secondary endpoint and was defined as a new event or change in antibiotic therapy for any four or more of the following symptoms: change in sputum, hemoptysis, increased cough and/or dyspnea, malaise, fever, weight loss, sinus pain, sinus drainage, change in physical examination of the chest, decrease in pulmonary function by 10%, or radiographic changes.

Table 3: Clinical Studies Supporting Approval of Tezacaftor/IVA

Study	Follow-up Duration	CFTR mutation	Absolute change in percent predicted FEV1 compared to placebo (least-squares mean difference)
106 (EVOLVE)	24 weeks	Homozygous for the F508del mutation	4.0% (3.1 to 4.8)
108 (EXPAND)	8 weeks	Heterozygous for F508del mutation and a second allele with a CFTR mutation predicted to have residual CFTR function	6.8% (5.7 to 7.8)
107 (unpublished)	12 weeks	CF patients ≥ 12 years, heterozygous for F508del-CFTR mutation and 2nd CFTR mutation not likely to respond to TEZ and/or IVA therapy	1.2% (-0.3 to 2.6)

Study 106 is a fair quality trial that compared TEZ/IVA to placebo that demonstrated a small, but statistically significant improvement in absolute change in $ppFEV_1$ in those homozygous for the F508del mutation.[21] LUM/IVA previously demonstrated minimal efficacy in this population and is FDA approved. The absolute change in ppFEV1 was 3.4% (95% CI 2.7 to 4.0) and the difference compared to placebo was 4.0% (95% CI 3.1 to 4.8). This absolute change is modest with unknown clinical significance. This is slightly increased from what was observed in trials evaluating LUM/IVA (absolute change from baseline of 2.5%).

There was no significant difference in BMI between TEZ/IVA and placebo (< 1% increase from baseline). Lastly, there was a statistically significant decrease in pulmonary exacerbations with TEZ/IVA compared to placebo (RR 0.65; 95% CI 0.48 to 0.88) and an improvement in quality of life, as measured by the respiratory domain of the CFQ scale. The absolute change from baseline was 5 points in the treatment group, which is slightly higher than the minimally clinically important difference of 4 points. The number of pulmonary exacerbations requiring either intravenous (IV) antibiotics and/or hospitalizations was also lower in the TEZ/IVA group (RR 0.53; 95% CI 0.34 to 0.82) and was fairly low in both groups (0.54 per patient per year in TEZ/IVA and 0.29 per patient per year in placebo group). Since there was not an IVA arm in this trial, it is difficult to demonstrate the contribution of each component to the treatment. Extensive exclusion and inclusion criteria limits generalizability of the results. Exclusion criteria included those with any significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV < 40%) or mild disease (FEV > 90%), and overall patients were generally young white adults from outside the U.S. Additionally, only approximately 20% of subjects were from the U.S.[21]

Study 108 is a poor-quality study that compared TEZ/IVA to IVA monotherapy and placebo in a 3-treatment crossover design study in subjects who are heterozygous for the F508del mutation and a second allele with a CF mutation predicted to have residual function (**Table 4**).[2] Neither IVA monotherapy or LUM/IVA have demonstrated improvement in lung function in this population. Each patient received two of the three interventions for eight weeks with an 8-week washout period in between. Criteria for including mutations were 1) having residual function based on population-level phenotypic data and 2) in vitro responsiveness to IVA. Overall, both TEZ/IVA and IVA monotherapy resulted in statistically significant improvements in $ppFEV_1$ (see evidence table). The difference between TEZ/IVA and IVA was modest, but also statistically significant (2.1%; 95% CI 1.2 to 2.9). [2] Both therapies also provided significantly better quality of life (CFQ-R respiratory domain) compared to placebo with no difference between the two treatment groups. Pulmonary exacerbations were an exploratory outcome only and there was no significant difference between either group and placebo. Concerns with this study include the short duration of treatment (8 weeks), the primary endpoint of absolute change in $ppFEV_1$ was calculated as an average of the four-week and eight-week measurements, and the study was not designed to detect differences in clinically important outcomes such as pulmonary exacerbations and BMI. Additionally, the crossover design may increase risk of blinding being broken or a carry-over effect in the results. There were a considerable amount of subjects who were not on standard of care with dornase alfa (~40%) and/or inhaled antibiotics (~70%). Additionally, to be included subjects had to have criteria for residual function defined as: either sweat chloride ≥ 60 mmol/L or evidence of chronic sinopulmonary disease. Lastly, not all of the individual mutations included clearly demonstrated an improvement in ppFEV1 with TEZ/IVA compared to IVA alone. However, the study was not powered to detect a difference at individual mutation level. [2]

Study 107 was a phase 3 randomized, double blind, placebo-controlled study which evaluated TEZ/IVA in subjects who are heterozygous for the F508del mutation and a second mutation predicted to be unresponsive to TEZ and/or IVA therapy over 12 weeks.[27] It is unpublished and cannot fully be assed for quality. Mutations that were unlikely to respond were identified by the following criteria: biological plausibility, clinical severity (average sweat chloride > 86 mmol/L), percentage of patients with pancreatic insufficiency, and in vitro testing. There was no significant difference in change from baseline in $ppFEV_1$ between TEZ/IVA and placebo (1.2%; 95% CI -0.3 to 2.6) and an overall change from baseline with treatment of 1.4%. There was no difference in any secondary endpoints (pulmonary exacerbations, quality of life or BMI) between the two groups demonstrating minimal efficacy in this patient population. [27]

Lastly, in vitro assay day was also used to support the use of TEZ/IVA in certain rare CFTR mutations. The FDA determined that an in vitro assay response above a certain threshold may be reasonably predictive of a clinical benefit. However, this data does not predict the magnitude of benefit that may be observed or not observed with therapy and more clinical data is needed before TEZ/IVA can be recommended in additional patient populations with CF.

Further data is needed to better assess efficacy of TEZ/IVA. Evidence remains insufficient to determine the effects of TEZ/IVA on long term disease progression or to know if TEZ/IVA is effective in patients with very severe CF ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >90%). Additionally, evidence remains insufficient to determine comparative efficacy of TEZ/IVA and LUM/IVA (LUM/IVA) or against other standard of care including dornase alfa and hypertonic saline.

Table 4: Second allele in patients heterozygous for the F50ddel CF mutation included for TEZ/IVA FDA Approval[27]

***CFTR* Mutations Predicted to Have Residual Function and That May Be Responsive to Ivacaftor**			
2789+5G→A	R74W	R352Q	R1070W
3849+10kbC→T	D110E	A455E	F1074L
3272-26A→G	D110H	D579G	D1152H
711+3A→G	R117C	S945L	D1270N
E56K	E193K	S977F	
P67L	L206W	F1052V	
E831X	R347H	K1060T	

Clinical Safety:

The most common side effects observed in clinical trials evaluating TEZ/IVA that occurred in a greater number of TEZ/IVA-treated patients than placebo-treated patients include headache, nausea, sinus congestion and dizziness (**Table 5**). Headache and nausea were the most common, but rates were only slightly higher than placebo. Serious adverse reactions that occurred more frequently than placebo included distal intestinal obstruction syndrome (3 patients [0.6%] vs. 0 patients for TEZ/IVA and placebo, respectively). [26] Overall discontinuations due to adverse reactions was low in clinical trials (1.6%) and comparable to placebo (2.0%).There were no reported deaths in trials.[26]

Table 5: Adverse Drug Reactions Which Occurred More Commonly in TEZ/IVA-Treated Patients Than Placebo-Treated Patients

Adverse Reactions	TEZ/IVA (n=334) N (%)	Placebo (n=343) N (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	12 (4)	8 (2)

Additional safety concerns that need to be monitored for include elevated transaminase levels and drug-drug interactions mediated through CYP3A4.[26] Transaminases are recommended to be assessed prior to treatment, every 3 months for the first year of treatment, and yearly afterward.[26] Since both TEZ and IVA are substrates of CYP3A4, concomitant use of strong CYP3A4 inducers may decrease TEZ/IVA efficacy and is not recommended.[26]

Several unanswered safety questions exist as TEZ/IVA was studied in a relatively small number of patients in clinical trials. There is insufficient information of safety data in very severe CF, very mild CF, or patients with significant comorbidities as these patients were not included in the clinical trials. Additionally, there is insufficient information to determine long-term safety of TEZ/IVA as clinical trial data is limited to 24 weeks.

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	TEZ is a CFTR corrector designed to improve the cellular processing and trafficking of normal and mutated CFTR protein to increase the amount of functional CFTR at the cell surface. IVA is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface.
Oral Bioavailability	Exposure 3 times higher when administered with fat-containing foods compared to a fasting state
Distribution and Protein Binding	TEZ 99% protein bound; IVA 99% protein bound
Elimination	TEZ: 72% eliminated through feces, 14% in urine; IVA: 88% eliminated through feces, minimal urine excretion
Half-Life	TEZ: 29 hours; IVA: 20 hours
Metabolism	CYP3A4

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator, IVA: ivacaftor, TEZ: tezacaftor

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Quality of life
2) Hospitalizations
3) Pulmonary exacerbations
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Absolute change in ppFEV1 from baseline to week 24 (study 106) or to the average of week 4 and week 8 (study 108)

Table 7. Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/ NNT**	**Safety Outcomes**	**ARR/ NNH**	**Risk of Bias/ Applicability**
1. Taylor-Cousar, et al. [21] Phase 3, RCT, DB, PC, PG Study 106	1. Tezacaftor 100 mg daily + IVA 150 mg twice daily 2. matched placebo	Demographics: • Mean FEV_1: 60% • Mean age: 26 yr • Concomitant hypertonic saline: 51% • Concomitant dornase alfa: 70% Key Inclusion Criteria:	ITT: 1. 251 2. 259 PP: 1. 235 2. 240 Attrition:	Primary Endpoint: Absolute change in percent predicted FEV_1 1. 3.4% 2. -0.6% LSM difference 4.0%; 95% CI 3.1 to 4.8; p<0.001	NA	Discontinuations due to AE: 1. 7 (2.8%) 2. 8 (3.1%) 95% CI & p-value NR Serious AE:	NA	**Risk of Bias (low/high/unclear)**: low Selection Bias: low; randomized with an interactive web response system, baseline characteristics similar but more patients in the placebo group were on standard therapies than in the treatment group (dornase alfa (72% vs. 66.5%), inhaled antibiotic (62.5% vs. 54.8%), and inhaled corticosteroids (63% vs. 56%))

EVOLVE	x 24 weeks	• ≥12 y/o • Homozygous for F508del mutation • FEV1 ≥ 40% and ≤ 90% • Stable CF disease. Key Exclusion Criteria: • Significant comorbidity • Risk factors for torsades de pointes • Hg < 10 g/dl • Abnormal liver function • GFR≤ 50 ml/min • Respiratory infection or CF exacerbation in previous 4 weeks • Colonization with *Burkholderia or Mycobacterium* • Alcohol or drug abuse in past year • Use of mod-strong inhibitors or inducers of CYP3A4	1. 16 2. 18	Secondary Endpoints: Total Number of Pulmonary Exacerbations through week 24 (annuazed rate) 1. 78 (0.64 events per year) 2. 122 (0.99 events per year) Rate ratio vs. placebo: 0.65; 95% CI 0.48 to 0.88; p=0.005 Percent of patients with an increase in the CFQ-R respiratory domain score of at least 4 points: 1. 51.5% 2. 35.7% OR 2.17; 95% CI 1.47 to 3.21 p-value NR	NA 16%/7	1. 31 (12.4%) 2.47 (18.2%) 95% CI & p-value NR	NA	Performance Bias: low; subjects and investigator blinded, double-dummy design Detection Bias: low; site monitor and study team blinded Attrition Bias: low; FAS (1. 248, 2. 256) used for efficacy analysis (all randomization patients who took 1 dose of study drug), low overall attrition and similar between groups Reporting Bias: high; funded by Vertex Pharmaceuticals. Vertex designed the protocol, analyzed the data. **Applicability**: Patient: Extensive exclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV < 40%) or with FEV > 90%, patients generally young white adults from outside the U.S. and a significant number of patients not on standard of care therapies Intervention: N/A Comparator: Lack of IVA arm makes it difficult to determine effect of each component Outcomes: FEV_1 is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV_1 translate to long term clinical benefits Setting: Multinational in 91 sites in the United States, Canada, and Europe (75% Europe)
2. Rowe, et al.[2] Phase 3, RCT, PC, DB, crossover design Study 108 EXPAND	1. tezacaftor 100 mg + IVA 150 mg BID 2. IVA 150 mg BID 3. placebo Subjects received 2 8-week treatment regimens with a washout	Demographics: • Baseline ppFEV1: 62% • Mean age: 34.8 yr • Class V noncanonical splice mutation: 60% • Class II to IV residual function mutations in the second allele: 40% • Concomitant dornase alfa: 61% • Concomitant hypertonic saline: 48% Key Inclusion Criteria: • ≥12 y/o • Heterozygous for F508del mutation and a	ITT: 1. 162 2. 157 3. 162 PP: 1. 160 2.157 3. 162 Attrition: 1. 2 2. 2 3. 6	Primary Endpoint: Absolute change in $ppFEV_1$ from baseline to the average of week 4 and 8 1. 6.5% 2. 4.4% 3. -0.3% *IVA vs. placebo:* LSM 4.7; 95% CI 3.7 to 5.8 P<0.001 *TEZ/IVA vs. placebo* LSM 6.8; 95% CI 5.7 to 7.8 P<0.001 *TEZ/IVA vs. IVA*	NA NA	Outcome: Discontinuations due to AE: 1. 0 (0%) 2. 2 (1%) 3. 1 (<1%) Severe AE (grade 3 or 4): 1. 4 (2%) 2. 8 (5%) 3. 9 (6%)	NA NA	**Risk of Bias (low/high/unclear)**: unclear Selection Bias: low; randomized to 1 of 6 treatment sequences** including 2 of the treatment regimens with an interactive web response system, baseline characteristics similar Performance Bias: low; subjects and investigator blinded, double-dummy design Detection Bias: low; site monitor and study team blinded, crossover design Attrition Bias: unclear; FAS used for efficacy analysis (all randomization patients who took 1 dose of study drug), low overall attrition (5%), but some variability between groups (10% in the group randomized to placebo first) Reporting Bias: high; funded by Vertex Pharmaceuticals. Vertex designed the protocol, analyzed the data.

	period of 8 weeks in between**	second allele with a CFTR mutation predicted to have residual CFTR function • FEV_1 ≥ 40% and ≤ 90% • Stable CF disease • Sweat chloride ≥ 60 mmol/L or evidence of chronic sinopulmonary disease* <u>Key Exclusion Criteria</u>: • See EVOLVE above		LSM 2.1; 95% CI 1.2 to 2.9 P<0.001 <u>Secondary Endpoints</u>: <u>Percent of patients with an increase in the CFQ-R respiratory domain score of at least 4 points:</u> 1. 105 (65%) 2. 91 (58%) 3. 53 (33%) *IVA vs. placebo:* 95% CI & p-value NR *TEZ/IVA vs. placebo* 95% CI & p-value NR *TEZ/IVA vs. IVA* 95% CI & p-value NR <u>Exploratory Outcome:</u> <u>Pulmonary Exacerbations:</u> 1. 11 (0.34 events per year) 2. 9 (0.29 events per year) 3. 20 (0.63 events per year) *IVA vs. placebo (rate ratio)* RR 0.46; 95% CI 0.21 to 1.01 P-value NR *TEZ/IVA vs. placebo:* RR 0.54; 95% CI 0.26 to 1.13 P-value NR *TEZ/IVA vs. IVA:* RR 1.18; 95% CI 0.49 to 2.87 P-value NR	NA NA NA NA NA NA NA			**Applicability**: <u>Patient</u>: Extensive exclusion and inclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV < 40%) or with FEV > 90%, patients generally young white adults from outside the U.S. <u>Intervention</u>: Crossover trial design increases risk of a "carry over" treatment effect <u>Comparator</u>: Unclear on appropriateness of IVA as a comparator since it was found to be not effective in those homozygous for F508del <u>Outcomes</u>: The 8 week outcomes were actually an average of the 4 week and 8 week measurements, pulmonary exacerbations was an exploratory outcome. 8 weeks is not long enough follow-up to evaluate clinically important outcomes. <u>Setting</u>: Multinational including sites in North America (~50%) and Europe

<u>Abbreviations</u> [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CV = cardiovascular; DB = double blind; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; GFR = glomerular filtration rate; ITT = intention to treat; HTN = hypertension; IVA = IVA; LSM = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo controlled; PG = parallel group; PP = per protocol; $ppFEV_1$ = percent predicted forced expiratory volume in one second; RCT = randomized controlled trial; yr = year

*Manifested by at least 1 of the following: persistent colonization/infection with typical CF pathogens, chronic cough and sputum production, persistent chest abnormalities, nasal polyps or chronic sinusitis

**Sequence 1: TEZ/IVA - washout – IVA; Sequence 2: IVA – washout – TEZ/IVA; Sequence 3: TEZ/IVA – washout – placebo; Sequence 4: placebo – washout – TEZ/IVA; Sequence 5: IVA – washout – placebo; Sequence 6: placebo – washout - IVA

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	GRAN PACK	KALYDECO	IVA	N
ORAL	TABLET	KALYDECO	IVA	N
ORAL	TABLET	ORKAMBI	LUM/IVA	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November week 4, 2017
1 IVA.mp. 337
2 LUM.mp. 137
3 kalydeco.mp. 22
4. Cystic Fibrosis Trtansmembrane Conductance Regulator/ 8792
5 orkambi.mp. 16
6. 1 or 2 or 3 or 4 or 5
7. cystic fibrosis.mp or Cystic Fibrosis/ 26187
8 6 and 7
9 limit 8 to (English language and humans and yr="2015-Current" and (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)) 12

Oral Cystic Fibrosis Modulators

Goals:

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- 90 days to 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)

Preferred 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 (patient already on ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #5	

Approval Criteria		
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented mutation in the CFTR gene that ivacaftor is FDA approved for (see below)? FDA approved CFTR mutations include: E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC –T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X	**Yes:** Go to #18	**No:** Go to #9 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
~~8.~~9. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
~~9.~~10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Go to #14
~~10.~~11. Does the patient have a diagnosis of cystic fibrosis and is 6 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an CF mutation test?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)

Approval Criteria		
~~12.~~13. Is a baseline FEV1 provided and between ≥40% and ≤90% of predicted normal for age, sex and height for those ≥12 years of age and at least 40% for children ages 6 through 11 years?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #18	**No:** Pass to RPh. Deny; medical appropriateness If no baseline, request a baseline value before approving therapy.
14. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient have a diagnosis of cystic fibrosis and is 12 years of age or older?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Go to #18	**No:** Go to #17 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)

Approval Criteria		
17. Does the patient have a documented heterozygous Phe508del mutation in the CFTR gene with at least one mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and FDA labeling? Note: A list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor include: A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
~~13.~~18. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #19	**No:** Pass to RPh. Deny; medical appropriateness
~~14.~~19. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #20
~~15.~~20. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #21 If unknown, these labs need to be collected prior to approval.	

Approval Criteria		
21. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness
~~16.~~22. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days. Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on IVA (see **Renewal Criteria**)	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness
3. If the prescription is for lumacaftor/ivacaftor or tezacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.	

Renewal Criteria		
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 3 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

Dosage and Administration:

Ivacaftor:

- Adults and pediatrics age ≥6 years: 150 mg orally every 12 hours with fat-containing foods
- Children age 2 to <6 years:
  - < 14 kg: 50 mg packet every 12 hours
  - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Age ≥6 years: one 150 mg tablet once daily
    - Age 2 to < 6 years with body weight < 14 kg: 50 mg packet once daily; with body weight ≥ 14 kg : 75 mg packet of granules once daily
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **twice weekly** (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **once daily** (half of normal dose)
Rifampin	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort Grapefruit Juice		

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥12 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - 2 tablets in the morning and 1 tablet in the evening
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet twice daily, or less, after weighing the risks and benefits of treatment.
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

Tezacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years: 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
  - Severe impairment (Child-Pugh class C):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
    - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
  - When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
    - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

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Newer Diabetes Treatments Drug Class Update with New Drug Evaluation: Semaglutide and Ertugliflozin

Date of Review: July 2018

Date of Last Review: September 2017
End Date of Literature Search: 05/23/2018

Generic Name: semaglutide
Generic Name: ertugliflozin, ertugliflozin/sitagliptin, ertugliflozin/metformin

Brand Name (Manufacturer): Ozempic® (Novo Nordisk)
Brand Name (Manufacturer): Steglatro™, Steglujan™, Segluromet™ (Merck & Co., Inc.)
Dossier Received: ertugliflozin (yes), semaglutide (no)

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

Purpose for Class Update:
To evaluate the safety and efficacy of semaglutide and ertugliflozin (and combinations) which were recently approved for blood glucose lowering in patients with type 2 diabetes mellitus (T2DM). High quality new evidence published since the last review will also be presented.

Research Questions:
1. In patients with T2DM, is there any new comparative evidence for non-insulin antidiabetic therapies based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. In patients with T2DM, is there any new comparative evidence for non-insulin diabetes treatments based on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, etc.)?
3. Are there subpopulations of patients with T2DM for which specific therapies may be more effective or associated with less harm?
4. What are the efficacy and harms evidence for the two new non-insulin diabetes treatments, ertugliflozin and semaglutide?

Conclusions:
- A Drug Effectiveness Review Project (DERP) update on newer diabetes therapies, three new guidelines/standards, one new randomized controlled trial and two new drug reviews were reviewed for this class update. The evidence pertains mostly to adult patients with T2DM, mildly elevated HbA1c levels, and unspecified healthcare coverage. Limitations to the evidence included short-term study duration and industry funding for a majority of the included studies.

DERP REVIEW
- The DERP review on newer diabetes medications and combinations was published in September of 2017.[1] The most clinically relevant outcomes with moderate or high quality evidence are summarized below.

Cardiovascular Outcomes

- Moderate strength of evidence was demonstrated for reduction in the composite outcome of CV death, nonfatal myocardial infarction (MI) or nonfatal stroke compared to placebo for the following therapies: empagliflozin (ARR 1.6%/NNT 63 over 3.1 years), canagliflozin (CANVAS ARR 1.4%/NNT 71 over 5.7 years and CANVAS-R ARR 1.1%/NNT 91 over 2.1 years), and liraglutide (ARR 1.9%/NNT 53 over 3.5 years).[1] For this same endpoint, the following therapies were found to produce no cardiovascular benefit and no harm compared to placebo: alogliptin, lixisenatide, semaglutide, saxagliptin, and sitagliptin.
- Cardiovascular death was reduced with empagliflozin (3.7% vs. 5.9% over 3.1 years) and liraglutide (4.7% vs. 6.0% over 3.8 years) compared to placebo based on moderate quality evidence as determined by DERP.[1] No difference in CV death was seen between treatment and placebo for saxagliptin, sitagliptin, and lixisenatide.

CLINICAL EFFICACY

HbA1c

Within Class Comparisons

- For within class comparisons DERP found that there was moderate evidence of a statistical benefit in HbA1c lowering favoring the first therapy listed in the following comparisons: daily lixisenatide vs. daily liraglutide and once-weekly exenatide vs. exenatide twice daily.[1] The difference in HbA1c lowering between the treatments was approximately 0.5% to 0.6%, suggesting benefit in patients who are close to achieving their HbA1c goal.

Between Class Comparisons

- DERP found moderate strength of evidence of significant differences between classes of antidiabetic treatments for the outcome of HbA1c lowering. Canagliflozin 300 mg decreased HbA1c by a mean difference of -0.16% (95% CI, -0.29 to -0.02) more than sitagliptin 100 mg which is unlikely to be clinically impactful. A higher percent of patients obtained a HbA1c less than 7% with empagliflozin compared to linagliptin based on moderate strength of evidence.[1] Moderate strength of evidence found no difference between empagliflozin and sitagliptin.

Newer Diabetes Medications

- DERP found moderate evidence of more HbA1c reduction with metformin compared to sitagliptin (weighted mean difference [WMD] -0.30%; 95% CI, -0.52 to -0.09). [1]

Changes in Weight

- Moderate evidence found canagliflozin, empagliflozin and dapagliflozin to cause more weight loss compared to sitagliptin ranging from 6 to 10 pounds which could be clinically impactful.[1]
- The fixed-doe combination product (FDCP) of empagliflozin/linagliptin was found to cause more weight loss compared to linagliptin.
- Metformin was associated with more weight loss, ranging from -1.2 kg to -1.7 kg, when compared to sitagliptin (moderate evidence).

Evidence on Harms

- Liraglutide was associated with a higher incidence of withdrawal due to adverse events compared to sitagliptin (RR 3.28; 95% CI, 1.81 to 5.93).[1]

New Drugs

Semaglutide:

- A CV outcomes study found semaglutide to be noninferior to placebo based on a phase 3, double-blind, double-dummy, noninferiority, randomized trial of fair quality lasting a mean duration of 2.1 years in patients with CV disease or at high risk of CV disease (60 years or older and at least 1 CV risk factors).[2] The incidence of the primary composite outcome (CV death, nonfatal MI or nonfatal stroke) occurred in 6.6% of patients treated with semaglutide compared to 8.9% of patients treated with placebo (HR 0.74; 95% CI, 0.58 to 0.95; P<0.001 for noninferiority). In a subgroup analysis in patients with only CV risk factors (primary prevention patients), there was no benefit over placebo of semaglutide therapy and also no benefit over placebo seen in patients from only US treatment sites (HR 0.84; 95% CI 0.57 to 1.34). Results are most applicable to patients with a history of CV disease, kidney disease or both. Primary outcome analysis was done on the intention to treat (ITT) population which can bias results toward no difference between groups in trials with a noninferiority design. Semaglutide patients were found to have better glucose control compared to placebo (HbA1c mean difference -1.0%), which may have influenced study results. The trial was not powered to determine statistical superiority between semaglutide and placebo and was funded by industry.
- Semaglutide efficacy was demonstrated in six trials studying HbA1c reduction from baseline over 30-56 weeks.[3–8] Noninferiority trials of fair quality compared semaglutide to active comparisons; sitagliptin, insulin glargine, exenatide ER and dulaglutide.[3–6] Estimated HbA1c treatment differences (ETD) between semaglutide and active treatments were -0.38% to -1.06%, proving noninferiority and superiority. Differences in HbA1c between semaglutide compared to placebo ranged from –1.35% to -1.75%.[7,8] Semaglutide was associated with greater weight loss, up to approximately 4 kg more than active treatment comparisons (P<0.05). Adverse events were similar to other glucagon-like peptide-1 receptor agonists (GLP-1 RAs), with gastrointestinal related adverse events being the most common. Semaglutide was associated with an increased risk for diabetic retinopathy complications compared to placebo (3% versus 1.8%, respectively; HR 1.76; 95% CI, 1.11 to 2.78), which has not been demonstrated with other GLP-1 RAs.[2]

Ertugliflozin:

- Ertugliflozin was recently approved as monotherapy and in combination with sitagliptin and metformin.[9] Placebo controlled studies found HbA1c lowering similar to other sodium-glucose cotransporter-2 (SGLT-2) inhibitors with lowering of up to -0.9%.[10–13] An active treatment comparisons with glimepiride demonstrated noninferiority for ertugliflozin 15 mg (estimated treatment difference [ETD] 0.1%; 95% CI, -0.0 to 0.2) but not at the lower dose of 5 mg.[14] Combination ertugliflozin and sitagliptin were found to be more effective than monotherapy components.[15]
- Genital and urinary tract infections were associated with ertugliflozin use, which is similar to other SGLT-2 inhibitors. An increased risk of lower limb amputations with ertugliflozin in at-risk patients was demonstrated across the phase 3 trials; 1 (0.1%) in non-ertugliflozin treated patients, 3 (0.2%) in the ertugliflozin 5 mg group and 8 (0.5%) in the ertugliflozin 15 mg group.[9]

Randomized Controlled Trial

- A CV safety study comparing exenatide extended release (ER) to placebo, in patients with T2DM and CV disease (70% of participants) and those at high risk of CV disease (30%), found exenatide ER to be no more harmful or effective in CV risk reduction than placebo based on an incidence of the primary endpoint of 11.4% in exenatide ER treated patients compared to 12.2% for placebo (HR 0.91: 95% CI, 0.83 to 1.00; P<0.001 for noninferiority and P=0.06 for superiority).[16]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended for the non-insulin class of antidiabetic therapies based on review of efficacy and safety data.
- Add new formulations to existing prior authorization (PA) criteria.

- Evaluate comparative drug costs in executive session.

Prior Review Summary and Policy Recommendations

- Evidence supports the use of metformin for initial therapy in patients with T2DM requiring medication to reach HbA1c goals.[17,18] There is no universal recommendation for the optimal second line antidiabetic therapy, as most second-line therapies lower HbA1c to a similar extent.[19] Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of a sulfonylureas (SU) in patients who require additional glucose lowering in addition to metformin.[18] National Institute for Health and Care Excellence (NICE) recommends the addition of a SU, pioglitazone, DPP-4 inhibitor or SGLT-2 based on efficacy and safety data.[17] Much attention is also focused on the CV effects of antidiabetic treatments and some guidance advocates use of specific therapies in patients with atherosclerotic cardiovascular disease (ASCVD).[20] Most newer therapies have shown a neutral impact on composite CV endpoints. Small benefits have been demonstrated for canagliflozin, empagliflozin and liraglutide; however, reductions compared to placebo have only ranged from 1.1% to 1.9% and trials have had many limitations, including: lack of CV benefit in North American populations, lack of transparency on cause of CV death, industry funding and only applicable to patients at high risk or history of CV disease, average age of 63-64 years and on multiple other antidiabetic and cardioprotective treatments.[21–23] For these reasons the evidence from these studies doesn't apply to a large proportion of patients with T2DM. Additionally, adverse events need to be considered when choosing antidiabetic treatment. Serious adverse events include the following: an increased risk of amputations in T2DM patients at high CV risk or history of CV disease treated for with canagliflozin or ertugliflozin compared to placebo, increased risk of hospitalization due to heart failure when compared to placebo with saxagliptin and alogliptin, increased risk of ketoacidosis with SGLT-2 inhibitors, increased risk of retinopathy complications with semaglutide compared to placebo, potential increase in pancreatitis with dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 RAs, exacerbation of heart failure and increased risk of bone fracture with thiazolidinediones (TZD) and increased risk of hypoglycemia with SU compared to other active treatments.[2,17,18,24]
- Antidiabetic therapies were last reviewed in September of 2017 which resulted in no changes to the PDL or PA criteria. Current Oregon Health Plan (OHP) fee-for-service policy for non-insulin antidiabetic treatment allows for metformin, SUs and TZDs for use without restriction (**Appendix 1**). DPP-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are options after trials of metformin and SU or contraindications to these drugs as outlined in the PA criteria in **Appendix 6**. The DPP-4 inhibitor, sitagliptin, is also a preferred drug but requires that patients meet specific clinical PA criteria. SGLT2 inhibitors are available as last-line therapy as described in the clinical PA criteria.

Background:

Approximately 287,000 adult Oregonians have T2DM. It is estimated that over 38,000 of these patients are OHP members.[25] OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[26] Despite a variety of treatment options, a significant number of patients fail to meet HbA1c goals within 3 years of being diagnosed and 50% of patients require combination therapy to control their disease.[27,28]

Underlying characteristics that lead to hyperglycemia and T2DM are insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary for treatment of hyperglycemia associated with T2DM in most patients.[29] Pharmacotherapy improves hyperglycemia by increasing glucose uptake, increasing glucose secretion and/or increasing insulin sensitivity. Goal glucose levels are dependent upon patient characteristics, such as age and comorbidities; however, guidelines recommend a goal HbA1c of less than 7% for most patients but a range of less than 6.5% to less than 8% may be appropriate.[30,31] Classes of non-insulin antidiabetic agents currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT-2 inhibitors, SUs, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines recommend metformin a first line treatment in most patients with T2DM.[17,30,32,33] There is no consensus

on a universally recognized second-line treatment and therefore, selection should be dependent on degree of glucose lowering required to assist in obtaining goal HbA1c levels, patients specific characteristics including comorbidities and harms of therapy. [17,30,32,33]

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, HbA1c, severe adverse events and hypoglycemia rates. Hemoglobin A1C is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be ≥0.3%.[19] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term and to directly compare their impact on microvascular and macrovascular complications.

In 2008, the FDA started requiring that CV risk of antidiabetic therapies be evaluated. Cardiovascular studies have been published for each of the newer classes of antidiabetic therapies; however, definitive conclusions on class effects of benefits and harms have yet to be determined. Additionally, limitations of the evidence in CV studies, such as limited applicability to patients with CV disease or at high risk of CV disease, as well as small benefits of treatment prevent universal recommendations of antidiabetic therapies with suggestive CV benefit. A comparison table of effectiveness and harms can be found in **Appendix 5**.

Abbreviated Drug Utilization Evaluation:
Quarterly costs for antidiabetic therapies are driven by newer drugs from the SGLT-2, GLP-1 RA and DPP-4 classes, which have increased 5% since the last update. Metformin, SUs and TZDs account for 94% of claims but only 5% of the cost overall. Utilization of preferred antidiabetic therapies is 98% for metformin, SU and TZDs and 31% for newer therapies, with the inclusion of SGLT-2 inhibitors which have no preferred treatments within the class.

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 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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:
<u>DERP – Newer Diabetes Medication and Combinations</u>
In September 2017 DERP released a review on newer medications for patients with type 2 diabetes.[1] Newer diabetes medications were defined as: amylin agonists, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors. Twenty-six trials, 3 observational studies and 4 systematic reviews were included. Most of the evidence comes from patients who are white, middle-aged, obese, 10 year or less history of diabetes and HbA1c baseline levels of less than 9%. Placebo run-in periods were required for many trials which can bias results in favor of patients who will be adherent to therapy. Evidence based on retrospective cohort trials,

indirect comparisons, open-label extension studies or with limited applicability to OHP FFS patients were not included for reasons outlined in the Drug Use Research and Management (DURM) methods. Secondary endpoints that were not statistically or clinically significantly different between therapies were excluded.

Cardiovascular Trials

Evidence for the CV effect of newer diabetes medications was studied for SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 agonists (**Table 1**).[1] All the trials but the semaglutide trial have been previously presented in diabetes class updates. Therefore, only the semaglutide CV trial will be presented in detail. The following characteristics were similar for all trials:

- Trials were placebo controlled
- Patients had established CV disease or multiple CV risk factors
- Mean age was 61-66 years
- One-third of patients were women
- Baseline HbA1c ranged from 7.2% to 9.7%
- Patients had a 7-14 year history of diabetes
- All trials allowed additional glucose lowering drugs
- Six of eight trials were considered good quality. The LEADER and CANVAS trials were considered fair quality.

Table 1. Comparison of CV Outcomes Across Drug Trials.[1]

Author, Year **Trial Name** **Drug** **Number of Patients**	**Population**	**CV Death, Nonfatal MI, or Nonfatal Stroke**	**CV Death**
SGLT2 inhibitors			
Zinman, 2015 EMPA-REG OUTCOME Empagliflozin 7,020	Established CV disease HbA1c: 8.1 Duration of diabetes: NR	Event rate (3.1 y FU): 10.5% vs. 12.1% HR 0.86 (95% CI, 0.74 to 0.99) *moderate strength of evidence*	Event rate (3.1 y FU): 3.7% vs. 5.9% HR 0.62 (95% CI, 0.49 to 0.77) *moderate strength of evidence*
Neal, 2017 CANVAS and CANVAS-R Canagliflozin 10,142	History of CV disease (age ≥30 years) or ≥ 2 CV disease risk factors HbA1c: 8.2 Duration of diabetes :13.5 y	Both trials (combined FU of 2.4 y): HR 0.86 (95% CI, 0.75 to 0.97) CANVAS (5.7 y FU): Event rate: 15% vs. 16% *moderate strength of evidence* CANVAS-R (2.1 y FU): Event rate: 5.5% vs. 6.6% *moderate strength of evidence*	Event rate (combined FU of 2.4 y): 4.6% vs. 4.3% HR 0.87 (95% CI, 0.72 to 1.06) *low strength of evidence*
DPP-4 Inhibitors			
White, 2013 EXAMINE	Recent acute coronary syndrome HbA1c: 8.0	Event rate (1.5 y FU): 11.3% vs. 11.8%	Event rate (1.5 y FU): 4.1% vs. 4.9%

Alogliptin 5,380	Duration of diabetes: 7.2 y	HR 0.96 (≤ 1.16); P = 0.32 *moderate strength of evidence*	HR 0.85 (95% CI, 0.66 to 1.10) *low strength of evidence*
Scirica, 2013 SAVOR-TIMI 53 Saxagliptin 16,492	Established CV disease (age ≥ 40 years) or ≥ 2 CV disease risk factors HbA1c: 8.0 Duration of diabetes: 10 y	Event rate (2 y KM): 7.3% vs. 7.2% HR 1.00 (95% CI, 0.89 to 1.12) *moderate strength of evidence*	Event rate (2 y FU): 3.2% vs. 2.9% HR 1.03 (0.87 to 1.22) *moderate strength of evidence*
Green, 2015 TECOS Sitagliptin 14,671	Established CV disease HbA1c: 7.2 Duration of diabetes: 12 y	Event rate (3.0 y FU) 10.2% vs. 10.2% HR 0.99 (95% CI, 0.89 to 1.10) *moderate strength of evidence*	Event rate (3.0 yr FU) 5.2% vs. 5.0% HR 1.03 (95% CI, 0.89 to 1.19) *moderate strength of evidence*
GLP-1 Agonists			
Marso, 2016 SUSTAIN-6 Semaglutide 3,297	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7 Duration of diabetes: 14 y	Event rate (2.1 y FU): 6.6% vs. 8.9% HR 0.74 (95%CI, 0.58 to 0.95) For noninferiority *moderate strength of evidence*	Event rate (2.1 y FU): 2.7% vs.2.8% HR 0.98 (95% CI, 0.65 to 1.48) *insufficient evidence*
Pfeffer, 2015 ELIXA Lixisenatide 6,068	Recent acute coronary syndrome HbA1c: 7.7 Duration of diabetes: 9.3 y	Not reported – used an alternated composite endpoint of unstable angina, CV death, nonfatal MI or stroke. No difference compared to placebo was found.	Event rate (2.1 y FU) 5.1% vs. 5.2% HR 0.98 (95% CI, 0.78 to 1.22) *moderate strength of evidence*
Marso, 2016 LEADER Liraglutide 9,340	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7 Duration of diabetes: 13 y	Event rate (3.8 y FU): 13.0% vs. 14.9% HR 0.87 (95% CI, 0.78 to 0.97) *moderate strength of evidence*	Event rate (3.8 y FU): 4.7% vs. 6.0% HR 0.78 (95% CI, 0.66 to 0.93) *moderate strength of evidence*

Abbreviations: CI = confidence interval; CV = cardiovascular; FU = follow up; HbA1c = hemoglobin A1c; HR = hazard ratio; NR = not reported; y = years

Semaglutide CV Trial (SUSTAIN-6)

In addition to the results in Table 1, other important outcomes are presented below:

- Semaglutide was found to have a 1.1% decreased risk of nonfatal stroke compared to placebo (HR 0.61; 95% CI, 0.38 to 0.99) based on moderate strength of evidence.[1]
- The risk of nonfatal MI was similar between semaglutide and placebo, 2.9% and 3.9%, respectively (low strength of evidence).
- The risk of hospitalization was 3.6% with semaglutide and 3.3% with placebo, suggesting no difference (low strength of evidence).
- The incidence of retinopathy complications was 3.0% with semaglutide compared to 1.8% with placebo (HR 1.76; 95% CI, 1.11 to 2.78). The composite outcome of retinopathy complications included diabetes-related blindness, vitreous hemorrhage, or need for treatment with photocoagulation or intravitreal agents.

- New or worsening nephropathy was less with semaglutide compared to placebo, 3.8% vs. 6.1% (HR 0.64; 95% CI, 0.46 to 0.88).
- Subgroup analyses found no clinically significant differences between semaglutide and placebo based on history of prior CV disease, chronic HF, prior MI or stroke, or established CV disease versus CV risk factors only.

Within Class Comparisons

Twelve trials evaluated within class comparisons which lasted anywhere from 16-52 weeks and included 66 to 835 patients with ages from 44 to 57 years.[1] Most trials included patients that were inadequately controlled on metformin, sulfonylureas, a TZD or combination of these antidiabetic agents.

- *Sitagliptin vs. saxagliptin*: similar HbA1c lowering at 24 weeks, -1.07% vs. -1.34%, respectively based on low strength of evidence. Adverse events and withdrawals due to adverse events were not statistically significantly different between groups.
- *Dulaglutide once weekly vs. daily liraglutide*: drugs were compared over 26 weeks (both groups on background metformin) and found similar HbA1c reductions, -1.42% vs. -1.36%, respectively. Additionally, both groups achieved a HbA1c of less than 7% in 68% of patients (low strength of evidence).[1] Adverse events were similar. Weight loss was numerically greater with liraglutide compared to dulaglutide but clinical benefit was small, -2.90 kg versus -3.61 kg, respectively.
- *Weekly albiglutide vs daily liraglutide*: both groups on background metformin, TZDs, sulfonylureas or combination therapy with greater HbA1c reductions in patients receiving liraglutide, -0.99% vs. -0.79%, respectively (treatment difference -0.21%; 95% CI, 0.08% to 0.34%; low strength of evidence).[1] Fifty-two percent of patients receiving liraglutide obtained an HbA1c less than 7% compared to 42% for albiglutide (RR 1.23; 95% CI, 1.06 to 1.42). Patient receiving liraglutide experienced 1.55 kg more weight loss compared to albiglutide patients.
- *Daily lixisenatide vs. daily liraglutide*: patients taking metformin in both groups, HbA1c reductions were -1.8% with lixisenatide versus 1.2% with liraglutide (treatment difference -0.6%; 95% CI, -0.8% t0 -0.4%; moderate strength of evidence).[1] More patients receiving lixisenatide obtained an Hba1c less than 7% compared to liraglutide (74.2% vs. 45.5%; P<0.0001). Adverse events and decreases in body weight were similar between the two groups.
- *Twice daily exenatide vs. weekly dulaglutide*: background therapies included metformin and/or pioglitazone which resulted in 78% of patients taking dulaglutide 1.5 mg and 66% of patients taking dulaglutide 0.75 mg obtained a HbA1c of less than 7% compared to 52% taking exenatide (P<0.001 for all comparisons)(low strength of evidence).[1] Dulaglutide 1.5 mg weekly had similar weight loss and adverse events as exenatide.
- *Exenatide XR (once-weekly) vs. exenatide twice daily:* meta-analysis of three trials found -0.46% (95% CI, -0.69 to -0.23) more HbA1c lowering with exenatide XR compared to exenatide twice daily (moderate strength of evidence).[1]
- *Liraglutide once daily vs. exenatide twice daily*: HbA1c lowering was -1.12% with liraglutide compared with -0.79% with exenatide (both groups on background metformin or sulfonylurea or both)(MD -0.33%; 95% CI, -0.47 to -0.18; P<0.0001) based on low strength of evidence.[1]

Between Class Comparisons

Twenty publications were identified for between class comparisons of antidiabetic therapies. All but two trials were considered fair or good quality. Two studies graded as poor quality evidence did not meet inclusion criteria for DURM reviews as outlined in the methods.[1]

DPP-4 inhibitors were compared to GLP-1 analogs in eight studies that were graded as fair quality. Patients ranged from 47 to 63 years old with women comprising 34% to 52% of the population.

- *Sitagliptin vs. exenatide XR*: low strength of evidence found exenatide XR to lower HbA1c more than sitagliptin at 26 weeks in patients also taking metformin (WMD -0.48%; 95% CI, -0.69 to -0.26).[1] Sixty-two patients taking exenatide XR obtained HbA1c less than 7% compared to 39% of patients

taking sitagliptin (RR 1.57; 95% CI, 1.34 to 1.83). More weight loss was demonstrated in patients taking exenatide XR compared to sitagliptin with a WMD of -1.32 kg (95% CI, -1.87 to -0.76); however is unlikely to be clinically impactful.

- *Sitagliptin vs. exenatide*: insufficient evidence.
- *Sitagliptin vs. liraglutide*: in patients also taking metformin, liraglutide 1.2 mg once daily was found to lower HbA1c -0.34% (95% CI, -0.51% to -0.16%) more than sitagliptin 100 mg once daily at 26 weeks.[1] Liraglutide 1.8 mg once daily lowered HbA1c by -0.60% (95% CI, -0.77 to -0.43) more than sitagliptin 100 mg once daily. Both findings were based on low strength of evidence. An extension phase lasting 52 weeks confirmed HbA1c findings of the 26-week study. Difference in mean weight loss was 2.3 kg more with liraglutide compared to sitagliptin. There was moderate evidence that withdrawals due to adverse events were higher in patients taking liraglutide compared to sitagliptin (RR 3.28; 95% CI, 1.81 to 5.93). A second study found that similar HbA1c reductions were seen in patients taking liraglutide 1.2 mg and sitagliptin 100 mg at 26-weeks.
- *Sitagliptin vs. albiglutide*: weekly albiglutide 30 mg was more effective in lowering HbA1c compared to sitagliptin 100 mg daily in patients taking metformin after 104 weeks of treatment. HbA1c lowering was -0.63% with albiglutide compared to -0.28% with sitagliptin (P<0.001) based on low strength of evidence. Weight loss was not significantly different between groups.[1]
- *Sitagliptin vs. dulaglutide*: low strength of evidence found a higher number of patients were able to obtain a HbA1c of less than 7% in patients taking dulaglutide 0.75 mg and dulaglutide 1.5 mg compared to sitagliptin 100 mg, 55%, 61% and 38%, respectively (P<0.001 for both dulaglutide versus sitagliptin comparisons).[1] An additional study out to 104 weeks demonstrated more patients obtaining an HbA1c less than 7% taking dulaglutide compared to sitagliptin.

DPP-4 inhibitors were compared to SGLT-2 inhibitors in nine trials of fair to good quality and 2 good quality systematic reviews. Patients were 52-59 years old with T2DM and 43% to 67% were men.

- *Sitagliptin vs. canagliflozin*: canagliflozin 300 mg was found to decrease HbA1c more than sitagliptin 100 mg based on moderate quality of evidence. Pooled data found a mean difference in HbA1c lowering was -0.16% (95% CI, -0.29 to -0.02) more for canagliflozin compared to sitagliptin (moderate strength of evidence).[1] Canagliflozin therapy resulted in more weight loss compared to sitagliptin with a mean difference of -2.91 kg (95% CI, -3.50 to -2.33) based on moderate evidence. Incidence of mycotic infections were higher with canagliflozin compared to sitagliptin (RR 11.96; 95% CI, 2.84 to 50.41 in men and RR 3.99; 95% CI, 2.15 to 7.40 in women).
- *Sitagliptin vs*. *empagliflozin*: A 12-week study found a similar incidence of patients obtaining a HbA1c less than 7% in patients taking empagliflozin 10 mg or empagliflozin 25 mg compared to sitagliptin, 38%, 37% and 34%, respectively (moderate strength of evidence).[1] Weight loss ranged from -2.26 to -4.30 kg with empagliflozin (10-25 mg) compared to -0.4 kg to 0.18 kg with sitagliptin based on moderate evidence (P<0.05 for both empagliflozin to sitagliptin comparisons). An extension study lasting an additional 78 weeks found a similar incidence in all three groups of patients reaching an HbA1c less than 7%. A second study in patient who were treatment naïve found similar numbers of patients obtaining an HbA1c of less than 7% in patients taking empagliflozin 10 mg, empagliflozin 25 mg and sitagliptin, 35%, 44% and 38% (P>0.05 for empagliflozin versus sitagliptin comparisons).[1] Genital infections were 4 times greater with empagliflozin compared to sitagliptin. Pooled analysis of the two studies found moderate evidence of no difference in HbA1c lowering between empagliflozin and sitagliptin.
- *Sitagliptin vs. dapagliflozin:* low strength of evidence from one small study found HbA1c reductions of -0.8% with dapagliflozin compared to -0.6% with sitagliptin, which were not statistically or clinically different.
- *Linagliptin vs. empagliflozin*: pooled data from two, 24 week studies of either treatment naïve patients or patients on background metformin, found a higher chance of obtaining an HbA1c of less than 7% with empagliflozin compared to linagliptin (OR 3.3: 95% CI, 1.9 to 4.7) (moderate quality evidence).[1] Genital mycotic infections occurred in 7% of patients taking empagliflozin compared to 3% taking linagliptin (RR 2.50; 95% CI 1.11 to

5.47). Weight loss was 1-2 kg more for both empagliflozin doses compared to linagliptin based on moderate evidence (P<0.05). Risk of hypoglycemia and urinary tract infections were similar between groups.

- *Saxagliptin vs. dapagliflozin*: one study of 355 patients found a similar number of patients obtaining a HbA1c less than 7% with saxagliptin 5 mg and dapagliflozin 10 mg, 17% and 23%, respectively (low strength of evidence).[1] The mean weight change with dapagliflozin treatment was 2.4 kg compared to 0 kg with saxagliptin. The risk of genital infections was 6% with dapagliflozin compared to 0.6% with saxagliptin (RR 9.83; 95% CI, 1.27 to 76).

The GLP-1 agonist, exenatide 5 mg once weekly, plus the SGLT2 inhibitor, dapagliflozin 10 mg daily, was compared to the monotherapy components in a fair-quality trial of 685 patients who were uncontrolled on metformin. HbA1c lowering was similar for all groups with decreases from baseline of -1.4% to 2.0% based on low quality evidence.

Fixed-dose Combination Products (FDCP)

There were fifteen fair to good quality trials identified that studied FDCP (**Table 2**). Most patients had been previously treated with oral antidiabetic therapy with a mean baseline HbA1c of 8%.

Table 2. Fixed-dose Combination Product Trial Results.[1]

Comparison	Study Quality (number of studies)*	Outcome Studied	Results	Strength of Evidence†
GLP-1 Agonists and Long-Acting Insulins				
Lixisenatide + insulin glargine (Soliqua™) **vs.** **lixisenatide** **or** **insulin glargine** (background metformin or long-acting insulin)	Fair to good (2)	Percent of patients with HbA1c of <7%	FDCP: 55-84% lixisenatide: 33% glargine: 30-78% FDCP vs. lixisenatide: MD 40.6% (95% CI, 33.6 to 47.6) FDCP vs. glargine: MD 14.3% (95% CI, 8.4 to 20.3) and MD 25.5% (95% CI, 18.9 to 32.1)	Moderate
Liraglutide + insulin degludec (Xultophy®) **vs.** **degludec** **or** **liraglutide** **or** **insulin glargine** (background metformin, insulin naïve or insulin glargine and metformin)	Fair to good quality (3)	Percent of patients with HbA1c of <7%	FDCP: 60% degludec: 23% OR 5.44 (95% CI, 3.42 to 8.66) P-value not reported FDCP: 72% insulin glargine: 47% (P<0.001); *CI not provided* FDCP: 81% degludec: 65% OR 2.38 (95% CI, 1.78 to 3.18)	Low to moderate

			FDCP: 81% liraglutide: 60% (P<0.0001)	
SGLT2 Inhibitors and DPP-4 Inhibitors				
Empagliflozin + linagliptin (Glyxambi®) **vs.** **empagliflozin** **or** **linagliptin** (background metformin or drug naïve)	Quality not reported (2)	HbA1c reduction from baseline	<u>Study 1</u> FDCP 25/5 mg: -1.08% linagliptin 25 mg: -0.67% empagliflozin 5 mg: - 0.95% FDCP vs. linagliptin: MD -0.41% (95% CI, -0.61% to -0.22%) FDCP vs. empagliflozin: MD -0.14% (95% CI, -0.33% to 0.06%) FDCP 10/5 mg: -1.24% empagliflozin: -0.83% linagliptin 5 mg: -0.67% FDCP vs. empagliflozin: MD -0.41% (95% CI, -0.61% to -0.21%) FDCP vs. linagliptin: MD -0.57% (95% CI, -0.76% to -0.37%) <u>Study 2</u> FDCP 25/5mg: -1.19% empagliflozin 25 mg: -0.62% linagliptin 5 mg: -0.70% FDCP 25/5 mg vs. empagliflozin 25 mg: MD -0.58% (95% CI, -0.75% to -0.41%) FDCP 25/5 mg vs. linagliptin 5 mg: MD -0.50% (95% CI, -0.67% vs. -0.32%) FDCP 10/5mg: -1.08% empagliflozin 25 mg: -0.66% linagliptin 5 mg: -0.70%	Moderate

			FDCP 10/5 mg vs. empagliflozin 10 mg: MD -0.42 (95% CI, -0.59% to -0.25%) FDCP 10/5 mg vs. linagliptin 5 mg: MD -0.39% (95% CI, -0.56% to -0.21%)	
DPP-4 Inhibitors with other Oral Diabetes Medicines				
Alogliptin + pioglitazone (Oseni®) **vs.** **alogliptin 12.5 mg or 25 mg** **or** **pioglitazone 30 mg**	Quality not reported (1)	Percent of patients with HbA1c of <7%	FDCP 12.5/30mg: 53% FDCP 25/30 mg: 63% pioglitazone 30mg: 34% alogliptin: 24% FDCP 12.5/30 mg vs. pioglitazone: RR 1.58 (95% CI, 1.22 to 2.05) ARR 19%/NNT 6 FDCP 25/30 mg vs. pioglitazone: RR 1.86 (95% CI, 1.46 to 2.38) ARR 29%/NNT 4 FDCP 12.5/30 mg vs. alogliptin: Not SS FDCP 25/30 mg vs. alogliptin: RR 2.58 (95% CI, 1.92 to 3.46) ARR 39%/NNT 3	Low
Alogliptin + metformin (Kazano®) **(12.5/500 mg twice daily or 12.5/1000 mg twice daily)** **vs.** **alogliptin 25 mg daily** **or** **alogliptin 12.5 mg twice daily** **or** **metformin 500 mg twice daily** **or** **metformin 1000 mg twice daily**	Quality not reported (1)	HbA1c reduction from baseline	FDCP 12.5/500 mg: -1.22% FDCP 12.5/1000 mg: -1.55% alogliptin 25 mg: -0.52% alogliptin 12.5 mg: -0.56% metformin 500 mg: -0.65% metformin 1000 mg: -1.11% P<0.001 for all FDCP compared to monotherapy	Strength of evidence not provided

(treatment naïve)				
Linagliptin + metformin twice daily (Jentadueto®) vs. linagliptin vs. metformin	Quality not reported (2)	HbA1c reduction from baseline	*Favors FDCP for all comparisons* - Study 1: FDCP 5/1000mg vs. linagliptin 5mg: MD -0.70% (95%, CI, -0.98 to -0.42) FDCP 5/2000 mg vs. linagliptin 5 mg: MD -1.10 (95% CI, -1.38 to -0.82) FDCP 5/1000mg vs. metformin 1000 mg: MD -0.60% (95%, CI, -0.88 to -0.32) FDCP 5/2000mg vs. metformin 2000 mg: MD -0.50% (95%, CI, -0.78 to -0.22) Study 2: FDCP 5/1500-2000mg vs. linagliptin 5 mg: MD 0.8% (95% CI, -1.1 to -0.5)	Moderate
Sitagliptin + metformin (Janumet®) vs. sitagliptin vs. metformin	Quality not reported (5)	HbA1c reduction from baseline	FDCP 100/2000mg vs. metformin: WMD -0.60 (95% CI, -0.75 to -0.45)	Moderate
SGLT2 Inhibitors with other Oral Diabetes Medications				
Canagliflozin 100 mg or 300 mg + metformin extended release vs. metformin XR	Quality not reported (1)	Percent of patients with HbA1c of <7%	FDCP 300: 56.8% metformin XR: 43.0% canagliflozin 300 mg: 42.8% FDCP 300 mg vs. metformin XR:	Low

or **canagliflozin 100 mg**			RR 1.32 (95% CI, 1.10 to 1.59) ARR 14%/NNT 8 FDCP 300 mg vs. canagliflozin 300mg: RR 1.32 (95% CI, 1.11 to 1.60) ARR 14%/NNT 8 FDCP 100 mg: 49.6% metformin XR: 43.0% canagliflozin 100 mg: 38.8% FDCP 100 vs. metformin XR: NS FDCP 100 vs. canagliflozin 100 mg: RR 1.28 (95% CI, 1.05 to 1.57) ARR 11%/NNT 9	
Abbreviations: ARR – absolute risk reduction; FDCP – fixed-dose combination product; HbA1c – hemoglobin A1c; MD – mean difference; NNT – number needed to treat; NR – not reported; NS – non-significant; SS – statistically significant; WMD – weighted mean difference Key: * study duration 24 weeks, ł strength of evidence was rated by DERP				

Table 3. Dual Antidiabetic Therapy (Not in Fixed Dose Combination Product).[1]

Comparison	Study Quality* (number of studies)	Outcome	Results	Strength of Evidence ł
Exenatide 2 mg weekly + dapagliflozin 10 mg daily **vs.** **exenatide 2 mg weekly** **or** **dapagliflozin 10 mg** (patients on background metformin)	Fair (1)	Percent of patients with HbA1c of <7%	DT: 45% exenatide: 27% dapagliflozin: 19% DT vs. exenatide: ARR 18%/NNT 6 P<0.001; *CI not provided* DT vs. dapagliflozin: ARR 26%/NNT 4 P<0.001; *CI not provided*	Not provided
Linagliptin 5 mg + metformin low dose (ld) metformin (1000 mg/day) **or** **linagliptin 5 mg + high-dose (hd) metformin (2000 mg/day)**	Good (1)	Percent of patients with HbA1c of <7%	linagliptin + ld metformin: 56.7% linagliptin + hd metformin: 56.3% P=NS	Not provided

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; DT – dual therapy; HbA1c – hemoglobin A1c; MD – mean difference; NNT – number needed to treat; NS – non-significant
Key: * study duration 14-28 weeks, ł strength of evidence was rated by DERP

Newer Diabetes Medications compared with Metformin

Comparisons between newer diabetes medications and metformin were identified in 20 studies lasting 12-26 weeks in a majority of studies. Studies were done primarily in patients without significant comorbidities (**Table 4**).

Table 4. Newer Diabetes Medications compared with Metformin.[1]

Comparison	Study Quality^ (number of studies)	Outcome	Results	Strength of Evidenceł
DPP-4 Inhibitors compared with Metformin				
Linagliptin 5 mg vs. metformin 500 mg twice daily (M500) or metformin 1000 mg twice daily (M1000)	Fair (2)	HbA1c reduction from baseline	linagliptin: -1.29% M1000: -2.07% linagliptin vs. M1000: MD -0.60% (95% CI, -0.88 to -0.32) linagliptin vs. M500: NS	Low
Sitagliptin 100 mg vs. metformin 2000 mg	Fair (3)	HbA1c reduction from baseline	Meta-analysis of trials 24-26 weeks*: metformin vs sitagliptin: WMD -0.30% (95% CI, -0.52 to -0.09)	Moderate
Saxagliptin 5 mg vs. metformin 2000 mg (uptitrated from 1500 mg)	Fair (2)	HbA1c reduction from baseline	saxagliptin 5 mg vs. metformin: WMD -0.31% (95% CI, -0.74% vs. 0.13) P=NS	Low
GLP-1 agonists compared to metformin				
Exenatide XR 2 mg vs. metformin 2000 mg	Fair (1)	HbA1c reduction from baseline	exenatide XR: -1.53% metformin: -1.48% P=0.62; *CI not provided*	Low
Dulaglutide 0.75 mg or 1.5 mg vs. metformin 1500-2000mg	Fair (1)	Percent of patients with HbA1c of <7%	dulaglutide 0.75 mg: 63% dulaglutide 1.5 mg: 62% metformin: 54% P=0.02 for both comparisons; *CI not provided*	Low
SGLT2 Inhibitors Compared with Metformin				
Dapagliflozin 5 mg and 10 mg vs. metformin XR	Fair (3)	HbA1c reduction from baseline	dapagliflozin 5 mg vs. metformin XR: WMD -0.12% (95% CI, -0.15 to -0.08) dapagliflozin 10 mg vs. metformin XR:	Low

			WMD -0.11% (95% CI, -0.11 to -0.05)	
Empagliflozin 10 mg or 25 mg vs. metformin	Fair (2)	HbA1c reduction from baseline	*Study 1* empagliflozin 10mg: -0.50% empagliflozin 25 mg: -0.60% metformin: -0.70% *P-values and CI not provided* *Study 2* empagliflozin 10mg: -1.36% empagliflozin 25 mg: -1.35% metformin: -1.47% *P-values and CI not provided*	Moderate
Canagliflozin 100 mg or 300 mg vs. metformin ER	Fair (1)	Percent of patients with HbA1c of <7%	canagliflozin 100 mg: 39% canagliflozin 300 mg: 43% metformin ER: 43% *comparisons not SS, p-values not provided*	Low
Abbreviations: CI – confidence interval; HbA1c – hemoglobin A1c; ER – extended release; MD – mean difference; NS – non-significant: SS – statistically significant; WMD – weighted mean difference				
Key: * additional trials support pooled results but were not included due to significant trial heterogeneity, ^18-52 weeks, ł strength of evidence was rated by DERP				

Subgroup Analyses

- Empagliflozin, canagliflozin and dapagliflozin were associated with a higher incidence of genital infections compared to sitagliptin, saxagliptin or linagliptin which was consistent for males and females. The relative risk was 3.91 (95% CI, 1.92 to 7.99) for females and 3.62 (95% CI, 2.20 to 5.97) for males.[1]

New Guidelines:

The American Diabetes Association (ADA) published their annual Standards of Medical Care in Diabetes for 2018 in January.[34] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

A second guidance on the cardiovascular management of non-pregnant adults with diabetes was published by the ADA in April of 2018.[20] However, details are not included due to the same limitations cited above for the Standards of Medical Care in Diabetes.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2018.[35] Similar to the ADA recommendations, this management algorithm was authored by a majority of authors with industry affiliations and the methods for guideline development were not disclosed. Due to these limitations, the algorithm will not be presented.

The International Diabetes Federation (IDF) published clinical practice recommendations for managing type 2 diabetes in primary care.[36] Recommendations were based on worldwide diabetes treatment guidelines. Guidelines were graded by the Agree II instrument with scores ranging from 36-97%. The practice recommendations were based a combination of guidance that has met criteria for inclusion into Drug Use Research and Management documents and on guidelines that are not included due to methodological flaws. Therefore, the IDF recommendations will not be included in detail.

New Formulations or Indications:
Exenatide ER once weekly single dose auto-injector formulation (Bydureon BCise™) is a GLP-1 RA approved by FDA in October 2017 for patients with T2DM as an adjunct to diet and exercise.[37] This new formulation joins the currently available once weekly injectable exenatide ER formulation, Bydureon™, and is thought to be easier for patients to administer. A noninferiority trial in T2DM patients comparing Bydureon BCise (BB) to exenatide, as add-on to oral antidiabetic therapy, found similar HbA1c lowering, -1.39% to -1.03%, respectively. In a second comparison of BB to sitagliptin, BB was found to non-significantly lower HbA1c by -0.28% (95% CI, -0.62 to 0.02) more than sitagliptin, in patients taking metformin.[37] Most common adverse reactions with BB were injection-site nodules and nausea. Similar to other GLP-1 RAs BB has a black box warning for risk of thyroid c-cell tumors.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 183 citations were manually reviewed from the initial literature search. After further review, 182 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 trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Safety Outcome	Trial Methodology	Results	Limitations
Holman, et al[16]	Exenatide ER 2mg weekly vs. Placebo weekly 3.2 years	Adult patients with T2DM (n=14,752), 73% with previous CV disease	Composite outcome of first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	- Primary outcome on ITT population - non-inferiority margin set at 1.3 for the upper limit of the CI for the HR - Supportive analysis was done on PP population	Exenatide: 11.4% Placebo: 12.2% HR 0.91 (95% CI, 0.83 to 1.00) P<0.001 for noninferiority and P=0.06 for superiority	- Primary outcome done on ITT population which biases results in favor of no difference between treatments in trials with a NI design; however, PP population results supported noninferiority findings. - Higher use of SGLT-2 inhibitors (which may have CV benefit in exenatide group - Higher use of lipid lowering medication, including statins, in the exenatide group - Results applicable to patients with previous CV disease - Industry funded
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; ITT – intention-to-treat; NI - non-inferiority; PP – per protocol; T2DM – type 2 diabetes mellitus						

NEW DRUG EVALUATION: ertugliflozin (Steglatro™)

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.

Clinical Efficacy:

Once-daily ertugliflozin is a SGLT-2 inhibitor approved by the FDA in 2017 as monotherapy and in fixed dose combination products with metformin (Segluromet™) or sitagliptin (Steglujan™). Approval for ertugliflozin was based off of seven trials in patients with T2DM; five placebo-controlled, two active-treatment comparisons (glimepiride and sitagliptin).[10–15] The CV effects of ertugliflozin are currently being studied with a completion date in 2019. One study specifically evaluated ertugliflozin in patients with moderate renal impairment and changes in HbA1c were not found to be significantly different from placebo.[38] Therefore, ertugliflozin is not recommended in these patients and this trial will not be critically evaluated. All trials had similar inclusion criteria of enrolling adult patients with T2DM that were predominately healthy with normal renal function.[9]

Efficacy Trials

Placebo-controlled comparisons of ertugliflozin were studied for 26 weeks (1 trial had an extension study without formal comparison data) in adult patients with T2DM. Three trials were monotherapy comparisons with or without background therapy and one trial compared ertugliflozin/sitagliptin to placebo.[10–13] All trials were multicenter, double-blind, randomized controlled trials enrolling 291-621 patients. Reductions in the primary endpoint of HbA1c lowering from baseline were -0.7% for ertugliflozin 5 mg and -0.8% to -0.9% for ertugliflozin 15 mg compared to placebo.[10–12] For the combination comparison of ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg versus placebo, HbA1c decreased at week 26, -1.6%, -1.7% and -0.4%, respectively.[13] Ertugliflozin was found to be superior to placebo in all placebo-controlled study comparisons (P<0.05).

Ertugliflozin was compared to sitagliptin in patients with T2DM inadequately controlled on metformin for 52 weeks in a phase 3, double-blind, multicenter, fair quality, randomized controlled trial. Patients (n=1233) were randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg/sitagliptin 100 mg (E5/S) or ertugliflozin 15 mg/sitagliptin 100 mg (E15/S).[15] Enrolled patients were a mean age of 55 years, and baseline HbA1c of 8.6%. In contrast to other trials, this trial included a shorter duration of diabetes history, 5 years. The distribution of males and females enrolled in each group were similar except for the sitagliptin group which had 62% males compared to 51% in the other four groups. North American sites represented 30% of the patient population and Europe had the highest patient representation with approximately 40% of patients. The study was funded by industry and had a low risk of bias for all other study domains except for an unclear risk of detection bias. The primary endpoint was change from baseline in HbA1c at 26 weeks, patients were followed for a total of 52 weeks (**Table 6**). HbA1c reduction favored the combination of E5/S compared to ertugliflozin (LSMC -0.5%; 95% CI -0.6 to -0.3; P<0.001) and for E15/S compared to ertugliflozin (LSM -0.4%; 95% CI, -0.6 to -0.3; P<0.001).[15] Combination therapy was also more effective at reducing HbA1c compared to sitagliptin monotherapy; E5/S vs. sitagliptin (LSM -0.4%; 95% CI, -0.6 to -0.3; P<0.001) and E15/S vs. sitagliptin (LSM -0.5%; 95% CI, -0.6 to -0.3; P<0.001).[15] The percent of patients obtaining an HbA1c less than 7% and amount of weight loss also favored combination therapy (**Table 6**). The percent of patients with an HbA1c less than 7% decreased in all groups at 52 weeks; however, least square mean differences between groups for HbA1c reductions were similar to week 26 results and reductions were still clinically significant.

Table 6. Efficacy Outcomes for Ertugliflozin versus Sitagliptin.[15]

Treatment Group	HbA1c Reduction from Baseline	LS Mean Difference in HbA1c	Patients with HbA1c <7.0%	Weight Change
Ertugliflozin 5 mg	-1.0%		26%	-2.7 kg
Ertugliflozin 15 mg	-1.1%		32%	-3.7 kg
Sitagliptin 100 mg	-1.1%		33%	-0.7 kg
Ertugliflozin 5 mg/sitagliptin 100 mg	-1.5%	*E5/S100 vs. ertugliflozin* -0.5 (95% CI, -0.6 to -0.3) P<0.001 *E5/S100 vs. sitagliptin* -0.4 (95% CI, -0.6 to -0.3) P<0.001	52%	-2.5 kg
Ertugliflozin 15 mg/sitagliptin 100 mg	-1.5%	*E15/S100 vs. ertugliflozin* -0.4 (95% CI, -0.6 to -0.3) P<0.001 *E15/S100 vs. sitagliptin* -0.5 (95% CI, -0.6 to -0.3) P<0.001	49%	-2.9 kg

Limitations:

- Unclear risk of detection bias.
- Funded by industry.
- Short term trial with insufficient data on long-term efficacy and safety outcomes.
- Patients had a 5-year history of diabetes which is shorter than other diabetic treatment studies which may bias the results to increased HbA1c lowering due to less time of attenuation to therapy glucose lowering over time.

In a second active comparison trial ertugliflozin 5 mg or 15 mg was compared to glimepiride (mean dose 3 mg) in a noninferiority, phase 3, double-blind, randomized trial in 1326 patients who were inadequately controlled on metformin.[14] Glimepiride doses were initiated at 1 mg and titrated to a max dose of 8 mg based on a maximum tolerated dose. Patients were studied for 52 weeks and in a second phase of 52 weeks, which is published separately. Patients included in the trial were a mean age of 58 years with a 7.5-year history of T2DM. Baseline HbA1c was lower than comparator studies, with a mean value of 7.8%. Seventy-three percent of the participants were Caucasian and a majority were classified as obese based on body mass index (BMI). The study was industry funded and included patients from US sites but the specific number was not provided. The primary efficacy outcome was change in HbA1c from baseline. Noninferiority was determined if the upper bound of the 95% CI for HbA1c did not exceed 0.3%, which is a commonly accepted delta for trials evaluating antidiabetic therapy. Full analysis set was used for the primary outcome analysis. Ertugliflozin 15 mg was found to be noninferior to glimepiride (**Table 7**). The 5 mg dose of ertugliflozin had a value higher than 0.3% for the upper CI, and therefore was inferior to glimepiride. The per protocol analysis found both doses of ertugliflozin to be noninferior to glimepiride, supporting the primary outcome for the 15 mg dose. Weight loss favored ertugliflozin by a mean difference compared to glimepiride of -3.0 to -3.4 kg ($p<0.001$).[15]

Table 7. Efficacy Outcomes for Ertugliflozin versus Glimepiride.[14]

Treatment Group	HbA1c Reduction from baseline	LS Mean Difference	Weight Change
Ertugliflozin 5 mg	-0.6%	0.2% (95% CI, 0.1 to 0.3) *inferior*	-2.7 kg
Ertugliflozin 15 mg	-0.6%	0.1% (95% CI, -0.0 to 0.2) *noninferior*	-3.7 kg
Glimepiride (3 mg mean dose)	-0.7%	NA	-0.7 kg

Abbreviations: CI – confidence interval; NA = not applicable

Limitations:

- Analysis of full analysis set can bias results in favor of no difference (noninferiority) between treatments; however, the per protocol population supported noninferiority findings of the 15 mg ertugliflozin dose.
- Unknown external validity to US Medicaid patients without additional details on study sites.
- Insufficient details on detection blinding.
- High attrition rate (19-24%) could bias results in favor of no difference between treatments.
- Inherent conflict of interest with trial funding by manufacturer.

Clinical Safety:

The most common adverse effects seen in 2% of patients treated with ertugliflozin compared to placebo were female and male genital infections, urinary tract infections, and headache (**Table 8**).[9] Hypoglycemia was rare in placebo-controlled studies with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, 2.6%, 2.6% and 0.7%, respectively.

Table 8. Common Adverse Reactions Occurring in Patients Treated with Ertugliflozin Compared to Placebo.[9]

Adverse Reaction	Ertugliflozin 5 mg (N=519)	Ertugliflozin 15 mg (N=510)	Placebo (N=515)
Female genital mycotic infections	9%	12%	3%
Male genital mycotic infections	4%	4%	0.4%
Urinary tract infections	4%	4%	4%
Headache	4%	3%	2%
Vaginal pruritus	3%	2%	0.4%

As with other SGLT-2 inhibitors, ertugliflozin has warnings for hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, increased low-density lipoprotein cholesterol (LDL-C) and hypoglycemia when used with insulin or insulin secretagogues. Ertugliflozin was found to have a higher incidence of lower limb amputations in patients who were considered at-risk subjects (e.g., preexisting CV disease, cerebrovascular and/or peripheral arterial disease). Across the phase 3 trials the risk was 1 (0.1%) in non-ertugliflozin treated patients, 3 (0.2%) in the ertugliflozin 5 mg group and 8 (0.5%) in the ertugliflozin 15 mg group.[9]

Table 9. Ertugliflozin Pharmacology and Pharmacokinetic Properties.[9]

Parameter	
Mechanism of Action	Blocks reabsorption of glucose from the glomerular filtrate from entering back into the circulation by blocking the SGLT2 transporter. This results in reduced renal absorption of filtered glucose and lowers the renal threshold for glucose causing an increase in urinary glucose excretion.
Oral Bioavailability	100%
Distribution and Protein Binding	Highly protein bound (93.6%)
Elimination	41% in the feces and 50% urine
Half-Life	16.6 hours
Metabolism	UGT1A9 and UGT2B7-mediated O-glucuronidation. CYP-mediated (oxidative) metabolism is around 12%.

NEW DRUG EVALUATION: semaglutide (Ozempic®)

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.

Clinical Efficacy:
Semaglutide is a once-weekly GLP-1 RA indicated for use in patients with T2DM, bringing the number of GLP-1 RAs to seven. Approval of semaglutide was based on six multi-national efficacy trials, 2 trials conducted in Japan and a CV safety trial. In the efficacy studies semaglutide was compared to placebo, exenatide, insulin glargine, sitagliptin and dulaglutide in trials lasting 30-56 weeks.[3–8] To minimize GI adverse events, the dose of semaglutide was initiated at 0.25 mg weekly and increased to 0.5 mg after 4 weeks. Patients randomized to receive semaglutide 1.0 mg were titrated after up after an additional 4 weeks. The primary efficacy endpoint of HbA1c change from baseline was the same for all efficacy trials. Two trials comparing semaglutide to placebo (one with background basal insulin and one in treatment naïve patients) were conducted with similar findings to active-comparator trials.[7,8]

Efficacy Trials
Six semaglutide efficacy studies have been published; two placebo-controlled and four noninferiority, active treatment comparison trials. These types of trials are excluded if possible, due to limitations outlined in DURM methods, but are required for inclusion for this NDE due to lack of higher quality evidence. Two additional trials including only Japanese patients from Japan were excluded from the NDE due to low external validity.[39,40] All trials were funded by industry.

Semaglutide 0.5 mg or 1.0 mg was compared to daily sitagliptin 100 mg in patients (n=1231) with T2DM inadequately controlled on metformin, TZDs or both.[5] The trial was a multi-center, parallel group, noninferiority study. Patients were treated for 56 weeks using a double-dummy design to preserve blinding. Obese adult T2DM patients with a mean age of 55 years and baseline HbA1c of 8.1% from non-US sites were enrolled. Semaglutide was considered noninferior to sitagliptin if the upper boundary of the 95% CI of the estimated treatment difference was below the noninferiority margin of 0.3%. Results were analyzed for the ITT population and no analysis of the per protocol population was done. The difference in HbA1c lowering between semaglutide 0.5 mg and sitagliptin was -

0.77% (95% CI, -0.92 to -0.62; P<0.001) and -1.06% (95% CI -1.21 to -0.91) with semaglutide 1.0 mg (p<0.001 for both comparisons for noninferiority and superiority).[5] The proportion of patients who obtained an HbA1c less than 7% was 63% with semaglutide 0.5 mg, 74% with semaglutide 1.0 mg and 27% with sitagliptin. Body weight was decreased by -2.25 kg more with semaglutide 0.5 mg and -4.20 kg more with semaglutide 1.0 mg (p<0.001 for both comparisons).

A second efficacy trial was an open-label comparison between semaglutide 0.5 mg and 1.0 mg and insulin glargine in adult patients with T2DM inadequately controlled on metformin, with or without sulfonylureas, who were insulin naïve.[3] The trial was a noninferiority, parallel group, multicenter, phase 3, randomized study of 1089 participants. Patients receiving semaglutide were titrated up on a fixed-dose escalation regimen and glargine was initiated at 10 IU/daily and titrated weekly based on pre-breakfast self-monitored glucose levels. Patients were a mean age of 56 years, baseline HbA1c of 8.2%, mean BMI of 33.0 kg/m^2 and 77% were Caucasian. The primary outcome was based on a modified intent to treat (mITT) population and semaglutide was considered noninferior to glargine if the noninferiority margin was less than 0.3%. The decrease in HbA1c from baseline was -1.21% with semaglutide 0.5 mg, -1.65% with semaglutide 1.0 mg and -0.83% with glargine. Treatment differences were the following: semaglutide 0.5 mg -0.38% (95% CI, -0.52 to -0.24); semaglutide 1.0 mg -0.81% (95% CI, -0.96 to -0.67) (p<0.001 for both comparisons).[3] Fifty-seven patients receiving semaglutide 0.5 mg obtained a HbA1c less than 7% compared to 73% taking semaglutide 1.0 mg and 38% using glargine (P<0.0001 for both comparisons). Differences in weight loss favoring semaglutide ranged from 4.6 kg to 6.3 kg compared to glargine. Severe hypoglycemia was statistically and clinically significantly more common with glargine (11%) compared with semaglutide 0.5 mg (4%) and semaglutide 1.0 mg (6%). Withdrawals due to adverse events were 6% with semaglutide 0.5 mg, 8% with semaglutide 1.0 mg and 1% with glargine. Adverse GI events accounted for the most common reason for discontinuation.

An additional open-label trial comparing semaglutide 1.0 mg to once-weekly exenatide ER 2.0 mg was studied in patients (n=813) taking 1-2 oral antidiabetic drugs (OADs) and followed for 56 weeks.[4] Patients were a mean age of 57 years, baseline HbA1c of 8.3%, mean BMI of 34 kg/m^2, 97% were taking metformin and 48% were taking sulfonylureas. Similar to other trials, the noninferiority margin was set at 0.3%. The mean change in HbA1c from baseline was -1.5% for semaglutide and -0.9% for exenatide ER (ETD -0.62%; 95% CI, -0.80 to -0.44; P<0.001 for noninferiority and superiority).[4] An upper bound of 0.44% of the confidence interval suggests a clinically relevant change in HbA1c. Other studies of exenatide ER have demonstrated a HbA1c lowering of 1-2%, suggesting noninferiority to semaglutide but not superiority.[41,42] Body weight was decreased more with semaglutide compared to exenatide ER (ETD -3.78 kg; 95% CI, -4.58 to -2.98; P<0.0001). Adverse GI effects were common and occurred in 42% of semaglutide treated patients and 33% of exenatide ER treated patients. The incidence of injection site reactions was more common with exenatide ER compared to semaglutide, 22.0% versus 1.2%, respectively.[4]

An open-label, multicenter, phase 3, noninferiority trial compared once weekly semaglutide to once weekly dulaglutide in 1201 adult patients with T2DM and on metformin monotherapy.[6] Patients were an average age of 56 years with a baseline HbA1c of 8.2% and predominately Caucasian. Patients were randomized to semaglutide 0.5 mg, semaglutide 1.0 mg, dulaglutide 0.75 mg or dulaglutide 1.5 mg. Comparisons were between the lower doses of semaglutide and dulaglutide and the higher doses of semaglutide and dulaglutide. The analysis was done on the ITT population with an HbA1c noninferiority margin of 0.4%. The primary endpoint was change in HbA1c from baseline at 40 weeks with a secondary outcome analysis of bodyweight. Results for HbA1c lowering and weight are presented in **Table 10**. The number of patients obtaining an HbA1c of less than 7% ranged from 68%-79% for semaglutide and 52%-67% for dulaglutide, which statistically favored semaglutide for low (ARR 16%/NNT 7) and high dose comparisons (ARR 12%/NNT 9). An analysis of HbA1c lowering in the per protocol population found similar results as the ITT findings; ETD -0.42 (95% CI, -0.58 to -0.26; P<0.001) for the low dose comparison and ETD -0.38 (95% CI, -0.54 to -0.22; P<0.001) for the high dose comparison.

Table 10. Efficacy Outcomes for Once-weekly Semaglutide versus Once-Weekly Dulaglutide.[6]

Treatment Group	HbA1c Reduction from baseline	Estimated Treatment Difference in HbA1c	Weight Change
Semaglutide 0.5 mg (S.5)	-1.5%	*S.5 vs. D.75:* -0.40% (95% CI, -0.55 to -0.25) P <0.0001	-4.6 kg
Dulaglutide 0.75 mg (D.75)	-1.1%	*noninferior and superior*	-2.3 kg
Semaglutide 1.0 mg (S1)	-1.8%	*S1 vs. D1.5* -0.41% (95% CI, -0.57 to -0.25) P<0.0001 *noninferior and superior*	-6.5 kg
Dulaglutide 1.5 mg (D1.5)	-1.4%		-3.0 kg

Abbreviations: CI – confidence interval; HbA1c – hemoglobin A1c

An oral formulation of semaglutide is being studied and phase 2 studies have shown efficacy in HbA1c lowering when compared to placebo and subcutaneous semaglutide.[43] Submission for regulatory approval of the oral formulation is expected in 2019.

CV Safety Trial

Semaglutide 0.5 mg and 1.0 mg were compared to placebo in patients 50 years and older with T2DM and a history of CV disease or chronic kidney disease or 60 years and older with risk factors for CV disease in a phase 3, double-blind, double-dummy, multi-center, noninferiority, randomized controlled trial (**Table 13**).[2] Patients were a mean age of 65 years, had a 14-year history of T2DM, a baseline HbA1c of 8.7% and 34% were from US treatment sites. Comorbidities of included patients were: hypertension (90%), cholesterol abnormalities (31%), coronary artery disease (23%), obesity (24%), myocardial ischemia (23%) and osteoarthritis (20%).[2,44] Eighty-three percent of patients had CV disease, kidney disease or both. A majority of patients were also taking angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and other antidiabetic therapies, which was similar between groups. The noninferiority margin was set at 1.8 for the upper boundary of the 95% CI of the hazard ratio. This was chosen based on data from other studies which showed a 1.8% event rate of the primary outcome to be considered conservative but not low. The primary outcome was measured in the ITT population for the composite endpoint of CV death, nonfatal MI or nonfatal stroke.

The composite primary outcome occurred in 6.6% of patients taking semaglutide doses compared to 8.9% in the placebo group (HR 0.74; 95% CI, 0.58 to 0.95; P<0.001 for noninferiority).[2] The upper bound of the CI was less than 1.8 in the semaglutide group, supporting noninferiority. Additionally, the upper bound of the HR was 0.95 which is an acceptable finding indicating no increased risk of CV risk with semaglutide, which is more important than the point estimate in noninferiority trials. The study was not powered for superiority so superiority testing was not pre-specified. The decrease seen with semaglutide was driven by the reduction in stroke risk compared to placebo, 1.6% vs. 2.7% (HR 0.61; 95% CI, 0.38 to 0.99; P=0.04).[2] The incidence of nonfatal MI was lower with semaglutide compared to placebo (MD -1.0%; P=0.12) but unlikely to be clinically impactful. Death due to CV causes was 2.7% with semaglutide compared to 2.8% with placebo (HR 0.98; 95% CI, 0.65 to 1.48; P=0.92). The estimated number of patients that would need to be treated over 24 months to prevent one event was 45, as estimated by Kaplan-Meier analysis. A subgroup analysis of patients with only CV risk factors demonstrated no benefit of semaglutide therapy compared to placebo based on a HR of 1.0 (95% CI, 0.41 to 2.46) and there was no benefit demonstrated in a subgroup analysis in patients from US treatment sites (HR 0.87; 95% CI, 0.57 to 1.34).

Limitations:

- All studies were funded by industry.
- Use of ITT analysis for the primary outcome can bias the results in favor of no difference between groups when using a noninferiority design. A per protocol analysis would be a more appropriate and well-designed non-inferiority studies will provide both analyses.
- Study methods suggest optimization of approved antidiabetic therapies to obtain effective glycemic control in both groups in the CV study; however, HbA1c values were 0.7% to 1.0% lower in patients treated with semaglutide compared to placebo (P<0.001) which could bias results in favor semaglutide due of evidence of benefit with improved glucose levels.

Clinical Safety:

As with all GLP-1 RAs there is a boxed warning due to the risk of thyroid c-cell tumors. The most common adverse reactions for semaglutide seen in clinical trials were: nausea, vomiting, diarrhea, constipation and abdominal pain (**Table 11**).[24] The risk of hypoglycemia was 2-4% in clinical trials with semaglutide compared to 0% for placebo. No episodes of severe hypoglycemia were observed in either group. Semaglutide was associated with a higher incidence of withdrawals due to adverse events primarily due to GI disorders. Discontinuation rates due to adverse events ranged from 6-10% for semaglutide compared to 1-3% for placebo. Mild increases in lipase and amylase concentrations seen with semaglutide and other GLP-1 RAs warrant continual monitoring to ensure long-term use does not increase the risk of pancreatitis.

Unlike other GLP-1 RAs there was an increased risk for diabetic retinopathy complications in 3% of semaglutide-treated patients compared to 1.8% of placebo-treated patients (HR 1.76; 95% CI, 1.11 to 2.78).[44] A rapid decrease in glucose levels may be the causative reason for the increased risk; however, improved glucose control has previously been shown in other studies to decrease the risk of microvascular complications. Further studies are needed to provide clarity on the long-term risk benefit of semaglutide on microvascular outcomes.

Table 11. Adverse Reactions for Semaglutide compared to Placebo Reported in ≥5 % of Patients.[24]

Adverse Reaction	Semaglutide 0.5 mg (N=260)	Semaglutide 1.0 mg (N=261)	Placebo (N=262)
Nausea	16%	20%	6%
Vomiting	5%	9%	2%
Diarrhea	9%	9%	2%
Abdominal Pain	7%	6%	5%
Constipation	5%	3%	2%

Table 12. Semaglutide Pharmacology and Pharmacokinetic Properties.[24]

Parameter	
Mechanism of Action	GLP-1 analogue that lowers glucose by insulin secretion and reduces glucagon secretion.
Oral Bioavailability	NA
Distribution and Protein Binding	Highly (>99%) protein bound.

Elimination	Renal and hepatic
Half-Life	1 week
Metabolism	Proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

Abbreviations: NA – not applicable

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Number of patients obtaining an A1c <7%
2) Mortality
3) Macrovascular outcomes
4) Microvascular outcomes
5) Serious adverse events
6) Study withdrawals due to an adverse event

Primary Study Endpoint:

1) Composite of CV death, nonfatal MI, or nonfatal stroke

Table 13. Comparative Evidence Table for Semaglutide.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Marso, et al[2] PC, PG, DB, RCT	1. Semaglutide 0.5 mg or 1.0 mg weekly 2. Placebo 0.5 mg or 1.0 mg Dose was initiated at 0.25 mg weekly and titrated after 4 weeks until maintenance dose was reached 104-week treatment phase and 109-week observation	Demographics: - Mean age: 65 years - Male: 61% - Duration of T2DM: 14 years - Baseline HbA1c: 8.7% - Established CV disease or kidney disease or both: 83% Key Inclusion Criteria: - T2DM - ≥ 50 years old with established CV disease or chronic kidney disease stage 3 or higher or ≥ 60 years with ≥ 1 CV risk factor	ITT: 1. 1648 2. 1649 PP: 1. 1623 2. 1609 Attrition: 1. 1.5% 2. 2.4%	Primary Endpoint: Composite of CV death, nonfatal MI, or nonfatal stroke: Semaglutide: 108 (6.6%) Placebo: 146 (8.9%) HR 0.74 (95% CI, 0.58 to 0.95) P<0.001 for non-inferiority Secondary Endpoints: CV Death: Semaglutide: 44 (2.7%) Placebo: 46 (2.8%) HR 0.98 (0.65 to 1.48) P=0.92 Nonfatal MI: Semaglutide: 47 (2.9%) Placebo: 64 (3.9%) HR 0.74 (95% CI, 0.51 to 1.08) P=0.12	NA for all	Withdrawals due to Adverse Events: Semaglutide: 107 (13%) Placebo: 55 (7%) Gastrointestinal Disorders: Semaglutide: 425 (52%) Placebo: 292 (36%) Severe or Symptomatic Hypoglycemia: Semaglutide: 185 (23%) Placebo: 175 (21%) Serious Adverse Events: Semaglutide: 283 (34%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1:1:1 by an interactive voice web response system. Performance Bias: (low) Placebo was volume-matched to maintain blinding. Detection Bias: (low) Data analysis done by manufacturer. Outcomes were adjudicated by an independent committee that was blinded to treatment assignment. Attrition Bias: (low) Attrition was low in both groups. Analysis was done on ITT population. Reporting Bias: The study was funded by the manufacturer. **Applicability**: Patient: Eighty-three percent of patients had established CV disease, kidney disease of both and 17% had CV risk factors. Patients were allowed to be on other OADs. Eighty-four percent of patients were also taking ARBs or ACE inhibitors. Seventy-seven percent were taking lipid lowering medications.

		- HbA1c >7% - ≤ 2 antihyperglycemic drugs +/- insulin <u>Key Exclusion Criteria</u>: - Treatment with a DPP-4 inhibitor within 30 days of screening - Treatment with a GLP-1 RA or insulin (other than basal or premixed) within 90 days of screening - Acute coronary or cerebral vascular event - Dialysis		Nonfatal Stroke: Semaglutide: 27 (1.6%) Placebo: 44 (2.7%) HR 0.61 (95% CI, 0.38 to 0.99) P=0.04 <u>Retinopathy Complications</u>: Semaglutide: 50 (3%) Placebo: 29 (1.8%) HR 1.76 (95% CI, 1.11 to 2.78) P=0.02 <u>New or Worsening Nephropathy</u>: Semaglutide: 62 (3.8%) Placebo: 100 (6.1%) HR 0.64 (95% CI, 0.46 to 0.88) P=0.005		Placebo: 314 (38%) 95% CI and p-values not reported		<u>Intervention</u>: FDA approved dose of semaglutide. <u>Comparator</u>: Placebo comparison adequate to determine no excess CV risk of semaglutide. <u>Outcomes</u>: Composite outcome of CV death, nonfatal MI or nonfatal stroke required by FDA. <u>Setting</u>: Twenty countries and 230 sites. 34% from US sites.
<u>Abbreviations</u> [alphabetical order]: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double blind; HbA1c = hemoglobin A1c; HR = hazard ratio; ITT = intention to treat; mitt = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OAD = oral antidiabetic therapy; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus								

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Appendix 1: Current Preferred Drug List

GLP-1 Receptor Agonists

Generic	Brand	FormDesc	PDL
EXENATIDE	BYETTA	PEN INJCTR	Y
ALBIGLUTIDE	TANZEUM	PEN INJCTR	N
DULAGLUTIDE	TRULICITY	PEN INJCTR	N
EXENATIDE MICROSPHERES	BYDUREON	VIAL	N
EXENATIDE MICROSPHERES	BYDUREON BCISE	AUTO INJCT	N
EXENATIDE MICROSPHERES	BYDUREON PEN	PEN INJCTR	N
LIRAGLUTIDE	VICTOZA 2-PAK	PEN INJCTR	N
LIRAGLUTIDE	VICTOZA 3-PAK	PEN INJCTR	N
LIXISENATIDE	ADLYXIN	PEN INJCTR	N

SGLT-2 Inhibitors

Generic	Brand	FormDesc	PDL
CANAGLIFLOZIN	INVOKANA	TABLET	N
CANAGLIFLOZIN/METFORMIN HCL EXTENDED RELEASE	INVOKAMET XR	TAB BP 24H	N
CANAGLIFLOZIN/METFORMIN HCL	INVOKAMET	TABLET	N
DAPAGLIFLOZIN PROPANEDIOL	FARXIGA	TABLET	N
DAPAGLIFLOZIN/METFORMIN HCL	XIGDUO XR	TAB BP 24H	N
DAPAGLIFLOZIN/SAXAGLIPTIN HCL	QTERN	TABLET	N
EMPAGLIFLOZIN	JARDIANCE	TABLET	N
EMPAGLIFLOZIN/LINAGLIPTIN	GLYXAMBI	TABLET	N
EMPAGLIFLOZIN/METFORMIN HCL	SYNJARDY XR	TAB BP 24H	N
EMPAGLIFLOZIN/METFORMIN HCL	SYNJARDY	TABLET	N

DPP-4 Inhibitors

Generic	Brand	FormDesc	PDL
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
DAPAGLIFLOZIN/SAXAGLIPTIN HCL	QTERN	TABLET	N
EMPAGLIFLOZIN/LINAGLIPTIN	GLYXAMBI	TABLET	N
LINAGLIPTIN	TRADJENTA	TABLET	N
LINAGLIPTIN/METFORMIN HCL	JENTADUETO XR	TAB BP 24H	N
LINAGLIPTIN/METFORMIN HCL	JENTADUETO	TABLET	N
SAXAGLIPTIN HCL	ONGLYZA	TABLET	N
SAXAGLIPTIN HCL/METFORMIN HCL	KOMBIGLYZE XR	TBMP 24HR	N
SITAGLIPTIN PHOS/METFORMIN HCL	JANUMET XR	TBMP 24HR	N

Miscellaneous Antidiabetic Agents

Generic	Brand	FormDesc	PDL
METFORMIN HCL	GLUCOPHAGE XR	TAB ER 24H	Y
METFORMIN HCL	METFORMIN HCL ER	TAB ER 24H	Y
METFORMIN HCL	GLUCOPHAGE	TABLET	Y
METFORMIN HCL	METFORMIN HCL	TABLET	Y
ACARBOSE	ACARBOSE	TABLET	N
ACARBOSE	PRECOSE	TABLET	N
GLIPIZIDE/METFORMIN HCL	GLIPIZIDE-METFORMIN	TABLET	N
GLYBURIDE/METFORMIN HCL	GLUCOVANCE	TABLET	N
GLYBURIDE/METFORMIN HCL	GLYBURIDE-METFORMIN HCL	TABLET	N
METFORMIN HCL	RIOMET	SOLUTION	N
METFORMIN HCL	FORTAMET	TAB ER 24	N
METFORMIN HCL	METFORMIN HCL ER	TAB ER 24	N
METFORMIN HCL	GLUMETZA	TABERGR24H	N
METFORMIN HCL	METFORMIN HCL ER	TABERGR24H	N
MIGLITOL	GLYSET	TABLET	N
MIGLITOL	MIGLITOL	TABLET	N
NATEGLINIDE	NATEGLINIDE	TABLET	N
NATEGLINIDE	STARLIX	TABLET	N

PRAMLINTIDE ACETATE	SYMLINPEN 120	PEN INJCTR	N
PRAMLINTIDE ACETATE	SYMLINPEN 60	PEN INJCTR	N
REPAGLINIDE	PRANDIN	TABLET	N
REPAGLINIDE	REPAGLINIDE	TABLET	N
REPAGLINIDE/METFORMIN HCL	REPAGLINIDE-METFORMIN HCL	TABLET	N

Sulfonylureas

Generic	Brand	FormDesc	PDL
GLIMEPIRIDE	AMARYL	TABLET	Y
GLIMEPIRIDE	GLIMEPIRIDE	TABLET	Y
GLIPIZIDE	GLIPIZIDE	TABLET	Y
GLIPIZIDE	GLUCOTROL	TABLET	Y
GLYBURIDE	GLYBURIDE	TABLET	Y
CHLORPROPAMIDE	CHLORPROPAMIDE	TABLET	N
GLIPIZIDE	GLIPIZIDE ER	TAB ER 24	N
GLIPIZIDE	GLIPIZIDE XL	TAB ER 24	N
GLIPIZIDE	GLUCOTROL XL	TAB ER 24	N
GLYBURIDE,MICRONIZED	GLYBURIDE MICRONIZED	TABLET	N
GLYBURIDE,MICRONIZED	GLYNASE	TABLET	N
TOLAZAMIDE	TOLAZAMIDE	TABLET	N
TOLBUTAMIDE	TOLBUTAMIDE	TABLET	N

Thiazolidinediones

Generic	Brand	FormDesc	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
PIOGLITAZONE HCL/METFORMIN HCL	ACTOPLUS MET XR	TBMP 24HR	N
ROSIGLITAZONE MALEATE	AVANDIA	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes.

Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group.

BACKGROUND: The cardiovascular effects of adding once-weekly treatment with exenatide to usual care in patients with type 2 diabetes are unknown.

METHODS: We randomly assigned patients with type 2 diabetes, with or without previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The coprimary hypotheses were that exenatide, administered once weekly, would be noninferior to placebo with respect to safety and superior to placebo with respect to efficacy.

RESULTS: In all, 14,752 patients (of whom 10,782 [73.1%] had previous cardiovascular disease) were followed for a median of 3.2 years (interquartile range, 2.2 to 4.4). A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.83 to 1.00), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety ($P<0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P=0.06$ for superiority). The rates of death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

CONCLUSIONS: Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo. (Funded by Amylin Pharmaceuticals; EXSCEL ClinicalTrials.gov number, NCT01144338 .).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to April Week 4 2018

Search Strategy:

#	Searches	Results
1	exenatide.mp.	2428
2	albiglutide.mp.	98
3	dulaglutide.mp.	120
4	exenatide microspheres.mp.	3
5	liraglutide.mp. or LIRAGLUTIDE/	1544
6	lixisenatide.mp.	202
7	canagliflozin.mp. or CANAGLIFLOZIN/	422
8	dapagliflozin.mp.	414

9	empagliflozin.mp.	485
10	sitagliptin.mp. or Sitagliptin Phosphate/	1523
11	alogliptin.mp.	320
12	saxagliptin.mp.	464
13	linagliptin.mp. or LINAGLIPTIN/	419
14	metformin.mp. or METFORMIN/	14563
15	acarbose.mp. or ACARBOSE/	2075
16	glipizide.mp. or GLIPIZIDE/	1042
17	glyburide.mp. or GLYBURIDE/	6444
18	miglitol.mp.	274
19	nateglinide.mp.	495
20	pramlintide.mp.	328
21	repaglinide.mp.	679
22	glimepiride.mp.	1061
23	chlorpropamide.mp. or CHLORPROPAMIDE/	2047
24	tolazamide.mp. or TOLAZAMIDE/	208
25	tolbutamide.mp. or TOLBUTAMIDE/	6502
26	pioglitazone.mp.	4513
27	rosiglitazone.mp.	5509
28	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 or 24 or 25 or 26 or 27	43940
29	limit 28 to (english language and humans and yr="2017 -Current")	1558
30	limit 29 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	183

Appendix 4: Prescribing Information Highlights

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

OZEMPIC (semaglutide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

INDICATIONS AND USAGE

OZEMPIC is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy (1, 5.2).
- Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis (1).

DOSAGE AND ADMINISTRATION

- Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly (2.1).
- Administer once weekly at any time of day, with or without meals (2.1).
- If a dose is missed administer within 5 days of missed dose (2.1).
- Inject subcutaneously in the abdomen, thigh, or upper arm (2.2).

DOSAGE FORMS AND STRENGTHS

Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:

- Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection (3).
- Single-patient-use pen that delivers 1 mg per injection (3).

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Known hypersensitivity to OZEMPIC or any of the product components (4).

WARNINGS AND PRECAUTIONS

- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Diabetic Retinopathy Complications: Has been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored (5.3).
- Never share an OZEMPIC pen between patients, even if the needle is changed (5.4).
- Hypoglycemia: When OZEMPIC is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.5).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.6).
- Hypersensitivity Reactions: Discontinue OZEMPIC if suspected and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with semaglutide (5.8).

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥5% of patients treated with OZEMPIC are: nausea, vomiting, diarrhea, abdominal pain and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-888-693-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Oral Medications: OZEMPIC delays gastric emptying. May impact absorption of concomitantly administered oral medications (7.2).

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

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

STEGLATRO™ (ertugliflozin) tablets, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
STEGLATRO is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg once daily in those tolerating STEGLATRO and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLATRO and periodically thereafter (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 5 mg and 15 mg (3)

----------CONTRAINDICATIONS----------
- Severe renal impairment, end-stage renal disease, or dialysis. (4, 5.3)
- History of serious hypersensitivity reaction to STEGLATRO. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypotension:* May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.3)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.5)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.6)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.7)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.8)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions associated with STEGLATRO (incidence ≥ 5%) were female genital mycotic infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.1, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

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

SEGLUROMET™ (ertugliflozin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue SEGLUROMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

INDICATIONS AND USAGE

SEGLUROMET is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin. (1)

Limitations of Use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION
- Individualize the starting dose based on the patient's current regimen. (2.1)
- Maximum recommended dose is 7.5 mg ertugliflozin/1,000 mg metformin twice daily. (2.1)
- Take twice daily with meals, with gradual dose escalation. (2.1)
- Assess renal function before initiating SEGLUROMET (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.
- SEGLUROMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:
- Ertugliflozin 2.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 2.5 mg and metformin hydrochloride 1,000 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 1,000 mg (3)

CONTRAINDICATIONS
- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of serious hypersensitivity reaction to ertugliflozin or metformin. (4)

WARNINGS AND PRECAUTIONS
- *Lactic Acidosis:* See boxed warning. (5.1)
- *Hypotension*: May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.6)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.7)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.8)
- *Vitamin B_{12}* Deficiency: Metformin may lower vitamin B12 levels. Measure hematological parameters annually. (5.9)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.10)

ADVERSE REACTIONS
- The most common adverse reactions associated with ertugliflozin (incidence ≥5%) were female genital mycotic infections. (6.1)
- Most common adverse reactions associated with metformin (incidence ≥5%): diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.2)

USE IN SPECIFIC POPULATIONS
- *Pregnancy:* Advise females of the potential risk to a fetus, especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.4, 8.6)
- *Hepatic* impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

Date: July 2018

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STEGLUJAN safely and effectively. See full prescribing information for STEGLUJAN.

STEGLUJAN™ (ertugliflozin and sitagliptin) tablets, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

STEGLUJAN is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. (1)

Limitations of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLUJAN and periodically thereafter (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

DOSAGE FORMS AND STRENGTHS

Tablets:

- Ertugliflozin 5 mg and sitagliptin 100 mg (3)
- Ertugliflozin 15 mg and sitagliptin 100 mg (3)

CONTRAINDICATIONS

- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.4)
- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. (4, 5.10, 6.2)
- History of serious hypersensitivity reaction to ertugliflozin. (4)

WARNINGS AND PRECAUTIONS

- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis in patients taking sitagliptin, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue. (5.1)
- *Hypotension:* May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating assess and correct volume status. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. There have been postmarketing reports of acute renal failure in patients taking sitagliptin, sometimes requiring dialysis. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.6)
- *Heart Failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.7)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.8)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.9)
- *Hypersensitivity:* There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly discontinue, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.10)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.11)
- *Severe and Disabling Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.12)
- *Pemphigoid:* There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue. (5.13)

ADVERSE REACTIONS

- Most common adverse reactions associated with ertugliflozin (incidence ≥5%): female genital mycotic infections. (6.1)
- Most common adverse reactions associated with sitagliptin (incidence ≥5%): upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.2, 5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

Appendix 5. Efficacy and Harms Comparison of Non-insulin Antidiabetic Therapies -

Table 14. Non-Insulin Glucose Lowering Drugs Effectiveness and Harms Comparisons

Drug Class	Relative A1C lowering[27]	Cardiovascular Data	Safety Warnings	Effect on Weight[19,20]
Biguanides • Metformin	1% to 1.5%	• UKPDS found that metformin may reduce the risk of CV mortality	• Very small risk of lactic acidosis in patients with poor renal function	• Neutral/ loss
Sulfonylureas (2nd generation) • Glyburide • Glipizide • Glimepiride	1.0% to 1.5%	• No evidence of CV risk reduction	• Risk of hypoglycemia is higher than other oral antidiabetic treatments[19]	• Gain
Thiazolidinediones • Pioglitazone • Rosiglitazone	1.0% to 1.5%	• Use in patients with pre-diabetes and history of stroke or TIA was found to decrease subsequent stroke or MI (ARR 2.8%/NNT 36) compared to placebo over 4.8 years[45] • No CV morbidity or mortality benefit when rosiglitazone was added to metformin and SU[46] • No benefit or harm on CV endpoints with the use pioglitazone compared to placebo (HR 0.90; 95% CI, 0.80 to 1.02; p=0.095)[47]	• Pioglitazone may increase the risk of bladder cancer compared to placebo[48] • TZDs increase the risk of HF exacerbations • TZDs increase the risk of bone fractures	• Gain
DPP-4 Inhibitors • Sitagliptin • Saxagliptin • Alogliptin • Linagliptin	0.5% to 1.0%	• Saxagliptin and alogliptin have demonstrated increased risk in HF related hospitalizations. No difference in CV mortality was demonstrated.[49,50] • Sitagliptin was found to provide no benefit or harm to CV endpoints[53] • Linagliptin is still being evaluated	• Saxagliptin and alogliptin have been linked to increased risk of heart failure [51] • DPP-4 inhibitors may increase risk of pancreatitis • DPP-4 inhibitors may increase risk of severe joint pain	• Neutral/ loss
SGLT2 Inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	0.5% to 1.0%	• Empagliflozin demonstrated a reduction in the composite endpoint of death from CV causes, nonfatal MI and nonfatal stroke when compared to placebo (ARR 1.6%/NNT 63) over 3.1	• Canagliflozin increases risk for amputations in patients with T2DM who have established CV disease or with 2 or more risk factors for CV disease[52]	• Loss

		years in patients with underlying CV disease.[21] • Canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo, 26.9 vs. 31.5/1000 patient-years, in patients with CV disease or at high risk for CV disease (CANVAS – ARR 1.4%/NNT 71 over 5.7 years and CANVAS-R – ARR 1.1%/NNT 91 over 2.1 years).[22]	• Canagliflozin and dapagliflozin are associated with acute kidney injury • SGLT2 inhibitors are associated with ketoacidosis and serious urinary tract infections • Canagliflozin may increase the risk of reduced bone mineral density and fracture • Ertugliflozin may be associated with increased risk of lower-limb amputations	
GLP-1 Receptor Agonists • Exenatide • Exenatide Once-weekly (ER) • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide • Semaglutide	1.0% to 1.5%	• Liraglutide was found to decrease the composite outcome of death from CV causes, nonfatal MI, nonfatal stroke compared to placebo (ARR 1.9%/ NNT 53) over 3.5 years in patients on standard therapy with a history of CV disease or at high risk of CV disease[23] • Semaglutide was found to be noninferior to the composite CV outcome, as defined above, compared to placebo, 6.6% vs. 8.9%, respectively (HR 0.74; 95%CI, 0.58 to 0.95; P<0.001 for noninferiority).[2] • Exenatide ER was found to be noninferior to placebo for the composite CV endpoint, 11.4% vs. 12.2%, respectively (HR 0.91; 95% CI, 0.83 to 1.00; P<0.001 for noninferiority).[22] • Lixisenatide demonstrated no benefit or harm when compared to placebo for the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (HR 1.02; 95% CI, 0.89 to 1.17)[54]	• GLP-1 RA class may increase the risk of pancreatitis • An increased risk of thyroid cell cancers was demonstrated in rodent models • An increased risk of diabetic retinopathy complications was found with semaglutide compared to placebo	• Loss

Meglitinides • Repaglinide • Nateglinide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Gain
Alpha-glucosidase Inhibitors • Acarbose • Miglitol	0.5% to 1.0%	• ACE Trial is ongoing	• No major safety warnings	• Neutral
Amylin Mimetics • Pramlintide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Loss

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; SU = sulfonylurea; TIA = transient ischemic attack; UKPDS = United Kingdom Prospective Diabetes Study

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 DPP-4 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR410-121-0030 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
3. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	Yes: Go to #4	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. 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: 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 as doses advanced, 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 but is often 850 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: *7/18 (KS), 7/17 (KS), 9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *1/15; 9/14; 1/14; 2/13*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

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 GLP-1 receptor agonists

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.
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 metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for semaglutide or dulaglutide?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the request for the Bydureon BCISE™ formulation of exenatide extended-release?	**Yes:** Go to #7	**No:** Go to #8
7. Is the patient using prandial or basal insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months
~~5.~~8. Is the patient currently taking insulin?	**Yes:** Go to #~~9~~6	**No:** Approve for up to 12 months

Approval Criteria		
~~6.~~9. Is the patient requesting exenatide (Byetta or Bydureon®), liraglutide, albiglutide, ~~dulaglutide~~ or lixisenatide (including combination products) and using basal insulin?	**Yes:** Approve for up to 12 months	**No:** ~~Go to #7~~ Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.
~~7. Is the patient requesting dulaglutide and using prandial insulin?~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.~~

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 Review: *7/18 (KS), 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *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 6 months

Requires PA:
- All SGLT-2 inhibitors

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 prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of T2DM?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and a sulfonylurea, have contraindications to these treatments or is requesting a SGLT-2 inhibitor to be used with metformin and a sulfonylurea? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2, or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Has the patient tried and failed (unable to maintain goal A1c) all of the following drugs, or have contraindications to all of these drugs? 1. Insulin 2. Thiazolidinedione 3. DPP-4 inhibitor 4. GLP-1 receptor agonist 5. Amylin analog	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Renewal Criteria		
Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2 , or • Ertugliflozin and eGFR <60 mL/min/ 1.73 m^2?~~?~~	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months

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 but is often 850 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: *7/18 (KS), 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *TBD; 10/13/16; 2/3/15; 1/1/14*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Asthma Biologics
OHSU Drug Effectiveness Review Project Summary Report

Date of Review: July 2018 **Date of Last Review:** July 2016

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

Research Questions:
1. What is the comparative efficacy for benralizumab, a recently approved biologic, compared to reslizumab and mepolizumab for the treatment of eosinophilic asthma?
2. What is the comparative tolerability and frequency of adverse events for benralizumab, reslizumab, and mepolizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of using omalizumab to treat patients with moderate-to-severe allergic asthma?
4. What is the evidence on the benefits and harms of using omalizumab to treat patients with chronic spontaneous urticaria (CSU)?
5. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which biologic medications used to treat asthma differ in efficacy, or frequency of adverse events?

Conclusions:

Interluekin-5 Antagonists in Eosinophilic Asthma (Benralizumab, Reslizumab, and Mepolizumab)
- High quality evidence demonstrates asthma exacerbations requiring oral corticosteroids were significantly less likely with benralizumab than placebo in patients with severe asthma (3 Randomized Controlled Trials (RCTs), rate ratio 0.62, 95% Confidence Interval (CI) 0.55 to 0.70).[1] In absolute terms, this difference was 0.37 fewer events per patient per year with benralizumab (95% CI 0.44 to 0.29), with an event rate of 0.98 in the placebo group.[2] Moderate quality evidence shows exacerbations requiring emergency department (ED) or hospital admission were significantly less likely with benralizumab than placebo in patients with severe asthma (2 RCTs, rate ratio 0.68, 95% CI 0.47 to 0.98).[1] The absolute difference for this outcome was 0.04 fewer events per patient per year with benralizumab (95% CI 0.06 to 0.002), with a rate of 0.11 in the placebo group.[2]
- Moderate quality evidence demonstrates the effectiveness of reslizumab in reducing asthma exacerbations requiring oral corticosteroids in adults with severe asthma when compared to placebo (2 RCTs, rate ratio 0.43, 95% CI 0.33 to 0.55).[1] The absolute difference was 0.93 fewer events per patient per year (range: 1.09 to 0.73 fewer) with a rate of 1.54 events per patient per year in the placebo group.[2] Moderate quality evidence demonstrates that asthma exacerbations requiring ED visits or hospitalizations are not significantly reduced when adults are treated with reslizumab (2 RCTs, rate ratio 0.67, 95% CI 0.39 to 1.17), with an absolute difference of 0.04 fewer events per patient per year (0.07 fewer to 0.02 more) and a rate of 0.12 in the placebo group.[2]

- High quality evidence shows clinically significant asthma exacerbations (those requiring oral corticosteroids) were significantly less likely in patients given mepolizumab than those given placebo (2 RCTs, rate ratio 0.45, 95% CI 0.36 to 0.55).[1] In absolute terms, for mepolizumab, there were 0.81 fewer events per patient per year (95% CI 0.66 fewer to 0.94 fewer); the rate in patients on placebo was 1.48 events per patient per year.[2] High quality evidence demonstrates patients treated with mepolizumab were significantly less likely to have exacerbations requiring ED treatment or hospital admission compared to patients who received placebo (rate ratio 0.36, 95% CI 0.20 to 0.66).[1] In absolute terms, there were 0.10 fewer events per patient per year (95% CI 0.05 to 0.12 fewer), with a rate in patients on placebo of 0.15 events per patient per year.[2]
- High quality evidence suggests the difference in Asthma Quality of Life Questionnaire (AQLQ) score was significantly greater with benralizumab treatment than with placebo (mean difference (MD) 0.23, 95% CI 0.11 to 0.35); however it was less than the minimum clinically significant difference of 0.5 or more change in score.[2] Moderate quality evidence suggests quality of life was statistically better with reslizumab, but the difference was not clinically significant (2 RCTs, MD 0.28, 95% CI 0.17 to 0.39).[2] High strength evidence shows mepolizumab improves quality of life both statistically and clinically (2 RCTs, MD -7.40, 95% CI -9.50 to -5.29).[2]
- Moderate quality evidence suggests lower rates of serious adverse events were observed with benralizumab compared to placebo in patients with asthma (5 RCTs, 11% vs. 14%, relative risk (RR) 0.78, 95% CI 0.64 to 0.96, I2=0%).[2] This is likely due to the inclusion of asthma exacerbations as serious adverse events, which were reduced with benralizuamb.[2] Moderate quality evidence found no differences in adverse events outcomes (7.6% vs. 9.3%, RR 0.81, 95% CI 0.57 to 1.75) or withdrawals due to adverse events (3.0% vs. 4.4%, RR 0.67, 95% CI 0.37 to 1.20) with reslizuamb compared to placebo patients with asthma.[2] Low quality evidence showed no difference in adverse effects between placebo and mepolizumab in patients with asthma (6.0% vs. 12%, RR 0.50, 95% CI 0.24 to 1.05).[2]
- As of December, 2017 mepolizumab received an expanded indication from FDA for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).[3]

IgE Antagonist in Allergic Asthma and Chronic Urticaria (Omalizumab)

- In children and adults with moderate-to-severe allergic asthma, moderate quality evidence demonstrates omalizumab reduces severe exacerbations requiring ED visits, office visits, or hospitalizations (16% vs. 26%, OR 0.55, 95% CI 0.42 to 0.60).[4] Among the subgroup with moderate-to-severe asthma, the reduction was also significant (7 RCTs, odds ratio (OR) 0.50, 95% CI 0.42 to 0.60), while in the subgroup with severe asthma there was not a significant reduction (2 RCTs, OR 1.0, 95% CI 0.5 to 1.99).[2] An analysis of exacerbations requiring the use of oral corticosteroids found that omalizuamb significantly reduced the rate of exacerbations in patients with moderate-to-severe asthma (2 RCTs, rate ratio 0.52, 95% CI 0.37 to 0.73).[2]
- Moderate quality evidence showed that omalizumab improved quality of life in patients with moderate-to-severe asthma, but the difference may not be clinically important (6 RCTs, MD 0.31, 95% CI 0.23 to 0.39).[2]
- Low to moderate quality evidence showed less adverse events with omalizumab compared to placebo in patients with moderate-to-severe asthma (4.5% vs. 6.4% OR 0.72, 95% CI 0.57 to 0.91).[2] Withdrawals due to adverse events were few, with no clear differences between groups.[2]
- Two observational studies evaluated harms of omalizumab therapy.[5,6] For malignancies that occurred during the course of the study, crude rates of 16.0 per 1000 patient-years with omalizumab and 19.1 with placebo were identified.[5] The crude (unadjusted for potential confounders) rate ratio was not statistically significant (0.84, 95% CI 0.62 to 1.13).[5] However, there were several issues identified with the study design including biased selection criteria, biased exclusion criteria, and the high discontinuation rates leading to the conclusion that these study results should be interpreted with caution.[7] In a second analysis cardiovascular (CV) and cerebrovascular events were evaluated.[6] The incidence of any cardiovascular or cerebrovascular event was 13.4 per 1000 patient-years with omalizumab, compared with 8.1 for the control group.[6] Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in CV risk associated with omalizumab administration cannot be excluded.[6]

- In patients with CSU, high quality evidence shows omalizumab significantly improves the chance for complete response as assessed by the urticaria activity score when compared to placebo (RR 4.55, 95% CI 3.33 to 6.23).[8] Quality of life was statistically better with omalizumab compared to placebo, but the difference was not clinically significant (high quality evidence).[2]
- No differences in adverse events outcomes were observed when data was pooled from 4 RCTs of omalizuamb used to treat patients with urticaria (RR 0.80, 95% CI 0.24 to 2.65).[2] Withdrawals due to adverse events were very low, 1% and 0.9% across the 4 RCTs with omalizumab and placebo, respectively.[2] The pooled relative risk is 1.03 (95% CI 0.24 to 4.41), with no heterogeneity (I2 = 0%).[2]

Recommendations:
- Recent evidence summarized in the Drug Effectiveness Review Project report for the asthma biologic medications does not support specific changes to the current Preferred Drug List (PDL).
- Add benralizumab to prior authorization (PA) criteria for monoclonal antibodies for asthma.
- Revise monoclonal antibodies for asthma PA criteria to include expanded indication for mepolizumab in patients experiencing eosinophilic granulomatosis with polyangiitis (EGPA).
- Evaluate costs in executive session to evaluate preferred drug list (PDL) status for benralizuamb.

Previous Conclusions:
- Moderate quality evidence over 32 weeks demonstrate mepolizumab 100 mg administered subcutaneously (SC) every 4 weeks reduces about one clinically significant asthma exacerbation (defined as an exacerbation that requires use of systemic corticosteroids, an ED visit, and/or hospitalization) in patients with severe eosinophilic asthma compared to placebo. Low quality evidence suggests mepolizumab 100 mg SC every 4 weeks may also reduce the rate of exacerbations that require hospitalization or ED visits compared with placebo by 0.12 events per year compared to placebo (0.08 vs. 0.20 events per year, respectively).
- Low quality evidence suggests mepolizumab may be associated with a statistically significant and clinically meaningful improvement in quality of life. The difference in total St. George's Respiratory Questionnaire scores from baseline between mepolizumab and placebo was -7.0 points (95% CI, -10.2 to -3.8). Low quality evidence also suggests mepolizumab may be associated with a statistically significantly symptom improvement. The difference in total Asthma Control Questionnaire (ACQ) scores from baseline between mepolizumab and placebo was -0.44 points (95% CI, -0.61 to -0.23); however, this difference did not exceed the minimal clinically important difference of 0.5 points.
- There is insufficient evidence to differentiate differences in efficacy between mepolizumab and other monoclonal antibodies approved for severe asthma.
- Safety data from Phase 3 trials and 2 long-term safety studies for mepolizumab reveal no major safety concerns at 1 to 3.5 years of treatment. Adverse events of interest for mepolizumab are similar to other monoclonal antibodies and include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity.
- Moderate quality evidence over 52 weeks supports the efficacy of reslizumab 3 mg/kg intravenous infusion every 4 weeks in reducing the number of patients experiencing at least one asthma exacerbation in adults (≥18 years) with severe eosinophilic asthma compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an absolute risk reduction (ARR) of 18% and a number-needed-to-treat (NNT) of 5 over 52 weeks. Low quality evidence suggests reslizumab 3 mg/kg IV every 4 weeks does not reduce the rate of exacerbations that require hospitalization or ED visits compared with placebo (RR 0.66; 95% CI 0.38 to 1.16).
- Moderate quality evidence suggests reslizumab is associated a clinically meaningful improvement in quality life, defined as a 0.5 point reduction or more in the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ).

- Reslizumab is associated with similar frequencies of serious adverse events as placebo, with the majority of events related to asthma exacerbations.
- Overall, there is moderate quality evidence that omalizuamb is more effective than placebo in reducing exacerbations and hospitalizations as adjunctive therapy to standard therapy in IgE-mediated moderate to severe asthma. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma.
- Although distinctly different, there is no evidence to support using omalizuamb in combination with either reslizumab or mepolizumab.

Previous Recommendations:
- Maintain mepolizumab and reslizumab as a non-preferred drugs subject to Prior Authorization (PA) criteria

Current Policy and Utilization Trends:
The Oregon Health Plan (OHP) provides coverage through PA criteria for the 2 biologic agents (mepolizumab and reslizumab) approved to manage eosinophilic asthma refractory to other asthma therapies. The most recently approved biologic agent for management of severe asthma, benralizumab, will be evaluated in this review for addition to the PDL. An additional biologic agent (omalizumab), is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizuamb is also indicated for management of chronic urticaria; however, this diagnosis is not funded according to the Health Evidence Review Commission (HERC) prioritized list.

During the first quarter of 2018 the only asthma biologic agent prescribed in the fee-for-service (FFS) population was omalizumab with 9 claims. Omalizuamb claims for coordinated care organizations (CCO) were slightly higher (14 claims) compared to the FFS claims and 8 CCO claims were processed for mepolizumab. The biologic agents accounted for 20% of the CCO costs associated with the miscellaneous pulmonary agents; however, claims for the 2 biologic agents were less than 1% of the total utilization for this class of drugs.

Background:
Asthma is a heterogeneous disease, characterized by chronic airway inflammation.[9] According to the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.[10] Mild asthma (step 1 or 2) is well controlled with low dose inhaled corticosteroid (ICS) therapy.[10] Moderate (Step 3), and severe (Steps 4 and 5) asthma may require more potent ICS and addition of other controller-drug treatments.[10] The 2018 Global Initiative for Asthma (GINA) guidelines recommend a biologic agent for patients with severe asthma unresponsive to controller-drug treatments.[9] Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.[11] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.[12]

Recognition that asthma is not a single disease, but multiple, overlapping, phenotypes of disease has changed the way asthma is categorized, and treated.[13,14] Phenotyping severe asthma based on demographic or clinical characteristics may help target treatments more effectively. Some asthma phenotypes include eosinophil predominant, neutrophil predominant, and allergic asthma.[14] Recent literature has proposed endotypes to further categorize phenotypes of severe asthma.[15] One endotype of eosinophilic asthma is Type 2 (T2)-high asthma indicating high levels of T-helper type 2 lymphocytes.[16] Patients with T2-high asthma have high levels of bronchial tissue IL-5 mRNA, high sputum levels of eosinophils, greater numbers of mast cells, and overexpression of periostin.[12] T2-high asthma responds well to ICS therapy, and patients that fail to respond to ICS agents may benefit from biologic medications.[17] The threshold for identifying elevated blood eosinophils that are a reliable marker for elevated sputum eosinophils (≥ 3%) is not entirely clear, but studies of biologic agents have used eosinophil blood levels from ≥150 cells/µL to ≥400 cells/µL.[17]

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and the newest formulation, benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. Reslizumab and mepolizumab are anti-IL-5 antibodies while benralizumab binds to the IL-5 receptor. Blocking IL-5 from binding to its receptor inhibits the growth, differentiation, activation, and survival of eosinophils.[18] The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Several monoclonal antibodies targeting different cytokines (IL-4 and IL-13) are currently being investigated for their safety and efficacy in treating severe asthma. These agents include dupilumab and lebrikizumab.

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Omalizumab has a boxed warning due to reports of serious and life-threatening allergic reactions; therefore administration in a healthcare setting under direct medical supervision is required.[19] Delayed anaphylaxis occurring 24 hours or later after omalizumab administration has also been reported.[19] It is recommended to provide patients with epinephrine to manage delayed anaphylaxis if it occurs as an outpatient after omalizuamb administration. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab, so the drug carries an FDA boxed warning recommending observation after infusion.[20] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[3,21] Adverse effects reported with mepolizumab include headache, injection site reactions, back pain and fatigue.[3] Herpes zoster infections have occurred in a small number of patients receiving mepolizumab, so vaccination is recommended if medically appropriate.[3] In clinical trials, the rate of serious adverse events with benralizumab was similar to placebo (12%-14%), and the most common adverse events include worsening asthma, nasopharyngitis, and upper respiratory tract infections.[22]

There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration and dosing regimen. In clinical trials, the definition of severe eosinophilic asthma ranged from greater than or equal to 150 eosinophils/µl to greater than or equal to 400 eosinophils/µl depending on the drug being investigated. Currently, all the monoclonal antibodies used to manage asthma must be administered by a health care provider. **Table 1** summarizes significant prescribing information for the 4 biologic agents with FDA approval to treat severe asthma.

Table 1. Monoclonal Antibodies Approved to Manage Severe Asthma[3,19-21]

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Benralizumab	Fasenra™	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/µL
Reslizumab	Cinqair®	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/µL
Mepolizumab	Nucala®	2015	IL-5	-Severe asthma with an eosinophilic phenotype	-Asthma: 100 mg SC every 4 weeks	-Asthma: ≥ 12 yo -EGPA: ≥ 18 yo	No	≥ 150 cells/µL at screening or ≥ 300

				-EGPA in adults	-EGPA: 300 mg SC every 4 weeks			cells/µL in the previous year
Omalizumab	Xolair®	2003	IgE	-Moderate to severe persistent asthma -Antihistamine refractory CSU	-Asthma: 75 to 375 mg SC every 2 to 4 weeks. (Dosing is determined by weight and serum IgE levels for asthma) -CSU: 150 to 300 mg SC every 4 weeks	-Asthma: ≥ 6 yo -CSU: ≥ 12 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: CSU = Chronic Spontaneous Urticaria; EGPA = Eosinophilic Granulomatosis with Polyangiitis; FDA = Food and Drug Administration; IgE = immunoglobulin E; IL-5 = interleukin-5; IV = intravenous; SC = subcutaneous; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased ED visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; and 4) improved symptom management. Three instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ) is a 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[23] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the minimally clinical important difference.[24] An ACQ score consistently greater than 1.5 indicates poor symptom control.[24] The AQLQ is a 32-item quality-of-life instrument that assesses both physical and emotional impact of disease.[25] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life.[25] The minimally clinical important difference for this assessment is a difference of 0.5 for each item.[25] The St. George's Respiratory Questionnaire (SGRQ) is a 50-item quality-of-life tool for patients with obstructive airway disease.[26] The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact.[26] Scores range from 0 to 100, with higher scores indicating more limitations.[26] A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.[26]

Chronic spontaneous urticaria (CSU) is defined as recurrent episodes of hives with or without angioedema, that last 6 weeks or more.[27] CSU affects 1% to 2% of the US population.[27] In most patients, there is no known allergic cause, although external factors such as stress, medications, or exercise can trigger the symptoms. The Urticaria Activity Score (UAS) is a broadly accepted tool used to assess CSU disease activity in clinical trials.[28] In the UAS-7, two symptoms (number of wheals and severity of itching), are documented by adult patients once a day for seven days in a row.[28] The answers related to each symptom are rated from 0 to 3 points, and the minimum and maximum daily score are 0 and 6 points, respectively, with higher values indicating stronger disease activity.[28] Treatment of CSU depends largely on 2nd generation H1-antihistamines, such as cetirizine or loratadine.[29] In several small trials leukotriene receptor antagonists (e.g. montelukast, zafirlukast) were successfully added to antihistamine therapy to assist with CSU symptom control.[30,31] In patients with CSU refractory to antihistamines or leukotriene receptor antagonists, omalizumab has been successfully added to these therapies to alleviate symptoms.[8]

Methods:

The April 2018 report on biologic drugs to treat asthma and chronic urticaria by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center (EPC) at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[2]

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
The literature search for the DERP report included published trials through December 2017 focused on biologic drugs for asthma and chronic urticaria. The search included adults or children with persistent or chronic asthma and adults with CSU in outpatient settings. Study designs included in the report included randomized clinical trials (RCTs) of at least 12 weeks duration, systematic reviews (SRs) and observational trials of at least 6 months duration to evaluate serious adverse events. The drug class report includes 15 RCTs, 2 observational studies, and 5 SRs, including 12,683 patients.[2] The majority of studies were fair to good quality.[2] Evidence for use of the IL-5 inhibitors (benralizumab, reslizumab, and mepolizumab) in patients with eosinophilic asthma was identified in 1 SR and an additional 1 trial each of benralizumab, mepolizumab, and reslizumab. Evidence for omalizumab in patients with allergic asthma was published in 3 SRs, 6 additional RCTs, and 2 observational studies. Omalizumab in chronic spontaneous urticaria was evaluated in one 1 SR and 2 additional RCTs. The results are organized by drug class, and then study population.

Interluekin-5 Inhibitors in Eosinophilic Asthma
Benralizumab in Moderate to Severe Asthma
A Cochrane review of IL-5 inhibitors in adults and children with moderate to severe asthma included 4 good-quality, placebo-controlled trials for benralizumab (N=2,648).[1] In these trials, benralizumab 20 mg or 30 mg was administered every 4 or every 8 weeks with 48 to 56 weeks of follow-up.[1] The FDA-approved benralizumab dose is 30 mg every 4 weeks for the first 3 doses, followed by 30 mg every 8 weeks.[21] The Cochrane SR defined clinically significant asthma exacerbations as those requiring oral corticosteroids for 3 or more days.[1] Exacerbations were significantly less likely with benralizumab than placebo (3 RCTs, N=2456; rate ratio 0.62, 95% CI 0.55 to 0.70).[2] In absolute terms, the difference was 0.37 fewer events per patient per year with benralizumab (95% CI 0.44 to 0.29), with an event rate of 0.98 in the placebo group.[2] Significant differences in exacerbation rates between benralizumab and placebo were seen both in patients with eosinophilic (≥ 300 cells/µL; rate ratio 0.59, 95% CI 0.51 to 0.68) and non-eosinophilic phenotypes (rate ratio 0.69, 95% CI 0.56 to 0.85).[2] Exacerbations requiring ED or hospital admission were significantly less likely with benralizumab than placebo (2 RCTs, N=1537; rate ratio 0.68, 95% CI 0.47 to 0.98) in patients with eosinophilia (≥300 cells/µL). The absolute difference was 0.04 fewer events per patient per year with benralizumab (95% CI 0.06 to 0.002), with a rate of 0.11 in the placebo group.[2]

Three high quality trials (N=1541) of patients with eosinophilic asthma measured quality of life using the 7-point AQLQ(S) + 12, which is the Standardized Asthma Quality of Life Questionnaire for subjects 12 years and older.[1] The difference in AQLQ(S) + 12 score was greater with benralizumab treatment than with placebo (MD 0.23, 95% CI 0.11 to 0.35).[2] Although this difference was statistically significant, it was less than the minimum clinically significant difference of 0.5 or more change in score.[2]

An additional RCT, the ZONDA trial, was published after the Cochrane review was completed.[32] This high quality trial (N=220) of adults with severe asthma randomized patients to benralizumab 30 mg or placebo administered every 4 weeks for 28 weeks, or every 4 weeks for the first 12 weeks, then every 8 weeks for the remaining 16 weeks of the trial.[2] The primary outcome in this trial was the percent reduction in oral corticosteroid dose from baseline to week 28.[32] The

median reduction of corticosteroid dose in the placebo arm was 25%, while in each benralizumab arm the median reduction in dose was 75% (p<0.001).[32] Among the secondary outcomes, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than the rate with placebo (marginal rate 0.83 vs. 1.83, p=0.003), and benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (marginal rate 0.54 vs. 1.83, p<0.001).[32] Quality of life as assessed by the AQLQ(S) + 12 score improved for patients treated with benralizumab compared with those given placebo, with the difference significant for treatment every 8 weeks (MD 0.45, 95% CI 0.14 to 0.76) although not every 4 weeks (MD 0.23, 95% CI 0.08 to 0.53).[2]

Serious adverse effect data was pooled by the DERP authors using results from the 4 trials in the Cochrane meta-analysis and the additional data from the ZONDA trial. Serious adverse effects were lower with benralizumab compared to placebo (5 RCTs, 11% vs. 14%, RR 0.78, 95% CI 0.64 to 0.96, I^2=0%).[2] This is likely due to the inclusion of asthma exacerbations as serious adverse events, which were reduced with benralizuamb.[2] Three good quality RCTs reported withdrawals due to adverse events. This data was pooled with the ZONDA trial and no significant difference in withdrawals due to adverse events was observed with benralizumab compared to placebo (4 RCTs, 2.2% vs. 1.0%, RR 1.84, 95% CI 0.92 to 3.68).[2] Differences in injection site reactions were reported in sub-group analysis of 2 trials.[2] When the DERP authors pooled this data, no statistically significant difference in skin reactions for patients treated every 8 weeks with benralizumab compared to placebo was observed (2.4% vs. 1.6%, relative risk [RR] 1.44, 95% CI 0.69 to 3.00.)[2]

Reslizumab in Moderate to Severe Asthma

The previously discussed Cochrane IL-5 inhibitor review included 4 placebo-controlled RCTs of reslizumab in adults with moderate to severe asthma.[1] Three of the RCTs required patients have blood eosinophils of greater than or equal to 400 cells/µL (N=1164), while the fourth study was of patients with non-eosinophilic asthma.[2] Patients in these studies were using medium doses of inhaled corticosteroids, and had a history of at least 1 clinically relevant asthma exacerbation in the past year.[2] Reslizumab was administered at 3 mg/kg intravenously every 4 weeks for 4 doses (2 RCTs) or for 13 doses (2 RCTs).[2] Two of the studies were high quality, and the others were moderate quality.[2]

In the 4 RCTs analyzed in the Cochrane SR, asthma exacerbations were reported as those requiring oral corticosteroids or those requiring an ED visit or admission to hospital.[1] Using the more conservative definition (requiring oral steroids), reslizumab significantly reduced the risk of exacerbation compared with placebo (2 RCTs, rate ratio 0.43, 95% CI 0.33 to 0.55).[1] The absolute difference was 0.93 fewer events per patient per year (range: 1.09 to 0.73 fewer) with a rate of 1.54 events per patient per year in the placebo group.[2] Based on the more serious definition of an exacerbation requiring an ED visit or hospital admission, reslizumab did not reduce the risk compared with placebo (2 RCTs, rate ratio 0.67, 95% CI 0.39 to 1.17), with an absolute difference of 0.04 fewer events per patient per year (0.07 fewer to 0.02 more) and a rate of 0.12 in the placebo group.[2] Quality of life as assessed by AQLQ scores was statistically better with reslizumab than with placebo (2 RCTs, MD 0.28, 95% CI 0.17 to 0.39). However, as the difference did not meet the established effect size of 0.5, it is unclear if this difference is clinically meaningful.[2]

An additional fair-quality trial included in the DERP report did not meet Cochrane review inclusion criteria of trial duration at least 16 weeks. This 12-week RCT enrolled adults with poorly controlled, moderate-to-severe asthma with sputum eosinophils greater than or equal to 3% (n=106).[33] The Cochrane review notes that studies evaluating blood and sputum eosinophil levels have found that blood eosinophil levels of greater than or equal to 400 cells/µL correlate well with sputum levels greater than or equal to 3%.[1] Subjects received reslizumab 3 mg/kg at baseline and every 4 weeks for a total of 4 doses or infusion of placebo.[33] The primary efficacy measure was the difference between the reslizumab and placebo groups in the change in the 7 question ACQ score from baseline to end of therapy.[33] A change of least 0.5 in the ACQ score is considered clinically significant.[23] Mean changes from baseline to end of therapy in ACQ score were -0.7 in the reslizumab group and -0.3 in the placebo group did not reach statistical significance (MD -0.38, 95% CI -0.76 to 0.01, p = 0.054).[33] Overall, 59% of patients in

the reslizumab group and 40% of patients in the placebo group achieved an improvement of at least 0.5 in ACQ score (OR 2.06, 95% CI 0.88 to 4.86, p=0.0973).[33] The 12-week study used a broad definition of exacerbations, which included a greater than 20% decrease in FEV_1, or ED visit or 3 days of oral corticosteroid treatment.[33] The results for reducing exacerbations did not reach statistical significance, but the absolute difference was large, 8% versus 19% (p=0.083).[2]

DERP analysis of adverse event outcomes was based on pooled data from 3 RCTs (N=1059).[2] There were no differences between reslizumab and placebo in serious adverse events (7.6% vs. 9.3%, RR 0.81, 95% CI 0.57 to 1.75).[2] There were also no differences between reslizumab and placebo in withdrawals due to adverse events (3.0% vs. 4.4%, RR 0.67, 95% CI 0.37 to 1.20).[2]

Mepolizumab in Severe Asthma

The Cochrane review of IL-5 inhibitors included placebo-controlled trials of both intravenous and subcutaneous mepolizumab.[1] Only the subcutaneous formulation is approved in the United States, so DERP authors excluded data from trials of intravenous mepolizumab. The Cochrane review included data from 2 good-quality trials of subcutaneous mepolizumab (N=1,127) in patients with severe eosinophilic asthma.[2] Clinically significant asthma exacerbations (those requiring oral corticosteroids) were significantly less likely in patients given mepolizumab than those given placebo (2 RCTs, N=936; rate ratio 0.45, 95% CI 0.36 to 0.55).[2] In absolute terms, for mepolizumab, there were 0.81 fewer events per patient per year (95% CI 0.66 fewer to 0.94 fewer); the rate in patients on placebo was 1.48 events per patient per year.[2]

Based on these 2 trials, those treated with mepolizumab were significantly less likely to have exacerbations requiring ED treatment or hospital admission (rate ratio 0.36, 95% CI 0.20 to 0.66).[1] In absolute terms, there were 0.10 fewer events per patient per year (95% CI 0.05 fewer to 0.12 fewer), with a rate in patients on placebo of 0.15 events per patient per year.[2] Quality of life was assessed using the SGRQ in 2 trials. A change of 4 or more points on this questionnaire is considered clinically significant.[1] In the Cochrane analysis quality of life improved more for patients treated with mepolizumab than for those given placebo (MD -7.40, 95% CI -9.50 to -5.29).[1]

The Cochrane review excluded results from a third RCT, the SIRIUS trial, because its primary outcome was reduction in glucocorticoid use. However the DERP authors included results from this trial in their report.[2] The SIRIUS trial was a high quality randomized, double-blind trial involving 135 patients with severe eosinophilic asthma.[2] Mepolizumab 100 mg administered subcutaneously every 4 weeks for 20 weeks was compared to placebo.[34] The primary outcome was the degree of reduction in the glucocorticoid dose (90 to 100% reduction, 75 to less than 90% reduction, 50 to less than 75% reduction, more than 0 to less than 50% reduction, or no decrease in oral glucocorticoid dose, a lack of asthma control during weeks 20 to 24, or withdrawal from treatment).[34] Other outcomes included the rate of asthma exacerbations, asthma control, and safety. The likelihood of a reduction in the glucocorticoid-dose stratum was greater in the mepolizumab group than in the placebo group (OR 2.39, 95% CI 1.25 to 4.56; p=0.008).[34] The median percentage reduction from baseline in the glucocorticoid dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group (p=0.007).[34] Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, p=0.04) and a reduction of 0.52 points with respect to asthma symptoms (p=0.004, 95% CI -0.87 to -0.17), as measured on the ACQ.[34] Quality of life improved more for patients treated with mepolizumab than for those given placebo (MD-5.8, 95% CI -10.6 to -1.0).[34]

In the DERP analysis of 3 RCTs evaluating subcutaneous mepolizumab, serious adverse events were not significantly different compared to placebo (6.0% vs. 12%, RR 0.50, 95% CI 0.24 to 1.05).[2] There was moderate statistical heterogeneity in this pooled analysis (I2=57%), due to variation in the magnitude of effect across the trial arms.[2] Because of this, DERP confidence in these findings is low; it could change with additional evidence.[2] Few patients withdrew due to adverse

events in the 2 trials in the Cochrane review or the SIRIUS trial (16 of 1,071 patients across the 3 trials); however, evidence was insufficient to compare rates between mepolizumab and placebo (1.1% vs. 1.9%, RR 0.63, 95% CI 0.22 to 1.77).[2]

IgE Antagonist in Allergic Asthma and Chronic Urticaria

Omalizumab in Allergic Asthma

A good-quality Cochrane systematic review of omalizumab in patients with moderate to severe allergic asthma included a total of 25 RCTs.[4] Ten of the trials (N=3261) evaluated subcutaneous omalizumab every 2 to 4 weeks in patients also receiving stable doses of inhaled corticosteroids, while 5 (N=1634) had a 12- to 28-week period of stable oral or inhaled corticosteroid dose, followed by a period of attempted steroid-dose reduction.[2] Dosing varied, ranging from 75 mg every 2 weeks to 375 every 4 weeks or was determined by weight and IgE-level.[2] The studies ranged from 16 to 60 weeks in duration, included both adults and children, and most studies were fair quality.[2] The review analyzed the studies according to whether they evaluated only a stable steroid dose, or if they evaluated stable-dose followed by dose-reduction of steroids, and according to severity of asthma (moderate-to-severe or severe only).[2] The omalizumab studies reported medically serious exacerbations; those requiring a hospitalization, an ED visit, or an office visit.[2] Based on 10 moderate quality RCTs (N=3261, all continuing inhaled corticosteroids), omalizumab resulted in a significant reduction in exacerbations when used every 2 to 4 weeks for 16 to 60 weeks in patients with allergic asthma when compared to placebo (16% vs. 26%, OR 0.55, 95% CI 0.42 to 0.60).[4] Among the subgroup with moderate-to-severe asthma, the reduction was also significant (7 RCTs, OR 0.50, 95% CI 0.42 to 0.60), while in the subgroup with severe asthma there was not a significant reduction (2 RCTs, OR 1.0, 95% CI 0.5 to 1.99).[2]

An analysis of exacerbations requiring the use of oral corticosteroids found that omalizuamb significantly reduced the rate of exacerbations in patients with moderate-to-severe asthma (2 RCTs, rate ratio 0.52, 95% CI 0.37 to 0.73).[4] In a single study of patients with severe asthma, the rate was significantly reduced in patients receiving inhaled corticosteroids and long-acting beta agonists as background therapy (rate ratio 0.66, 95% CI 0.45 to 0.97), but not significant in those receiving both oral and inhaled corticosteroids as background therapy (rate ratio 0.95, 95% CI 0.63 to 1.43).[2]

Limiting the analysis to studies of 52 weeks or longer, another fair-quality systematic review also found a reduction in serious asthma exacerbations (21% with omalizumab vs. 38% with placebo, RR 0.63, 95% CI 0.55 to 0.71).[35] Limiting the analysis to children (ages 6 to 20), the incidence of exacerbations was higher than in the overall population, but the reduction with omalizumab was also significant.[36] Twenty-seven percent of children taking omalizumab had an exacerbation, compared with 41% taking placebo (3 RCTs, RR 0.69, 95% CI 0.59 to 0.80).[36]

Quality of life was measured using the AQLQ, and was found to be significantly improved with omalizumab in patients with moderate-to-severe allergic asthma (6 RCTs, MD 0.31, 95% CI 0.23 to 0.39), however this difference was small and was not found to meet the pre-specified clinically important effect size of 0.5 improvement.[2] DERP identified an additional 8 studies not included in the Cochrane review. Two RCTs evaluated quality of life in moderate to severe asthma patients treated with omalizumab in Brazil[37] and China[38] however, the Chinese study was of poor quality for the measurement of quality of life and was used only to evaluate harms of omalizumab.[2] The smaller Brazilian study (N=116) of patients with severe allergic asthma reported differences in AQLQ scores of 0.8 at 12 weeks, and 1.4 at 20 weeks (both $p<0.001$).[37] This difference does meet the clinically relevant threshold of a 0.5-point or greater improvement.[2] The study from Brazil also reported that significantly more patients had clinically relevant improvement on the AQLQ (≥0.5 points) with omalizumab versus placebo at 20 weeks (71.6% vs. 22.2%, $p<0.001$).[37]

All of the RCTs reported serious adverse events including asthma exacerbations.[2] There were significant differences, favoring omalizumab over placebo. Overall, in the population with moderate-to-severe asthma, 4.5% had a serious adverse event with omalizumab, compared to 6.4% with placebo (OR 0.72, 95% CI 0.57

to 0.91).[2] Limiting the analysis only to longer-term studies (greater than 52 weeks), the incidences were slightly lower, but still favored omalizumab compared to placebo, (3.7% vs. 6.7%, RR 0.55, 95% CI 0.37 to 0.82).[2] In children, these incidences were 5.2% and 6.5% and the difference was not significant (RR 0.91, 95% CI 0.58 to 1.42), likely due to fewer patients.[2] Withdrawals due to adverse events were few, with no clear differences between groups.[2]

Two observational studies evaluated harms of omalizumab therapy (N=10,225).[5,6] The EXCELS study was a prospective cohort study (N=5041) conducted between 2006 and 2011 to assess long term safety of omalizumab, and was funded by Genentech and Novartis.[5] An imbalance in malignancy rates in patients who received omalizumab in clinical trials was the impetus for this study as the pooled trial data revealed malignancy rates of 0.5% (omalizuamb) versus 0.2% (control).[5] The omalizuamb prescribing information includes malignancy as a potential risk.[19] Patients with moderate-to-severe allergic asthma were followed for up to 5 years, with a mean of 3.7 for omalizumab and 3.5 for the control group (asthma patients that did not receive omalizumab).[5] The first analysis reported on malignancies that occurred during the course of the study, finding crude rates of 16.0 per 1000 patient-years with omalizumab and 19.1 with placebo, with no statistical difference based on unadjusted analysis.[5] The crude (unadjusted for potential confounders) rate ratio was not statistically significant (0.84, 95% CI 0.62 to 1.13).[5] The authors of the study concluded omalizumab is not associated with an increased risk of malignancy.[5] However, there were several issues identified with the study design including biased selection criteria, biased exclusion criteria, and the high discontinuation rates leading to the conclusion that these study results should be interpreted with caution.[7] At this time, there is insufficient evidence to draw conclusions about the risks of malignancy associated with omalizumab therapy.

In a second analysis from the EXCELS study, cardiovascular and cerebrovascular events were evaluated, in particular arterial thromboembolic events (ATEs).[6] This analysis was prompted by early reports suggesting increased CV and cerebrovascular events were associated with omalizuamb administration. Similar to the malignancy analysis, most events were reported only as crude incidence rates.[2] The incidence of any CV or cerebrovascular event was 13.4 per 1000 patient-years with omalizumab, compared with 8.1 for the control group.[6] Within the individual events reported, myocardial infarction and unstable angina had the largest difference between groups. The analysis of ATEs reported as serious adverse events during the study found a non-significant increase (adjusted hazard ratio 1.32, 95% CI 0.91 to 1.91).[6] Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in CV risk associated with omalizumab therapy cannot be excluded.[6] At this time, there is insufficient evidence to associated omalizumab administration with adverse CV effects.

Omalizumab in Chronic Urticaria

DERP authors identified 1 good-quality SR of 7 RCTs (N=1312) of omalizumab in patients with CSU.[8] In the 7 trials, omalizumab was dosed at 75 to 600 mg every 2 to 4 weeks; patients included both adults and children, and were refractory to typical treatments for CSU (primarily antihistamines).[2] All of the included studies reported complete response, defined as UAS-7 score scale of 0.[2] In the analysis of 7 RCTs, 28% of omalizumab patients achieved complete response, versus 6% with placebo (RR 4.55, 95% CI 3.33 to 6.23).[8] In a moderate quality RCT of Japanese and Korean CSU patients the response with omalizumab 300 mg was larger than the effect observed with 150 mg.[39] With 300 mg dosing, the rates were 35.6% versus 4.1% with placebo (OR 15.30, 95% CI 4.27 to 54.90), and with 150 mg they were 18.6% versus 4.1% with placebo (OR 5.36, 95% CI 1.43 to 20.08).[39]

Quality of life was measured by the Dermatology Life Quality Index (DLQI, range 0 to 30, lower scores are better) in 4 trials.[2] Quality of life was statistically improved, but the difference did not reach clinical importance. It has been suggested that a difference of at least 4 or 5 points is required for clinical importance on this scale.[40] The mean change from baseline was -9.2 versus –5.6 in the omalizumab 300 mg groups compared with placebo.[2] The DERP pooled estimate of effect (difference in the mean change from baseline) was -3.38 (95% CI -4.42 to -2. 34), with no heterogeneity (I2 = 0%).[2]

Four RCTs reported serious adverse events, with 4.8% (omalizumab) versus 4.4% (placebo) of patients experiencing a serious adverse event.[8] The DERP pooled analysis of these trials results in a relative risk of 0.80 (95% CI 0.24 to 2.65), indicating no difference in the incidence of serious adverse events between omalizumab 300 mg and placebo.[2] Withdrawals due to adverse events were very low, 1% and 0.9% across the 4 RCTs with omalizumab and placebo, respectively.[2] The pooled relative risk is 1.03 (95% CI 0.24 to 4.41), with no heterogeneity (I2 = 0%).[2]

New Indication:

As of December, 2017 mepolizumab received an expanded indication from FDA for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).[3] EGPA, formerly called Churg-Strauss Syndrome, is a rare vasculitis with persistent eosinophilia greater than 10% of the total white blood cell count (e.g., > 1500 cells/µL) that occurs primarily in patients with asthma.[41] Systemic corticosteroids are considered first line therapy followed by immunosuppressants in cases refractory to steriods. A multi-center clinical trial conducted in 136 subjects with relapsing and/or refractory EGPA randomized patients to either placebo or mepolizumab 300 mg subcutaneously every 4 weeks for 52 weeks.[42] Mepolizumab dosing used in this trial was higher than the dose approved by FDA for treatment of severe asthma. The two primary end points were the accrued weeks of remission over a 52-week period, and the proportion of participants in remission at both week 36 and week 48.[42] Mepolizumab treatment led to significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had ≥24 weeks of accrued remission; OR 5.91; 95% CI 2.68 to 13.03; P<0.001) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; OR 16.74; 95% CI, 3.61 to 77.56; P<0.001).[42] Of note, remission did not occur in 47% of the participants in the mepolizumab group versus 81% of those in the placebo group.[42] In the 52-week trial, the percentage of subjects who experienced systemic reactions was 1% (placebo) compared to 6% (mepolizumab).[3]

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Appendix 1: Current Preferred Drug List

Route	Form	Brand	Generic	PDL
SUB-Q	VIAL	NUCALA	MEPOLIZUMAB	N
INTRAVEN	VIAL	CINQAIR	RESLIZUMAB	N
SUB-Q	SYRINGE	FASENRA	BENRALIZUMAB	N
SUB-Q	VIAL	XOLAIR	OMALIZUMAB	N

Monoclonal Antibodies for Severe Asthma

Goal(s):

- Restrict use of monoclonal antibodies to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria).

Length of Authorization:

- Up to 12 months

Requires PA:

- Omalizumab
- Mepolizumab
- Reslizumab
- Benralizumab

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. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for omalizumab, mepolizumab, reslizumab, or benralizumab?	**Yes:** Go to # 5	**No:** Go to # 4
4. Is the request for another monoclonal antibody for severe asthma and does the indication match the FDA-approved indication.	**Yes:** Approve for 6 months	**No:** Go to # 5
~~3.~~5. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
~~4.~~6. Is the claim for mepolizumab or benralizumab in a patient under 12 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7~~5~~
7. Is the claim for omalizuamb in a patient under 6 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the claim for mepolizumab in an adult patient diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve 300 mg (3 x 100mg syringes) every 4 weeks x 1 year	**No:** Go to #9
~~5.~~9. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #10~~6~~	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
~~6.~~10. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #11~~7~~	**No:** Pass to RPh. Deny; medical appropriateness.
11. ~~Has the patient required at least 2 hospitalizations or ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, aminophylline, theophylline)?~~ Has the patient experienced greater than 2 exacerbations in the previous 12 months requiring additional medical treatment (oral corticosteroids, ER visit or hospitalization) while receiving a maximally-dose inhaled corticosteroid (Table 1) AND 2 additional controlled drugs (i.e. long-acting inhaled beta-agonist, montelukast, zafirlukast, or theophylline)?	**Yes:** Go to #12~~8~~ Document number of hospitalizations, ~~or~~ ED visits, or additional oral corticosteroid doses for asthma exacerbation in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~12. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #13~~9~~	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~13. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14~~0~~
~~9.~~14. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #15~~1~~

Approval Criteria		
~~10.~~15. If the claim is for mepolizumab, benralizumab or reslizumab, can the prescriber provide documentation of severe eosinophilic asthma~~phenotype~~, confirmed by blood eosinophil count ≥300 cells/µL in the past 12 months?	**Yes:** Approve once every 4 to 8 weeks for up to 12 months. Note: Initial benralizumab dose is 30 mg every 4 weeks x 3 doses followed by 30 mg every 8 weeks Document eosinophil count (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew mepolizumab for EGPA?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with mepolizumab therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
~~1.~~3. Is the patient currently taking a maximally-dosed inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast,~~aminophylline~~ theophylline)?	**Yes:** Go to #~~4~~2	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
~~2.~~4. Has the number of ED visits~~, or~~ hospitalizations, or additional oral corticosteroid doses in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *7/18 (DM); 7/16*
Implementation: *TBD, 8/16*

Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria

Final Report

Executive Summary

April 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaidagency and public agency partners.

Background

This report covers omalizumab, an anti-IgE monoclonal antibody approved to treat uncontrolled allergic asthma and chronic spontaneous urticaria resistant to antihistamines, and IL-5 monoclonal antibodies reslizumab, mepolizumab, and benralizumab, approved to treat severe asthma in patients with an eosinophilic asthma phenotype.

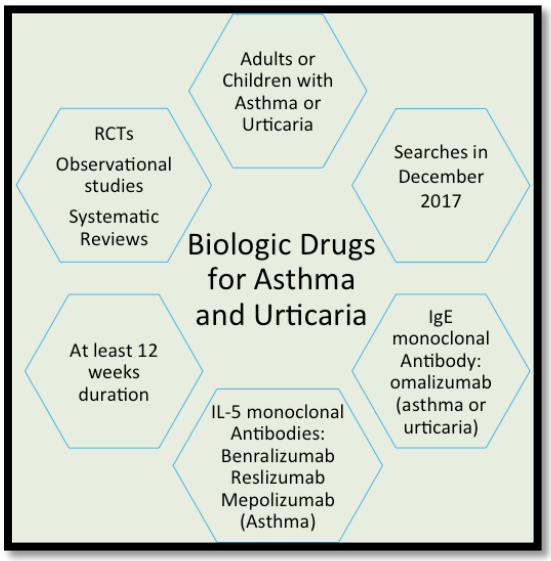
Asthma affects over 300 million people worldwide. Management of asthma is multifactorial with step-wise addition of medications determined by the frequency and severity of asthma symptoms. Steps range from 1 (intermittent asthma) to 5 (severe persistent asthma. Patients with uncontrolled Severe Step 5 asthma are potential candidates for biologic therapies, after confirming adherence and good inhaler technique. Phenotyping asthma (biologic markers and clinical history) can help identify patients who may benefit from biologic therapies. Eosinophilic inflammation identifies Type 2-high asthma, which may respond to anti-IL5 monoclonal antibodies that reduce eosinophils. Blood eosinophils are used as a surrogate marker for elevated sputum levels (>3%), but a reliable threshold has not been established. Studies have used thresholds of >150 cells/μL - ≥400 cells/μL. Patients with atopic (allergic) asthma, identified via skin testing, may benefit from the anti-IgE monoclonal antibody omalizumab.

Chronic spontaneous urticaria (CSU) is defined as recurrent episodes of hives (urticaria), with or without angioedema, that last 6 weeks or more. CSU affects 1% to 2% of the US population and typically lasts 2 to 5 years. In most patients there is no known allergic cause, although external factors can aggravate the symptoms. Treatment depends largely on 2nd generation H-1 antihistamines, including higher doses and dual antihistamine therapy. Oral corticosteroids are avoided, and omalizumab is reserved for refractory cases.

Key Questions

1. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with asthma?
    a. Are there subgroups of patients (e.g. elevated baseline eosinophils) for which biologic medications differ in benefits or harms?
2. Are there differences in effectiveness and adverse event outcomes of biologic medications compared with each other or placebo when added to other treatments for outpatients with chronic spontaneous urticaria?
    a. Are there subgroups of patients for which biologic medications differ in benefits or harms?

Inclusion Criteria



Overview of Included Evidence

There was no evidence directly comparing the drugs; all studies were placebo-controlled, add-on therapy. Using systematic reviews and newer trials, we included 15 trials of anti-IL-5drugs, 21 of omalizumab in asthma; and 7 trials in CSU. Most studies were good and fair quality.

Key Findings: Asthma

Drug (vs. Placebo)	Exacerbations –steroids	Exacerbations – ER/hospital	Quality of Life	Serious Harms	Subgroup analyses
IL-5 Monoclonal Antibodies					
Benralizumab: Summary	↓ +++	↓ ++	☒ +++	↓ ++	Exacerbation and Quality of life findings significant for eosinophils ≥ 150 cells/µl, but not for < 150.
Relative effects	Rate ratio 0.62 (0.55 to 0.70)	Rate ratio 0.68 (0.47 to 0.98) a	NA	RR 0.78 (0.64 to 0.96)	
Absolute effects	0.37 fewer events per patient per year (0.44 fewer to 0.29 fewer)	0.04 fewer events per patient per year (0.06 fewer to 0.002 fewer)[a]	Mean difference 0.23 (0.11 to 0.35)[a,b]	11% vs. 14%	
Reslizumab: Summary	↓ ++	☒ ++	☒ +++	☒ ++	Asthma control improved significantly in patients with higher eosinophils, worse symptoms, longer disease duration or nasal polyps. Single study of non-eosinophilic patients found no benefit.
Relative effects	Rate ratio 0.43 (0.33 to 0.55)	Rate Ratio 0.67 (0.39 to 1.17)	NA	RR 0.81 (0.57-1.75)	
Absolute effects	0.93 fewer events per patient per year (1.09 fewer to 0.73 fewer)	0.04 fewer events per patient per year (0.07 fewer to 0.02 more)	Mean Difference 0.28 (0.17, 0.39) b	7.6% vs.9.3%	
Mepolizumab: Summary	↓ +++	↓ +++	↑+++	☒ +	All patients studied had eosinophilia Exacerbation rates decreased significantly regardless of the number or type of other controller therapies used
Relative effects	Rate ratio 0.45 (0.36 to 0.55)	Rate ratio 0.36 (0.20 to 0.66)	NA	RR 0.50 (0.24 to 1.05)	
Absolute effects	0.81 fewer events per patient per year (0.66 fewer to 0.94 fewer)	0.10 fewer events per patient per year (0.05 fewer to 0.12 fewer)	Mean difference -7.40 (-9.50 to -5.29) [c]	6.0% vs. 12%,	
Anti-IgE Monoclonal Antibody: Omalizumab					
Omalizumab Summary	↓ ++ (steroid, ER, hospital)	NA	☒ ++	↓ ++	Reduction in exacerbations is significant in moderate to severe asthma, not in severe asthma
Relative effects	OR 0.55 (95% CI 0.42 - 0.60)	NA	NA	OR 0.72 (95% CI 0.57 - 0.91)	
Absolute effects	16% vs. 26%,	NA	Mean difference 0.31 (95% CI 0.23 - 0.39)	4.5% vs. 6.4%,	

[a] in subgroup of patients with eosinophils > 300 cells/µl; [b] Asthma Quality of Life Questionnaire (AQLQ); difference is statistically significant, but does not meet clinical importance threshold of 0.5 points; [c] St. Georges Quality of Life Scale; meets clinical importance threshold of 4 points.

+++, High confidence in findings; ++, Moderate confidence in findings; +, Low confidence in findings, ↓Decrease in outcome compared with placebo, ↑Increase in outcome compared with placebo, ☒No difference in outcome versus placebo

Key Findings: Chronic Spontaneous Urticaria

Omalizumab resulted in significantly more patients having complete response (8 RCTs, high SOE). Quality of life improved statistically, but did not reach clinically important differences (4 RCTs, high SOE). There were no differences in adverse event outcomes (4 RCTs, low SOE).

Key Findings: Urticaria

Outcome	Finding	Absolute & Relative Effects
Complete Response	↑+++	35.6% versus 4.1% OR 15.30 (4.27 to 54.90)
Quality of Life[a]	☒ +++	-9.2 versus –5.6 WMD -3.38 (-4.42 to -2. 34)
Serious AEs	☒ +	4.8% versus 4.4% RR 0.80 (0.24 to 2.65)
AE Withdrawals	☒ +	1.0% versus 0.9% RR 1.03 (0.24 to 4.41)

AE, adverse events; OR, odds ratio; RR, relative risk, WMD, weighted mean difference
a Does not meet threshold for clinical importance; difference of 4-5 points
+++, High confidence in findings; ++, Moderate confidence in findings; +, Low confidence in findings, ↓Decrease in outcome with o compared with placebo, ↑Increase in outcome compared with placebo, ☒No difference in outcome versus placebo

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DERP Systematic Review Methods

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. We searched MEDLINE through December 2017 and the Cochrane randomized trial database through 4th quarter, 2017. We requested dossiers of study information from manufacturers of included drugs. We created evidence tables, strength of evidence tables, and updated meta-analyses found in systematic reviews with newer trial data. Additional details on our methods can be found in Appendix A of the full report.

Conclusions

The body of evidence consisted of 15 placebo-controlled RCTs, 5 systematic reviews (of 28 RCTs), and 2 observational studies that were mostly fair to good quality. There were no trials directly comparing the anti-IL-5 drugs with each other. In patients with severe asthma, with elevated eosinophils, there was high-strength evidence that anti-IL-5 drugs benralizumab and mepolizumab reduce the incidence of asthma exacerbations requiring oral corticosteroids or an emergency department visit or hospitalization. Additionally, benralizumab and mepolizumab result in patients using lower doses of oral corticosteroids. Reslizumab reduced exacerbations requiring oral corticosteroids. In patients with allergic asthma, there was low- to moderate-strength evidence that omalizumab significantly reduces the incidence of asthma exacerbations, including those requiring oral corticosteroids or emergency department or hospital admission. In patients with chronic spontaneous urticaria, high-strength evidence found that omalizumab significantly improves the chance for complete response. High-strength evidence found that while quality of life was improved with these biologic drugs, the difference did not reach clinical importance except for mepolizumab. Adverse event evidence was lower strength; lower rates of serious adverse events were seen with benralizumab and omalizumab in asthma, but no differences were found for other drugs or in patients with urticaria.

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New Drug Evaluation: Edaravone injection, intravenous

Date of Review: July 2018
Generic Name: edaravone

End Date of Literature Search: 04/30/2018
Brand Name (Manufacturer): Radicava® (MT Pharma America, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy of edaravone compared to placebo or currently available treatments for amyotrophic lateral sclerosis (ALS)?
2. Is edaravone safe for treatment of ALS?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with edaravone?

Conclusions:

- There is insufficient evidence to determine if edaravone has any significant impact on functional status or disease progression in all ALS patients beyond 6 months. One small study of 137 patients over 24 weeks in early-stage Japanese ALS patients demonstrated a 2.49 difference on a 48-point ALSFRS-R scale [0 (worst) to 48 (normal)] compared to placebo [2.49 +/- 0.76 (95% CI, 0.99 to 3.98); P = 0.001].[1]
- There is insufficient evidence to evaluate the long-term safety of edaravone. The safety population included a total of 368 patients. Mortality rates were similar and serious adverse events were fewer in edaravone group versus placebo (1.1% and 2.2%; 17.4% and 22.3%, respectively).[2] The most common adverse events with edaravone treatment were contusion (15%), gait disturbance (13%), and headache (8%).[2]
- There is insufficient evidence to compare edaravone to any other ALS therapies or in specific subpopulations other than Japanese patients.

Recommendations:

- Recommend implementation of prior authorization criteria for edaravone (**Appendix 2**).

Background:

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's or Charcot's disease, is the most common degenerative and fatal motor neuron disease.[3] The Centers for Disease Control and Prevention (CDC) has estimated there are over 12,000 people in the United States with ALS or roughly 5 cases per 100,000 individuals.[4] ALS affects more males than females at a ratio of 1.7:1.[4] ALS symptoms typically do not develop until 50 years of age, and the desase is typically diagnosed between 55 and 65 years of age. Although there is variation in ALS presentation and progression, the average life expectancy is two to five years from the time of diagnosis.[4] Only about 10% of ALS patients live more than 10 years from disease onset.[5] The clinical standard for diagnosis of ALS is the Revised El Escorial World Federation of Neurology criteria which requires evidence of degeneration and dysfunction of upper motor neuron (UMN) and lower motor

neurons (LMN).[6] Early stages of ALS are marked by muscle stiffness, asymmetric limb weakness, cramping and fatigue.[6] Twenty percent of ALS patients exhibit bulbar symptoms such as slurred speech and dysphagia.[7] As ALS progresses, selective degeneration of upper and lower motor neurons eventually results in loss of coordination and muscle strength leading to complete paralysis, respiratory failure, and death.[7] Up to 30% of ALS patients may experience significant cognitive or psychological impairment as well as depression and mood imbalance.[8] Based on claims data, Oregon Medicaid has 105 identified cases of ALS, 54 of whom are in the Fee-For-Service (FFS) program. Claims data is unable to distinguish between the various stages of ALS.

The etiology of ALS is largely unknown, however, mitochondrial abnormalities, signs of oxidative stress, and elevated 3-nitrotyrosine and protein carbonyl levels have been observed in many patients.[3,9] Established risk factors for development of ALS are age and family history. Around 90% of ALS cases are sporadic (SALS) and affect individuals in their late 50s to early 60s. Only 10% of ALS cases are familial ALS (FALS) which typically emerge a decade earlier in the patient's 40s to early 50s.[4,9] Siblings and children of ALS patients are at increased risk of developing FALS.[3,9] One-fifth of FALS cases have revealed mutations in the copper/zinc ion-binding superoxide dismutase (SOD1) gene.[3,9,10] SOD1 has been theorized to be one of the protective enzymes responsible for the destruction of free superoxide radicals in the body and is required to block free-radical-induced DNA damage and prevent oxidative stress.[3,9,10] However, the direct link between SOD1 mutation and motor neuron degeneration of FALS patients is unclear as cases may also be linked to other mutations in Transactive Response DNA Binding Protein (TARDBP), Fused in Sarcoma (FUS), and Angiogenin (ANG) proteins.[3,9,10] There are no clinical laboratory tests that confirm diagnosis of nongenetically determined ALS.[6]

There is no cure for ALS and effective management is primarily focused on symptomatic and supportive care for the patient's physical, emotional and psychological needs.[11] Therapy outcomes which are of clinical value to ALS patients include mobility, muscle strength, quality of life, disease progression, and mortality. A variety of tools and clinical measures have been employed to manage and monitor ALS patients at various stages of functional decline.[11,12] Guidelines from the American Academy of Neurology (AAN) recommend noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) as important but underutilized treatments for ALS patients.[11] Noninvasive ventilation may be useful at earlier stages of ALS for the treatment of respiratory insufficiency in order to lengthen survival, slow forced vital capacity decline, and improve patient quality of life .[13] Spirometry with forced vital capacity (FVC) has been commonly used to diagnose diaphragmatic weakness and symptom progression in ALS patients.[13] Due to the loss of motor function, the majority of patients will eventually require assistance with activities of daily living (ADL).[13] PEG has been utilized in feeding to help stabilize patient weight and prolong survival.[11] The Respiratory Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is a tool widely used by clinicians to assess disease progression in ALS patients.[14] The ALSFRS-R enables clinicians to score the patient's physical function on a scale from 0 (worst) to 48 (normal).[14] The ALSFRS-R has been considered by some to be an improvement over the original ALSFRS due to its incorporation of 3 additional questions regarding dyspnea, orthopnea, and the need for respiratory support.[14,15] Some studies have used changes in the ALSFRS-R to make survival predictions.[16] However, there has been criticism regarding use of the ALSFRS-R scale because it may not be sensitive to heterogeneity in ALS disease progression especially among multiple domains over short time periods.[12,14] An additional validity concern of the ALSFRS-R is its reduced sensitivity for detection of change in low-functioning ALS patients as well as the potential for scores to be affected by mood or effort.[12,17] The minimum clinically important difference (MCID) on the ALSFRS-R score is unclear.[17] Changes in the ALSFRS-R have been correlated with patient-perceived changes of physical, emotional, and social function, but patients may be unable to perceive an intervention effect until its impact on the ALSFRS-R is 9 points or more.[18] Clinical trials have shown that the ALSFRS-R consistently declines at a rate of -0.92 units per month in ALS patients.[19] Surveys of clinicians estimate that an ALSFRS-R slope change (score vs. time) by 20-25% or more would be considered clinically meaningful.[19] Other measurements of function in ALS patients have also included strength testing to evaluate limb function.[12]

Pharmacological treatment options to slow disease progression are few, and there is no evidence that FALS or SALS patients respond better to any particular available therapy.[20] Gamma aminobutyric acid (GABA) modulators and recombinant human insulin-like growth factor-1 (IGF-1) have been studied to improve

function or survival in adult ALS patients, but there is insufficient evidence available to support use of either agent to mitigate the degenerative effects of the disease.[20,21,22] Until recently, the glutamate inhibitor riluzole was the only agent FDA approved for ALS treatment.[2] The AAN and National Institute for Heath and Care Excellence (NICE) guidelines have both recommended that riluzole be offered to ALS patients by a neurological specialist to slow disease progression.[11,23] A 2011 updated Cochrane Review examined the efficacy of riluzole in prolonging survival and in delaying the use of surrogates to sustain survival.[24] Evidence from four RCTs of acceptable methodological quality with 1477 ALS patients were reviewed.[24] Three of the four studies with full data on tracheostomy-free survival were compared.[24] Riluzole 100 mg per day provided a benefit for the homogeneous group of patients in the first two trials (hazard ratio (HR) 0.80, 95% confidence internal (CI) 0.64 to 0.99, P= 0.042).[24] The third trial included older patients with more advanced disease, however, the pooled treatment effects were still significant (HR 0.84, 95% CI 0.698 to 0.997, P= 0.046).[24] The results indicated that riluzole therapy for ALS patients was associated with an increased median survival benefit of 11.8 to 14.8 months versus placebo.[24] The exact mechanism for the therapeutic benefit of riluzole in ALS has not been determined. Assessment of functional improvement with the ALSFRS-R tool was not performed in riluzole-treated patients.[24]

Clinical Efficacy:

Edaravone is a free radical scavenger indicated for the treatment of adults with ALS.[2] Edaravone is thought to hinder functional nerve cell deterioration through the reduction of oxidative stress to the cell membranes.[23] The specific mechanism by which edaravone may function in the treatment of ALS in unknown.[2] Edaravone's utility in the treatment of ALS was first recognized in Japan and Korea, then approved for use in the United States in May 2017 as an orphan drug.[1,25] See **Appendix 1** for Highlights of Prescribing Information from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. The clinical trial by Abe et al. (Study 19) which contributed to edaravone's FDA approval in ALS patients is described below and evaluated in **Table 3**.

Key prognostic factors used to develop inclusion and exclusion criteria for Study 19 were initially identified through post-hoc analysis of a failed phase 3, randomized, double-blind, parallel-group, placebo-controlled trial of edaravone in Japanese ALS patients (n=206).[25,26] The primary efficacy end point was the mean change in ALSFRS-R score.[25] The study was unable to find a statistically significant different ALSFRS-R score between placebo and edaravone at 24 weeks [placebo -6.35 ± 0.84 vs. edaravone -5.70 ± 0.85 (95% CI, -0.90 to 2.19, p = 0.411)], but data from this trial was used to develop inclusion and exclusion criteria in Study 19.[25,26]

Study 19, was a fair-quality, 24-week, phase 3, double-blind, placebo-controlled, RCT (n=137) which evaluated the efficacy and safety of edaravone in a specific ALS population of independently-living Japanese patients.[1] The trial applied stricter enrollment critiera than the previous study. Subjects were required to undergo a 12-week pre-observational screening period to establish baseline function. Only participants with a diagnosis of definite or probable ALS with a disease duration of less than or equal to 2 years (rather than <3 years), a score of 2 or more on all items in the ALSFRS-R, and a FVC of at least 80% (rather than $\geq$70%) were allowed to complete the study.[1] The baseline characteristics between edaravone and placebo groups were generally well matched. Subjects had a mean disease duration of 1.1 years, the majority (72%) had a baseline disease severity of 2 on the 5 point Japanese ALS severity scale (5 = most severe), and 91% were on concomitant riluzole therapy (see **Table 3** for additional inclusion criteria and baseline characteristics).[1] Patients were randomized 1:1 to receive six cycles of 60 mg edaravone IV once-daily for 14 days followed by 14 days off drug or a matching placebo treatment.[1] All subsequent cycles (cycles 2-6) were 10 of 14 days on drug, followed by 14 days off drug.[1] The primary outcome measure was the least-squares mean change in ALSFRS-R score from baseline to 24 weeks (or at discontinuation if after cycle 3 of 6).[1]

At 24 weeks, edaravone patients demonstrated a statistically significant least squares mean difference in the ALSFRS-R score versus placebo from baseline through cycle 6 (-5.01 vs. -7.5, respectively), with an intergroup adjusted mean difference of 2.49 (95% CI, 0.99 to 3.98; P = 0.001).[1] Though statistically

significant, a -5.01 unit decline did not appear to meet the threshold for a clinically important change in the ALSFRS-R score compared to the expected -5.52 unit decline over 6 months cited in other medical studies.[18,19] Additionally, the outcome measure did not reach the 9-point or more ALSFRS-R improvement threshold reported to be discernable by patients.[18] It is unclear why placebo-treated patients in Study 19 declined at a much faster rate than expected. The ALSFRS-R measurement tool may not be sensitive to changes over a short-term trial, and therefore, the clinical relevance is unclear.

The study had several unanswered questions related to the integrity of the trial and applicability to the general ALS population. The study sponsor, Mitsubishi Tanabe Pharma Corporation, was involved in the study design, study monitoring, data collection and management, statistical analysis, data interpretation, and writing of the draft report of the analysis.[1] The 12-week observational period protocol details were not reported. Concealment of allocation and randomization procedure details were not fully disclosed. Only subjects with >80% FVC at baseline were included in the trial while those with scores of 3 or less on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency were excluded. Therefore, the efficacy of edaravone in treating more advanced ALS patients with respiratory issues is unknown. The inter-rater reliability of clinician ALSFRS-R score assessment was unclear and at least one patient evaluation at the end of cycle 2 was excluded from the efficacy analysis due to inadequate clinician training. The secondary endpoints of percent of FVC, Modified Norris Scale scores, grip strength, and pinch strength yielded mixed results, and the analyses were not statistically adjusted for multiplicity *a priori*. Additionally, there is no evidence that edaravone had any effect on patient survival. The trial was conducted entirely in Japan, therefore, efficacy rates for non-Asian populations is unknown. Overall, edaravone demonstrated uncertain clinical benefit in a small, select group of Japanese patients with early ALS. Until further studies are published to support use in a wider ALS population, the clinical effectiveness of edaravone for Oregon Medicaid patients is unclear.

Clinical Safety:

A total of 349 patients received edaravone in the ALS clinical trials, 306 patients received edaravone for at least 6 months (6 cycles), and 98 patients received edaravone for at least 12 months (12 cycles).[27] Safety analyses from pooled controlled clinical trials (n=368) showed no major imbalances between edaravone and placebo groups.[2,27] A similar mortality rate was observed in edaravone- versus placebo-treated patients [4/184 (2.2%) vs. 2/184 (1.1%), respectively].[27] All 6 patient deaths were due respiratory failure attributed to disease progression and not drug-related as judged by authors and the FDA.[26] Discontinuation rates due to adverse events were higher overall in placebo-treated patients (5%) than in edaravone-treated patients (2%) with the main driver related to respiratory, thoracic, and mediastinal disorders.[2,27] Serious adverse events (SAE) were reported more frequently in placebo treated patients (22%) than edaravone-treated patients (17%; statistical significance not reported) with dysphagia listed as the most common occurrence at similar rates in both edaravone and placebo groups (9.8% and 10.3%, respectively).[27] No SAEs were identified as distinctly drug-related.[2,27] The most common adverse events in at least 5% of the edaravone-treated subjects that occurred at 2% or higher frequency compared to placebo included contusion, gait disturbance, headache, eczema, and contact dermatitis (**Table 1**).[2,27] Since the trials were of short duration and included small numbers of patients with early stages of ALS, the long-term safety effects remain unknown.

Table 1. Selected Adverse Reactions with an Incidence in ≥5% of Edaravone-treated Patients and ≥2% than Placebo [2,27]

	Edaravone (n=184)	Placebo (n=184)
Contusion	15%	9%
Gait disturbance	13%	9%
Headache	8%	5%
Eczema	7%	2%
Dermatitis, contact	6%	3%

Patients should be monitored for hypersensitivity and sulfite reactions.[27] The limited ECG data provided did not identify a QT prolongation signal, and there was no thorough QT (TQT) study performed.[27] No REMS was required for edaravone.[27]

No look-alike/sound-alike error risk potential was identified.

Table 2. Pharmacology and Pharmacokinetic Properties.[2,27,28]

Parameter	
Mechanism of Action	Edaravone is a member of the substituted 2-pyrazolin-5-one class. The mechanism for therapeutic effects in amyotrophic lateral sclerosis is uncertain.
Oral Bioavailability	N/A – administered as an intravenous infusion
Distribution and Protein Binding	Albumin: 92%
Elimination	Renal excretion: 1% unchanged; 70% to 90% as the glucuronide form; and 5% to 10% as the sulfate conjugate
Half-Life	4.5 to 6 hours
Metabolism	Metabolized to a sulfate conjugate and a glucuronide conjugate in the liver and kidney which are not pharmacologically active.

Comparative Endpoints:

Clinically Relevant Endpoints:
1) Functional or symptom improvement
2) Quality of life
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in ALSFRS-R score (baseline to cycle 6)

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Abe et al., 2017 (Study 19)[1] Radicava FDA Medical Review[27] Radicava FDA Summary Review[2] Radicava FDA Statistical Review[26] Phase 3 MC, DB, PC, RCT	1. Edaravone 60 mg IV infusion 2. Placebo (saline) IV infusion Cycle 1: once daily x 14 consecutive days followed by a 2-week drug-free period; in Cycle 2 and thereafter, once daily x 10 days within a 2-week period followed by a 2-week drug-free period. All patients completing 6 cycles of therapy were offered the option of continuing open-label treatment with edaravone for an additional 6 cycles.	Demographics: •57% male •67% of patients < 65 years of age •98% diagnosed with sporadic ALS (as opposed to familial) •60% of patients with probable ALS diagnosis •72% Grade 2 ALS severity (according to Japanese ALS Severity Classification, grade 1-5, 5 = most severe) •91% concomitant riluzole use •Mean baseline ALSFRS > 43 Key Inclusion Criteria: -Age 20-75 yo -Independent living status (grade 1 or 2 in the Japan ALS Severity Classification) -Decrease in the Revised ALS Functional Rating Scale (ALSFRS-R) score of 1-4 during a 12 week obs period -Scores ≥ 2 on all 12 items of ALSFRS-R -FVC > 80% -Definite or probable ALS (according to the El Escorial and revised Airlie House criteria) -Duration of disease from first sign of any ALS symptom, is 2 years or less.	ITT: 1. 69 2. 68 mITT: 1. 68 2. 66 Attrition: 1. 2 (3%) 2. 8 (12%)	Primary Endpoint: Least-squares mean change (± standard error) in the ALSFRS-R score at the end of cycle 6 or at discontinuation: Edaravone: -5.01 ± 0.64 Placebo: -7.50 ± 0.66 LSMD: 2.49 ± 0.76 (95% CI, 0.99 to 3.98); P = 0.001 Secondary Endpoints: Change in Percent FVC Edaravone: -15.61 ± 2.41 placebo: -20.40 ± 2.48 LSMD: 4.78 ± 2.84 (95% CI, -0.83 to 10.40), p=0.0942 Change in total Modified Norris Scale score (0-102 [best]) Edaravone: -15.92 ± 1.97 Placebo: -20.80 ± 2.06 LSMD: 4.89 ± 2.35 (95% CI, 0.24 to 9.54), p=0.0393 FDA statistical review[26] p=0.052 Change in grip strength(kg) – Mean for left and right hands Edaravone: -4.08 ± 0.54 placebo: -4.19 ± 0.56 LSMD: 0.11 ± 0.64; (95% CI, -1.15 to 1.38); p = 0.8583 Change in pinch strength(kg) – Mean for left and right hands Edaravone: -0.78 ± 0.14 placebo: -0.88 ± 0.14 LSMD: 0.10 ± 0.16 (95% CI, -0.23 to 0.42); p = 0.5478 Change in ALSAQ-40 score (200-40 [best]) Edaravone: 17.25 ± 3.39	N/A N/A NS N/A NS NS NS	Outcome: Death Edaravone: 2.2% Placebo: 1.1% Death within 6-month extension period Edaravone: 4% Placebo 4% SAE: Edaravone: 17% Placebo: 22% Discontinuation due to AEs: Edaravone: 2.2% Placebo: 5.4%	N/A N/A N/A N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Minimization method used with stratification for ALS diagnosis; baseline characteristics balanced; method of allocation concealment not described Performance Bias: Unclear. Edaravone and placebo were provided in ampules that were indistinguishable in appearance and packaging; patients unable to access the key code until unblinding; investigators masked to treatment groups but had key code access Detection Bias: Unclear. Funder and investigators were privy to access key code so whether blinding was successful or not was unknown Attrition Bias: Low. Few patients with missing data at the end of Cycle 6, data imputed by LOCF; differential attrition 6%; sensitivity analysis performed Reporting Bias: High Patient censoring rules not disclosed; The study funder (Mitsubishi Tanabe Pharma Corporation) was involved in study design, study monitoring, data collection and management, statistical analysis, data interpretation, and writing of the draft report of the study; most investigators received personal fees or were paid employees of Mitsubishi Tanabe; not all clinicians assessing ALSFRS-R score had adequate training which lead to at least one patient's analysis being excluded; did not address multiplicity of secondary endpoints *a priori*; secondary endpoint of time to death/disease progression not reported in table **Applicability**: Patient: Highly selective inclusion criteria limits applicability to a broader population; All Japanese patients with ALS Severity Score in categories 1 or 2; excluded patients with respiratory dysfunction and advanced ALS. Intervention: Efficacy assessed at multiple instances before pre-observation, at baseline before the start

		Key Exclusion Criteria: -Score ≤ 3 on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency -Spinal surgery history after ALS onset -CrCl ≤ 50mL/min		placebo: 26.04 ± 3.53 LSMD: -8.79 ± 4.03 (95% CI, -16.76 to -0.82); p = 0.0309 Number of events involving death or certain disease progression events (death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech) Edaravone: 2 Placebo: 6 Log-rank test, P = 0.1284 Generalized Wilcoxon test, P = 0.1415	N/A NS			of Cycle 1, and after the 2-week observation period of each treatment cycle; No supratherapeutic dose/exposure studied; Most subjects were concurrent users of rizuole, and changes in dose or regimen were not permitted Comparator: Placebo appropriate to determine efficacy. Comparison with riluzole may have been a more meaningful comparator to establish place in therapy. Outcomes: Short term subjective scale used to assess speed of decline at early stage ALS; No established MCID for ALSFRS-R; Trial was not designed to detect a survival difference as survival trials require large numbers of patients studied for long periods Setting: All 31 sites in Japan
Abbreviations: AE = adverse events; ARR = absolute risk reduction; ALSAQ40 = Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Respiratory; CI = confidence interval; CrCl = creatinine clearance; FVC = forced vital capacity; ITT = intention to treat; LOCF = last observation carried forward; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; obs = observational; PP = per protocol; SAE = serious adverse events; YO = years old							

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28. Radicava (edaravone injection) [prescribing information] Jersey City, NJ, MT Pharma America, Inc; 2017

Appendix 1: Prescribing Information Highlights

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

RADICAVA (edaravone injection), for intravenous use
Initial U.S. Approval: 2017

---------- **INDICATIONS AND USAGE** ----------
RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS) (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
The recommended dosage is 60 mg administered as an intravenous infusion over 60 minutes as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. (2)

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Injection: 30 mg/100 mL in a single-dose polypropylene bag (3)

---------- **CONTRAINDICATIONS** ----------
Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in RADICAVA (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- Hypersensitivity Reactions: Advise patients to seek immediate medical care (5.1)
- Sulfite Allergic Reactions: RADICAVA contains sodium bisulfite, which may cause allergic type reactions (5.2)

---------- **ADVERSE REACTIONS** ----------
Most common adverse reactions (at least 10% and greater than placebo) are contusion, gait disturbance, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MT Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

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

Revised: 5/2017

Edaravone (Radicava™)

Goal(s):

- To encourage use of riluzole which has demonstrated mortality benefits.
- To ensure appropriate use of edaravone in populations with clinically definite or probable amytrophic lateral sclerosis
- To monitor for clinical response for appropriate continuation of therapy

Length of Authorization:

Up to 12 months

Requires PA:

- Edavarone (pharmacy and physician 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 ICD10 code.	
2. Is this a treatment for amyotrophic lateral sclerosis (ALS) for a patient ≥20 years of age?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for continuation of therapy of previously approved FFS criteria (after which patient has completed 6-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a documented diagnosis of clinically definite or probable ALS based on revised El Escorial Criteria (rEEC)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is the patient currently on riluzole therapy, OR have a documented contraindication or intolerance to riluzole?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have documented percent-predicted forced vital capacity (%FVC) ≥ 80%?	**Yes:** Record lab result. Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there a baseline documentation of the revised ALS Functional Rating Scale (ALSFRS-R) score with ≥2 points in each of the 12 items?	**Yes:** Record baseline score. (0 [worst] to 48 [best]) Approve for 6 months based on FDA-approved dosing.*	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the medication being prescribed by or in consultation with a neurologist?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the prescribing physician provided documentation that the use of Radicava (edarvone) has slowed in the decline of functional abilities as assessed by a Revised ALS Functional Rating Scale (ALSFRS-R) with no decline more than expected given the natural disease progression (5 points from baseline over 6 months)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

* = see below for summary of FDA-approved dosage and administration. Consult FDA website for prescribing information details at www.fda.gov

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P&T/DUR Review: 7/18 (DE)
Implementation: TBD

***Dosage and Administration:**

60 mg (two consecutive 30 mg infusion bags) IV infusion over 60 minutes

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free period

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

OHSU Drug Effectiveness Review Project Summary Report – Non-Opioid Drugs to Treat Neuropathic Pain

Date of Review: July 2018 **Date of Last Review:** March 2017 (DURM); June 2011 (DERP)

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

Research Questions:

1. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), topical capsaicin, and topical lidocaine for neuropathic pain?
2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine for neuropathic pain?
3. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine versus opioids for neuropathic pain?
4. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin, and topical lidocaine versus opioids for neuropathic pain?
5. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in benefits and harms of anticonvulsants, tricyclic antidepressants, SNRIs, topical capsaicin patch, topical lidocaine, and opioids when used to treat neuropathic pain?

Conclusions:

- The strength of evidence for most outcomes within the OHSU Drug Effectiveness Review Project (DERP) report is low or insufficient, as data come from single studies and are imprecise.[1]
- Nortriptyline and morphine SR were not found to differ in alleviating pain or differ in adverse event outcomes after 4 weeks of treatment for chronic sciatica in a small, fair-quality randomized controlled trial (RCT).[1]
- Pregabalin and gabapentin were not found to differ in either pain control or adverse events in 2 small, fair quality RCTs.[1]
- When pregabalin was compared to duloxetine in diabetic neuropathy, the evidence was mixed depending on the outcome measured. For reduction in pain of at least 50%, duloxetine was superior to pregabalin in a good-quality, 8-week RCT (40.3% versus 27.8%, P<0.001).[1] However, there was no difference noted between pregabalin and duloxetine in mean change in pain (using visual analog scale of 0-100) in a fair-quality, 12-week trial.[1]
- Gabapentin reduced pain scores more than amitriptyline in a fair-quality, open-label, 12-week study in patients (n=25) with diabetic neuropathy (4 point intensity scale, -1.9 vs. -1.3, P=0.026).[1] The absolute difference observed in this trial was small. In a small, fair quality trial comparing gabapentin to amitriptyline in cancer patients with neuropathic pain, there was no difference in pain control or adverse event withdrawals at 6 months.[1]
- Moderate quality evidence indicates capsaicin patch and pregabalin were not significantly different in pain response, but fewer patients on capsaicin withdrew due to adverse events.[1]
- No evidence was identified that evaluated subgroups of patients for which benefits or harms of neuropathic pain treatments might differ.

- Lyrica® CR (pregabalin extended-release) was approved by the United States Food and Drug Administration (FDA) in October 2017 for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN).[2]
- Qudexy® XR and Trokendi XR (topiramate extended-release) received an expanded indication from the FDA in early 2017 for prophylaxis of migraine headache in adults and adolescents 12 years of age and older.[3,4]

Recommendations:
- No further review or research at this time.
- Maintain pregabalin extended-release tablets as a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP). Apply clinical prior authorization (PA) criteria to pregabalin extended-release tablets.
- Review costs in executive session.

Previous Conclusions:

Efficacy

Recent comparative trials do not reveal a clear preference for one class of medications over another for management of neuropathic pain. Moderate quality evidence exists to support the use of pregabalin to manage central neuropathic pain. Moderate quality evidence shows that duloxetine is an effective agent to manage chronic low back pain (LBP). Low quality evidence supports the safety and efficacy of desipramine and amitriptyline in management of DPN or PHN. Low quality evidence supports the efficacy of carbamazepine in trigeminal neuralgia, DPN, and post-stroke pain. Moderate quality evidence shows no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treatment of DPN. Moderate quality evidence indicates little or no effect for lamotrigine, oxcarbazepine and topiramate for treatment of neuropathic pain. There is insufficient evidence to demonstrate the efficacy of valproic acid, lacosamide, levetiracetam, and phenytoin in management of neuropathic pain.

There is insufficient evidence to evaluate the effect of antiepileptics to manage acute nonradicular LBP. There is insufficient evidence to support the use of topical lidocaine in mixed peripheral neuropathic pain. There is insufficient evidence to support the use of milnacipran for management of neuropathic pain.

Safety

There is insufficient comparative evidence in patients with neuropathic pain or chronic pain to assess comparative safety. Moderate quality evidence revealed approximately 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well. Withdrawals due to adverse events were much higher with antiepileptics than placebo. Moderate quality evidence showed that adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3). Adverse events noted with gabapentin included somnolence, dizziness, peripheral edema and gait disturbances. Low quality evidence showed that 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo.

Previous Recommendations:
- Revise prior authorization (PA) criteria to restrict use to funded pain conditions and include separate PA criteria for the following medications:
    - Pregabalin
    - Milnacipran
    - Lidocaine Patch
    - Topiramate Extended Release (non-preferred products)
- Add quantity limit of 3 patches/24 hours for topical lidocaine patches which is the maximum approved daily dose to insure safe use.

Methods:
The March 2018 report on non-opioid drugs to treat neuropathic pain by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
A number of non-opioids are available for treating neuropathic pain and are broadly characterized as anticonvulsants, antidepressants, or topical analgesics.[1] **Appendix 1** lists the specific medications included in the DERP report that are also part of the Oregon Medicaid Fee-for-Service Preferred Drug List (PDL). The objective of the DERP report is to compare the effectiveness and safety of the drugs shown in **Appendix 1** for neuropathic pain, and to provide evidence for potential alternatives to opioids. The types of neuropathic pain in adults with chronic pain (3 months or greater in duration) included in the DERP summary are:

- Painful diabetic neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Cancer-related neuropathic pain
- HIV-related neuropathic pain
- Central/post-stroke neuropathic pain
- Neuropathy associated with low back pain
- Peripheral nerve injury pain
- Phantom limb pain
- Guillain-Barre syndrome
- Polyneuropathy
- Spinal cord injury-related pain
- Complex regional pain syndrome

Searches were conducted through November 2017 and included RCTs of at least 8 weeks duration, cohort or case-control studies of harms, and network meta-analyses. Thirteen RCTs and 1 systematic review with a network meta-analysis (NMA) met DERP inclusion criteria. The NMA conclusions are excluded from this report because strength of evidence based on such indirect evidence is generally considered low.[1] The RCTs included 1 trial comparing an opioid to a neuropathic pain drug, 10 trials of anticonvulsant comparisons, 1 trial of tricyclic antidepressant comparisons, and 1 trial of topical analgesic comparisons. No evidence met the DERP criteria for SNRI comparisons.

Direct Comparisons

Neuropathic Pain Drugs compared with Opioids: Nortriptyline compared with Morphine

One small (N=55), fair-quality RCT compared nortriptyline (mean dose: 84 mg daily) with morphine sustained-release (SR) [mean dose: 62 mg daily] in patients with chronic sciatica.[5] Doses were titrated upwards over 2 weeks, then maintained at the highest tolerated dose for 2 weeks.[5] The mean duration of pain was 5 years, mean age was 53 years, and 45% of subjects were female. Using a pain rating scale of 0 to 10 (10 = worst pain), patients experienced a 14% reduction in leg pain with nortriptyline and a 7% reduction with morphine SR; this difference was not significant.[5] Average back pain was significantly better with nortriptyline compared with morphine SR (p=0.02).[5] Secondary outcomes (quality of life on the Short Form Health Survey [SF-36], depression on the Beck Depression scale, and disability on the Owestry Disability Index) were not significantly improved by either treatment.[5] Two patients withdrew due to adverse events while taking maximal doses of nortriptyline or morphine SR.[5] This evidence was insufficient for drawing conclusions because it consisted of a single small study that was not of good quality.[1]

Anticonvulsant Drug Comparisons: Pregabalin compared with Gabapentin or Gabapentin Enacarbil

Two small fair-quality trials compared pregabalin to gabapentin in patients with painful diabetic neuropathy (N=102)[6] and peripheral nerve injury (N=30) for 12 weeks.[7] There were no significant differences between drugs in pain control as evaluated by a 100-point visual analog scale (VAS) or adverse events in either of the two trials.[1]

A third fair-quality trial (n=420) compared pregabalin to 3 different doses of gabapentin enacarbil or placebo in patients with diabetic neuropathy.[8] The primary analysis in this study compared the drugs with placebo, and found no significant difference in mean change in 24-hour average pain intensity at 12 weeks.[8] The DERP analysis of head-to-head comparisons found a mixed pattern, with 1200 mg daily and 3600 mg daily of gabapentin enacarbil reducing pain scores more than pregabalin (-2.55 vs. -1.66, p=0.02; -2.54 vs. -1.66, p=0.01, respectively), while 2400 mg daily dose of gabapentin enacarbil was not significantly different from pregabalin (-1.90 vs. -1.66; p = 0.50).[1] Neither drug was significantly different compared to placebo on the SF-36 physical and mental component scores or on daily dose of rescue medications.[1] Overall, adverse events were frequent and similar between treatments, although peripheral edema was more frequent with pregabalin (p<0.01).[1] There was also a trend toward greater likelihood of discontinuing the study due to adverse events with the higher doses of gabapentin enacarbil.[1] However, evidence on adverse event withdrawals was insufficient to draw conclusions.[1]

Anticonvulsants compared with Antidepressants

Pregabalin compared with Duloxetine

One good-quality trial of patients with diabetic peripheral neuropathic pain compared standard doses of duloxetine (60 mg daily) to pregabalin (300 mg daily) in the first phase of a trial that was 8 weeks in duration (n=804).[9] Study participants in both trial phases were predominantly white (>80%) and had median pain duration of 2 years.[9] In the first phase of the trial, patients taking duloxetine experienced greater pain relief than patients taking pregabalin (40.3% of patients on duloxetine reported 50% or greater improvement on the Brief Pain Inventory Modified Short Form compared with 27.8% of patients on pregabalin, p<0.001).[1] There was no statistically significant difference in withdrawals due to adverse events (12.4% for pregabalin vs. 11.5% for duloxetine).[9] The second phase of the trial (n=339) was also 8 weeks in duration, and assessed patients not responding to standard doses of pregabalin or duloxetine. In the second phase, patients were randomized to combining the medications (duloxetine 60 mg daily and pregabalin 300 mg daily) or increasing each to its maximum recommended dose (duloxetine 120 mg daily or pregabalin 600 mg daily).[9] The trial found no significant differences in either pain control (p=0.068) or withdrawals due to adverse events (4.7% vs. 4.1%) between high-dose monotherapy compared with combination therapy.[1]

One fair-quality RCT compared gabapentin 300 mg to 1800 mg daily, duloxetine 20 mg to 120 mg daily, and pregabalin 75 mg to 300 mg daily (n=152).[6] This 12-week trial was conducted in India in patients with diabetic neuropathy, with an average duration of diabetes of 8.1 years. Pain decreased in both the duloxetine and pregabalin groups over time with no difference between groups as measured by a visual analog scale (VAS scale of 0 to 100), and there were no differences in adverse events and no withdrawals due to adverse events in either study group.[6] The evidence for withdrawals due to adverse events was insufficient for drawing conclusions because it consisted of a single small study that was not of good quality.[1] The applicability of this trial to the Oregon Medicaid Fee-For-Service- population is limited due to the demographics of the study population.

Gabapentin compared with Amitriptyline

One fair-quality study compared gabapentin to amitriptyline in 25 patients with diabetes.[10] The open-label study of diabetic neuropathy treated patients for 12 weeks and measured pain intensity on a scale from 0 (no pain) to 4 (excruciating pain).[10] While both drugs showed statistically significant decreases in pain scores, the decrease was greater with gabapentin than with amitriptyline (-1.9 vs. -1.3, P=0.026), although the absolute difference was small.[1] The results of this trial cannot be considered conclusive because of the small sample size and lack of blinding.[10]

In a fair quality trial of 88 cancer patients with neuropathic pain treated for 6 months, gabapentin or amitriptyline were co-administered with tramadol.[11] There was no difference between gabapentin and amitriptyline in pain intensity using a 0 to 4 VAS scale at the end of treatment (p>0.05).[11] There was also no difference in pain scores on a 10 point VAS at any point in the course of the study, including at the end of the study (p=0.482).[11] Evidence was insufficient to compare the use of rescue analgesia between two drugs.[1] There were no serious adverse events, and no patients withdrew because of adverse events.

Anticonvulsants compared with Topical Analgesics: Capsaicin Patch compared with Pregabalin

One fair-quality trial compared the 8% capsaicin patch with pregabalin in patients (n=559) with peripheral neuropathy.[12] Authors compared scores ranging from 0 to 10 on a numeric pain rating scale (NPRS) between baseline and 8 weeks of treatment.[1] Patients with a decrease in NPRS score of 30% or more were defined as responders.[1] At 8 weeks, there was no statistically significant difference in pain response between the capsaicin patch and pregabalin (56% vs. 55%, odds ratio (OR) 1.03, 95% CI 0.72 to 1.50).[12] However, patients treated with capsaicin responded sooner than those given pregabalin (7.5 days vs. 36.0 days, hazard ratio (HR) 1.68, 95% CI 1.35 to 2.08, p<0.0001).[12] Serious adverse events were not reported. No patient in the capsaicin group discontinued treatment due to adverse events, while 8.5% (n=24) of those treated with pregabalin did so.[12] The most common adverse effects reported with pregabalin were somnolence (16%) and dizziness (20%).[12] Application site pain (24%), erythema (21%), and burning sensation (16%) were the most frequently reported adverse effects with capsaicin.[12]

In summary, this DERP report evaluated non-opioid drugs to treat neuropathic pain. The strength of evidence for most outcomes within this report was low or insufficient, as data came from single studies and were imprecise.[1] Most comparisons failed to show significant differences in outcomes related to pain control or adverse events between treatments[1]. Studies failed to report on the use of rescue analgesia, and outcomes were reported differently across studies.[1] Previously published literature reported effective analgesia for neuropathic pain with pharmacotherapy was achieved in less than half of patients.[13-15]

New Formulations or Indications:

1.Lyrica® CR (pregabalin extended-release tablets) was approved by the FDA in October 2017 for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN).[2] The efficacy of pregabalin extended-release tablets has not been established for the management of fibromyalgia or as adjunctive therapy for adults patients with partial onset seizures.[2] Support for efficacy of pregabalin extended-release in DPN and PHN is based based on the efficacy of pregabalin immediate-release for these indications along with a 19-week, placebo-controlled RCT of pregabalin extended-release in adults with PHN.[2] According to the prescribing information for pregabalin extended-release, 73.6% of patients in the pregabalin extended-

release arm achieved at least 50% improvement in pain intensity compared to 54.6% of patients in the placebo arm.[2]

The recommended initial dose of pregabalin extended-release is 165 mg once daily after the evening meal. The dose may be titrated up to 330 mg per day within 1 week.[2] If patients with PHN do not experience significant pain relief following 2 to 4 weeks of treatment with pregabalin extended-release 330 mg per day, the dose may be increased to 660 mg per day as tolerated.[2] The maximum recommended dose of pregabalin extended-release for management of DPN is 330 mg per day and for PHN is 660 mg per day.[2] There is no evidence that the higher dose of pregabalin immediate-release confers additional significant benefit and this dose was less well tolerated in clinical trials.[2] Pregabalin extended-release tablets are not recommended for patients with creatinine clearance less than 30 mL/min or who are undergoing hemodialysis.[2] Due to extensive renal excretion, dosing adjustments of pregabalin extended-release are recommended for patients with creatinine clearance between 30 and 60 mL/min.[2] Pregabalin extended release tablets are available as 82.5 mg, 165 mg and 330 mg tablets.[2]

2.Qudexy® XR (topiramate extended-release) capsules received an expanded indication from the FDA in March 2017 for prophylaxis of migraine headache in adults and adolescents 12 years of age and older.[3] Another formulation of topiramate extended-release capsules (Trokendi XR®) received the expanded indication for migraine prophylaxis in adults and adolescents aged 12 years and older in April 2017.[4] Topamax® (topiramate immediate-release) capsules have been FDA-approved for migraine prophylaxis in adults and adolescents aged 12 years and older since March 2014.[16] Janssen, the manufacturer of Topamax® held exclusivity for migraine prophylaxis in the adolescent population until the patent expired in March 2017. The recommended dose for migraine prophylaxis with topiramate extended-release is 25 mg once daily at nighttime for the first week, followed by weekly dose increases increments of 25 mg to a maximum dose of 100 mg once daily.[3]

New FDA Safety Alerts:
No new safety alerts identified**.**

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Appendix 1: Current Preferred Drug List

Antiepileptics

Route	Form	Brand	Generic	PDL	Carveout
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	CAP DR SPR	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP DR SPR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	Y	
ORAL	TABLET	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	

ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	ROWEEPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	VIMPAT	LACOSAMIDE	Y	
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (BLUE)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (GREEN)	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMICTAL (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT (GREEN)	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT (GREEN)	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (BLUE)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (GREEN)	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR (ORANGE)	LAMOTRIGINE	V	Y
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	CAP SPRINK	TOPAMAX	TOPIRAMATE	N	
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N	
ORAL	CAP ER 24H	TROKENDI XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	QUDEXY XR	TOPIRAMATE	N	
ORAL	CAP SPR 24	TOPIRAMATE ER	TOPIRAMATE	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	

ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N
ORAL	TAB SUSP	SPRITAM	LEVETIRACETAM	N
ORAL	CAPSULE	LYRICA	PREGABALIN	N
ORAL	SOLUTION	LYRICA	PREGABALIN	N
ORAL	SOLUTION	VIMPAT	LACOSAMIDE	N
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N
ORAL	TABLET	FYCOMPA	PERAMPANEL	N
ORAL	ORAL SUSP	FYCOMPA	PERAMPANEL	N
ORAL	SOLUTION	BRIVIACT	BRIVARACETAM	N
ORAL	TABLET	BRIVIACT	BRIVARACETAM	N
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N
ORAL	TABLET ER 24H	LYRICA CR	PREGABALIN	N

Antidepressants: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants

Route	Form	Brand	Generic	PDL	Carveout
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	PAMELOR	NORTRIPTYLINE HCL	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	EFFEXOR XR	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	VENLAFAXINE HCL ER	VENLAFAXINE HCL	Y	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE SUCCINATE ER	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	TAB ER 24H	PRISTIQ	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y

ORAL	TAB ER 24	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y

Miscellaneous

Route	Form	Brand	Generic	PDL	Carveout
PO	TABLET	SAVELLA	MILNACIPRAN HCL		
PO	TAB DS PK	SAVELLA	MILNACIPRAN HCL		

Topical Analgesics

Route	Form	Brand	Generic	PDL	Carveout
TOPICAL	CREAM (G)	CAPSAICIN	CAPSAICIN	Y	
TOPICAL	CREAM (G)	ARTHRITIS PAIN RELIEVING	CAPSAICIN	Y	
TOPICAL	LIQUID	CAPSAICIN	CAPSAICIN	N	
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2018 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March Week 2 2018

1.	brivaracetam.mp.	130
2.	eslicarbazepine.mp.	192
3.	perampanel.mp.	184
4.	gabapentin.mp.	5147
5.	PREGABALIN/	1581
6.	oxcarbazepine.mp.	1600
7.	levetiracetam.mp.	2466
8.	topiramate.mp.	3880
9.	lamotrigine.mp	4519
10.	gabapentin enacarbil.mp.	69
11.	Valproic Acid/	11561
12.	CARBAMAZEPINE/	10436
13.	PHENYTOIN/	13025
14.	levomilnacipran.mp.	48
15.	milnacipran.mp.	582
16.	Desvenlafaxine Succinate/	254
17.	Duloxetine Hydrochloride/	1366
18.	Venlafaxine Hydrochloride/	2338
19.	doxepin.mp. or DOXEPIN/	1300
20.	protriptyline.mp.	398
21.	IMIPRAMINE/	9792
22.	AMITRIPTYLINE/	6372
23.	nortritpyline.mp.	2
24.	desimpramine.mp.	3
25.	CAPSAICIN/	9722
26.	LIDOCAINE/	23161
27.	1 or 2 or 3 or 4 or 5 or 6 or 7 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 or 24 or 25 or 26	93906
28.	limit 27 to (english language and humans and yr="2017 -Current" and "all adult (19 plus years)" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	222
29.	Neuralgia/	11530
30.	28 and 29	15

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

- Pregabalin and pregabalin extended release

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 prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is the request for pregabalin immediate release?	**Yes:** Go to #4	**No:** Go to #5
~~3.~~4. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to #5~~4~~

Approval Criteria		
~~4.~~5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #~~6~~5	**No:** Pass to RPh. Deny; not funded by the OHP.
~~5.~~6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	

Non-funded		
Fibromyalgia	X	

P&T Review: *7/18 (DM); 3/18; 3/17*
Implementation: *4/1/17*

Milnacipran

Goal(s):
- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:
- 90 days

Requires PA:
- Milnacipran

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 the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Approve for 90 days	**No:** Pass to RPh. Deny; not funded by the OHP

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	

Diabetic Neuropathy	
Postherpetic Neuropathy	
Painful Polyneuropathy	
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	X

P&T Review: *7/18 (DM); 3/17*
Implementation: *4/1/17*

Lidocaine Patch

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to 12 months (criteria specific)

Requires PA:

- Lidocaine Patch

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 the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP
3.Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 4
4.Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days
Renewal Criteria		
1. Does the patient have documented improvement from lidocaine patch?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness.

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Lidocaine Patch
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	

Non-funded	
Fibromyalgia	

P&T Review: *7/18 (DM); 3/17*
Implementation: *4/1/17*

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

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 diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: “Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal.”	

P&T Review: *7/18 (DM); 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

Non-Opioid Drugs to Treat Neuropathic Pain

Final Report

Executive Summary

March 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Background

Neuropathic pain comprises a wide range of heterogeneous conditions. The recent International Association for the Study of Pain's (IASP) taxonomy working group has redefined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." Neuropathic pain may result from a large variety of insults to the peripheral or central somatosensory nervous system, including trauma, inflammation, ischemia, and metabolic and neoplastic disorders. Common examples of peripheral neuropathic pain include diabetic neuropathy and postsurgical neuralgia. Central neuropathic pain includes central post-stroke pain, pain in multiple sclerosis, and pain after spinal cord injury. The main clinical characteristics of neuropathic pain are continuous or intermittent pain, typically described as burning, aching, or shooting in quality, and abnormal sensitivity of the painful site to normally innocuous stimuli such as light touch by garments, running water, or even wind (allodynia).

Up to 8% of the general population reports neuropathic pain at some time. In the United States, health care and disability-related costs associated with neuropathic pain are estimated at almost $40 billion annually. A number of medications (oral or topical) are available for treating neuropathic pain (Table 1). Pharmacotherapy for neuropathic pain has generally involved the use of antidepressants or anticonvulsants, but even with the current generation of these drugs, effective analgesia is achieved in less than half of this population.

Opioids are the most effective broad-spectrum analgesics available and are considered the cornerstone of therapy for moderate-to-severe acute pain, but their long-term use in neuropathic pain is controversial. Particularly in light of the current opioid misuse epidemic happening in the United States, questions of benefit relative to harms associated with treatment are prominent.

Choosing therapy for neuropathic pain is challenging because of the large number of medications available to treat this condition and the potential differences in effectiveness and harms between medications. The objective of this report is to compare the effectiveness and safety of the drugs shown in Table 1 for neuropathic pain, and to provide evidence for potential alternatives to opioids.

Scope and Key Questions

1. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), memantine, the capsaicin patch, and the lidocaine patch for neuropathic pain?
2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch for neuropathic pain?
3. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch versus opioids for neuropathic pain?
4. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch versus opioids for neuropathic pain?
5. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in benefits and

harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, the lidocaine patch, and opioids when used to treat neuropathic pain?

Methods Summary

We followed systematic review methodology developed for DERP and that are in accordance with current guidance for systematic reviews, for example, dual review of inclusion decisions, quality assessments and data abstraction. Detailed methods are available upon request. Literature searches were conducted through November 2017 (with a search for mementine studies in January 2018).

Inclusion Criteria

Populations: Adults with chronic (≥3 months in duration) neuropathic pain

Comparators

- Other neuropathic pain drugs
- Opioids (any, including long-acting, short-acting, tramadol, and codeine)

Study Designs

- Randomized controlled trials of at least 8 weeks duration
- Cohort or case-control study of harms
- Published indirect and network meta-analyses

Table 1. Included Drugs

Generic Name	Trade Name(s)	First Approval
Anticonvulsants		
Brivaracetam	Briviact®	02/18/2016
Eslicarbazepine acetate	Aptiom®	11/08/2013
Perampanel	Fycompa®	10/22/2012
Gabapentin Enacarbil	Horizant®	04/06/2011
Lacosamide	Vimpat®	10/28/2008
Pregabalin	Lyrica®, Lyrica CR®	12/30/2004
Oxcarbazepine	Oxtellar XR®, Trileptal®	01/14/2000
Levetiracetam	Keppra®, Keppra XR™, Roweepra®, Spritam®	11/30/1999
Topiramate	Trokendi XR®, Topamax®, Qudexy XR®	12/24/1996
Lamotrigine	Lamictal®, Lamictal CD®, Lamictal ODT®, Lamictal XR®	12/27/1994
Gabapentin	Gralise®, Neurontin®	12/30/1993
Valproic acid/ Divalproex	Depakote®, Depakote ER®, Depakene®, Depacon®	02/28/1978
Carbamazepine[a]	Carbatrol®, Epitol®, Equetro®, Teril®, Tegretol®, Tegretol® XR	03/11/1968
Phenytoin	Dilantin®, Dilantin®-125, Phenytek®	01/6/1953
N-Methyl-D-aspartate receptor antagonists		
Memantine	Namenda®, Namenda XR®	10/16/2003
Serotonin-norepinephrine reuptake inhibitors		
Levomilnacipran	Fetzima®	07/25/2013
Milnacipran	Savella®	01/14/2009
Desvenlafaxine	Khedezla®, Pristiq®	02/29/2008
Duloxetine	Cymbalta®	08/3/2004
Venlafaxine	Effexor XR®	10/20/1997
Tricyclic antidepressants		
Doxepin	Silenor™	03/17/2010
Protriptyline	Vivactil®	08/24/1995

Imipramine	Tofranil®	05/22/1984
Amitriptyline	Generic	11/21/1977
Nortriptyline	Pamelor®	08/01/1977
Desipramine	Norpramin®	11/20/1964
Topical analgesics		
Capsaicin	Qutenza®	11/16/2009
Lidocaine	Lidoderm®	03/19/1999

[a] An injectable form of carbamazepine (Carnexiv™) is available.
Discontinued drugs and formulations are not listed in the table.

Results

Overview

This systematic review evaluated non-opioid drugs to treat neuropathic pain. We included 13 randomized controlled trials (RCTs), 10 of pregabalin versus other included drugs and 1 systematic review with a network meta-analysis. We found only 1 trial of opioids and none on serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, the lidocaine patch or memantine. For details of included studies, please see the full report.

Key Findings

Neuropathic Pain Drugs compared with Opioids

- Nortriptyline and morphine SR were not found different on pain or adverse event outcomes after 2 weeks at the highest tolerated dose in a small, fair-quality RCT.

Comparisons of Anticonvulsant Drugs

- Pregabalin compared with gabapentin or gabapentin enacarbil in painful diabetic neuropathy
  - Pregabalin and gabapentin were not different in pain control or adverse events in 2 small, fair-quality RCTs.
  - A fair-quality trial of pregabalin and 3 doses of gabapentin enacarbil (or placebo) found inconclusive results - **gabapentin enacarbil 1200 mg daily and 3600 mg daily reduced pain significantly more than pregabalin (-2.55 vs. -1.66, P=0.02; -2.54 vs. -1.66, P=0.01)** while 2400 mg daily was not significantly different. Adverse events were frequent and similar between treatments.

Comparisons of Anticonvulsant Drugs with Antidepressant Drugs

- Pregabalin compared with duloxetine in painful diabetic neuropathy
  - Evidence was mixed, depending on the outcome measured. For reduction in pain of at least 50%, duloxetine was superior to pregabalin in a good-quality, 8-week RCT **(40.3% versus 27.8%, P<0.001)** (strength of evidence: low). However, there was no difference in mean change in pain (using visual analog scale of 0-100) in a fair-quality, 12-week trial. Adverse event withdrawals were infrequent in both trials.
- Pregabalin compared with amitriptyline
  - An unpublished fair-quality trial found no difference in pain control between treatments (strength of evidence: low). There was no difference in adverse event outcomes.
- Gabapentin compared with amitriptyline
  - Gabapentin reduced pain scores more than amitriptyline in a fair-quality, 12-week study in patients with diabetic neuropathy **(-1.9 vs. -1.3, P=0.026).**
  - There was no difference in pain control or adverse event withdrawals at 6 months in a fair-quality study of cancer patients with neuropathic pain.

Comparisons of Anticonvulsant Drugs with Topical Analgesics

- Capsaicin patch compared with pregabalin
  - Capsaicin patch and pregabalin were not significantly different in pain response at 8 weeks in a fair-quality trial in patients with peripheral neuropathy (strength of evidence: moderate). In the subgroup of patients with **post-traumatic nerve injury, significantly more had achieved 30% or more improvement in pain with capsaicin patch (53% vs. 41%, RR 1.31, 95% CI 1.02 to 1.68)**.
  - **Significantly fewer patients withdrew due to adverse events with capsaicin than with pregabalin (0% vs. 8.5%, RR 0.04, 95% CI 0.005 to 0.29)** (strength of evidence: low).

Conclusions

This systematic review evaluated non-opioid drugs to treat neuropathic pain. The strength of evidence for most outcomes within this report was low or insufficient, as data came from single studies and were imprecise. Most comparisons failed to show significant differences in outcomes related to pain control or adverse events between treatments. Studies failed to report on the use of rescue analgesia, and outcomes were reported differently across studies. Key findings, or outcomes for which there was data to assess the strength of evidence, are summarized below.

Pregabalin and gabapentin were not found to be different in either pain control or adverse events. Findings indicate that gabapentin enacarbil may be better for pain than pregabalin, but further studies are needed. Evidence was mixed in comparing pregabalin with duloxetine, with one study finding duloxetine to be superior in reducing pain, but another showing no difference in mean change in pain. Additional larger, head-to-head studies are needed. Gabapentin was found to reduce pain scores significantly more than amitriptyline. Capsaicin patch and pregabalin were not significantly different in pain response in patients with peripheral neuropathy (strength of evidence: moderate), but significantly fewer patients withdrew due to adverse events with capsaicin than with pregabalin (strength of evidence: low).

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Prior Authorization Criteria Update: Sedatives

Purpose of Update:
The purpose of this prior criteria authorization update is to clarify the United States Food and Drug Administration (FDA)-recommended initial and maximum doses of zolpidem and to address use in palliative care settings.

The FDA-recommended initial dose for women is 5 mg for the immediate release formulation and 6.25 mg for the extended-release formulation while the recommended initial dose for men is either 5 mg or 10 mg for the immediate release formulation and either 6.25 mg or 12.5 mg for the extended-release formulation.[1,2] For both men and women, the FDA-recommended maximum daily dose is 10 mg for the immediate release formulation and 12.5 mg for the extended-release formulation.[1,2] Proposed updates to the prior authorization criteria clarify these recommendations to ensure safe and appropriate utilization.

The addition of palliative care setting management is proposed based on past prior authorization reconsideration requests. Similar management strategies in palliative care settings exist in the current Oregon Health Plan (OHP) fee-for-service (FFS) benzodiazepine and opioid prior authorization criteria.

Recommendation:

- Update the prior authorization criteria to clarify FDA-recommended initial and maximum daily dose recommendations as well as use in palliative care settings.

Proposed Prior Authorization Criteria:

Sedatives

Goal(s):

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent concomitant use of sedatives, benzodiazepines, and opioids.
- Restrict long-term sedative use to due to insufficient evidence and to limit adverse effects.
- Limit zolpidem use the maximum FDA recommended daily dose based on gender.

Length of Authorization:

Up to 12 months (criteria specific)

Requires PA:

- All sedatives
- Concomitant use of more than one benzodiazepine, more than one non-benzodiazepine sedative, or the combination of a benzodiazepine and non-benzodiazepine sedative in the prior 30 days.
- Sedatives that exceed a total quantity of 30 doses within 60 days

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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose	
		Male	Female
Zolpidem IR	Ambien	10 mg (initial and maximum dose)	5 mg (initial maximum dose) 10 mg (maximum dose)
Zolpidem ER	Ambien CR	12.5 mg (initial and maximum dose)	6.25 mg (initial maximum dose) 12.5 mg (maximum dose)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #4
4. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for up to 12 months.	**No:** Go to #5

Approval Criteria		
~~4.~~5. Does patient have diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #~~6~~5	**No:** Go to #~~7~~6
~~5.~~6. Is patient on CPAP?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics, due to depressant effect, are contraindicated.
~~6.~~7. Is the patient being treated for co-morbid: • Depression; • Anxiety or panic disorder; or • Bipolar disorder? **AND** Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?	**Yes:** Approve for up to 12 months.	**No:** Go to #~~8~~7
~~7.~~8. Has the patient been treated with another non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #~~9~~8	**No:** Pass to RPh; Go to #10~~9~~
~~8.~~9. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and approve duplication for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness.
~~9.~~10. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #1~~0~~

Approval Criteria		
~~10.~~11. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *7/18 (JP); 3/17; 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *TBD; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

References:

1. Ambien® (zolpidem tartrate) [product information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC, Mar 2017.
2. Ambien CR® (zolpidem tartrate extended-release) [product information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC, Mar 2017.

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Prior Authorization Review: New Drug Policy

Purpose for the Review:
In January 2018, the following prior authorization (PA) criteria for new drugs was implemented. At this time, the policy was modified to include evaluation of new drugs costing more than $5000 per claim or per month. The goal of this policy was to evaluate use of high cost agents and prevent inappropriate off-label use until reviewed by the Oregon Pharmacy & Therapeutics Committee. Due to system limitations and because new physician administered drugs often do not have specific billing codes, this PA was only implemented for point-of-sale pharmacy claims. New drugs which require PA under this policy based on costs are listed in **Table 1**.

Table 1. New high cost drugs

Generic	Brand	FDA Orphan Status	FDA approved indication
tolvaptan	JYNARQUE	Yes	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease
burosumab-twza	CRYSVITA	Yes	X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older
fostamatinib disodium	TAVALISSE	Yes	Thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
avatrombopag maleate	DOPTELET	Yes	Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure

Since implementation of the policy there have been no paid or denied fee-for-service (FFS) claims for these medications. Patients were included in the analysis if they had a paid or denied FFS claim from January 1, 2018 to May 31, 2018 for one of the new drugs. Denied claims were defined as a claims with an Error code of 3002 “Prior Authorization Required” or 3022 “Non-preferred drug. Prior Authorization Required” and without any of the codes listed in **Appendix 2**. Patients were excluded if they had Medicare Part D coverage. Despite the lack of claims, several questions have been raised regarding implementation of this policy. Proposed changes are listed in **Appendix 1** and intend to help clarify which drugs fall under this policy, provide information on how price thresholds are calculated, and include a time limit for the policy. Language was also added to state that this policy does not apply to new oral oncology drugs. Oncology treatments are often approved for very specific populations and it would be difficult to adjudicate oncology claims using this PA criteria without additional drug or disease specific questions. If needed, new oncology drugs may be addressed with criteria specifically developed based on a review of the evidence. Additionally, in order to minimize issues regarding access to medication as this policy continues to be implemented, providers will be notified when new drugs are added to the policy.

Conclusion and Recommendation:
- No safety concerns identified.
- Modify PA criteria as proposed in **Appendix 1**.

New Drug Policy

Goal:

- Restrict coverage of selected new drugs until the Oregon Pharmacy & Therapeutics Committee can review the drug for appropriate coverage. New drug criteria will apply until drug specific criteria are developed or for a maximum of 1 year (whichever is less). This policy does not apply to new oncology drugs.

Length of Authorization:

- Up to 6 months

Requires PA:

- ~~A new drug, identified by the reviewing pharmacist during the weekly claim processing drug file load, in a class where existing prior authorization policies exist.~~
- ~~A new drug that is used for a non-funded condition on the Oregon Health Plan (OHP) List of prioritized services~~
- A new drug, identified by the reviewing pharmacist during the weekly claim processing drug file load, which is not in a PDL class with existing prior authorization criteria, costing more than $5,000 per claim or $5,000 per month based on wholesale acquisition cost.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the medication FDA-approved for the requested indication and does the requested dosing align with the FDA-approved dosing?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the drug being used to treat an OHP-funded condition ~~AND is the requested treatment funded by the OHP for that condition~~? ~~Note: Treatments referenced on an unfunded line of the prioritized list are not funded by the OHP.~~	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is baseline monitoring recommended for efficacy or safety and has the provider submitted documentation of recommended monitoring parameters?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medial appropriateness.

Approval Criteria		
5. Does the requested therapy have an orphan drug designation and is this the only FDA-approved therapy for the funded condition?	**Yes:** Approve for up to 6 months or length of treatment (whichever is less).	**No:** Go to #~~5~~6
6. Pass to RPh. The prescriber must provide documentation that alternative drugs approved by the FDA for the funded condition are not appropriate due to history of therapeutic failure, an adverse event, or a contraindication. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

P&T / DUR Review: *7/18 (SS); 11/17; 11/15; 12/09*
Implementation: *TBD; 1/1/18; 1/1/16; 1/1/10*

Appendix 2. Error Codes for denied claims

Error Code	Error Description
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
4002	Non-Covered Drug
576	CLAIM HAS THIRD-PARTY PAYMENT
4999	THIS DRUG IS COVERED BY MEDICARE PART D
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
513	RECIPIENT NAME AND NUMBER DISAGREE
3343	Questionable TPL amount
643	INVALID OTHER COVERAGE CODE
238	RECIPIENT NAME IS MISSING
2807	MATCH CODE INVALID
2809	DOB IS INVALID
4007	NON-COVERED NDC DUE TO CMS TERMINATION
1016	NON-PARTICIPATING MANUFACTURER
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
221	DAYS SUPPLY MISSING
219	QUANTITY DISPENSED IS MISSING
268	BILLED AMOUNT MISSING
222	DAYS SUPPLY INVALID
2808	DOB IS MISSING