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, September 28, 2017 1:00 pm – 5:00 pm
Barbara Roberts Human Services Building, Room 137 A-D
500 Summer St. SE
Salem, OR 97301

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	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)

II. DUR ACTIVITIES

1:10 PM	A. Quarterly Utilization Reports	R. Citron (OSU)
	B. ProDUR Report	R. Holsapple (DXC)
	C. RetroDUR Report	D. Engen (OSU)
	D. Oregon State Drug Reviews	K. Sentena (OSU)
	1. Updates in the Management of COPD	
	2. New Biologics for Treatment of Moderate to Severe Psoriasis	

III. DUR OLD BUSINESS

1:20 PM	A. Low-dose Quetiapine	S. Servid (OSU)
	1. Removal of Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
	B. Hydroxyzine HCl	S. Servid (OSU)
	1. Removal of Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

	C. Biologics for Autoimmune Conditions 1. Update Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
	IV. PREFERRED DRUG LIST NEW BUSINESS	
1:55 PM	A. Antidiabetic Agents 1. Non-insulin Class Update/Prior Authorization Criteria 2. Insulin Class Update with DERP Summary/Prior Authorization Criteria 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:35 PM	B. Hepatitis C Class Update 1. Class Update/Prior Authorization Criteria 2. Mavyret™ (glecaprevir/pibrentasvir) New Drug Evaluation 3. Vosevi™ (sofosbuvir/velpatasvir/voxilaprevir) New Drug Evaluation 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:15 PM	BREAK	
3:25 PM	C. ADHD Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:35 PM	D. Literature Scans 1. Antipsychotics, Parenteral 2. Growth Hormones 3. Newer Antiemetics 4. Pancreatic Enzymes 5. Platelet Inhibitors 6. Topical Steroids 7. Topical Antipsoriatics 8. Public Comment 9. Discussion of Clinical Recommendations to OHA	 D. Moretz (OSU) D. Engen (OSU) K. Sentena (OSU) M. Herink (OSU)
4:05 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
5:00 PM	VII. 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 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
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
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 27, 2017, 1:00-5:00 PM
Human Services 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: Rich Clark, MD, MPH; Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; Cathy Zehrung, RPh; Stacy Ramirez, PharmD

Members Present by Phone: James Slater, PharmD

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Dee Weston; Sarah Servid, PharmD; Deanna Moretz, PharmD, BCPS; Lindsay Newton; Dave Engen, PharmD, CGP; Kathy Sentena, PharmD; Kim Wentz, MD; Julia Verhulst, PharmD

Staff Present by Phone: Megan Herink, PharmD, MBA

Audience: *Helen Kim, Synergy; Rick Frees, Vertex; *Drew Gragham, *Wren Graham, Olivia Washington, *Jamie Saukko; *Dustin Saukko; Joe Schrek, Allergan; Bobbie Duim, DMS; *Susara Arroyo, Mario Arroyo, Russ Rahimtoola, Shawn Moncrieff, Heather Romero, *Skip Miller; Krista Pickett; Magdalene Miller; Diego Hayon; *Tanner Odom, Biogen; *Jon D. Moulton; Jennifer Shidler, Genzyme; Karsen Bala, Biogen; Bob Gustofer, Avexis; Mindy Schimpf, UCB; Chioma Ezenduka, UCB; *Michelle Mui, UCB; Matt Seibet, BioGen; Venus Holder, Lilly; Anthony Wheeler, Lilly; *Christine Getman; *Scott Foertmeyer; Kelsey Svaren; Bill McDougall, BioGen; Cheryl Fletcher, Abbvie; *Meghal Khakherms, Abbvie; Leo Yasmski, Merck; *Celia Vander Velden; Mary Kemhus, Novartis; Virgil Guthrre, OSU; Nena Hartman; Sylvia Churchill; Mike Donabedian, Sarepta Therapeutics; *Lisa Borland, Sarepta Therapeutics; *Jesse Hong, Purdue; Wilmon Grant, Biogen; Stephanie Yamamoto, Johnson & Johnson; Robert Snediker, Johnson & Johnson; JR Roe Mallindkrodt; *Erika Finanger, OHSU; *C. Shepherdson; H. Shepherdson; I. Shepherdson; H. McBroom; L. McBroom; E. McBroom; N. McBroom; J. McBroom; R. McBroom; *Tammy, Christopher and Emily Hay; *Miriam Ischander; Tim McFerron, Alkermes; *Anthony Hager, BMS; Jeanna Colabianchi, Sunovion; Robert Snediken, Janssen; Amy Burns, AllCare; Kayla Burnette, AllCare; DJ Clark, AllCare; Darren Coffman, HERC; Cathy Gross, Purdue

(*) Provided verbal testimony

Written testimony provided:

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:03 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.
C. Approval of agenda and May minutes presented by Mr. Citron. (pages 5 - 8)

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

II. DUR OLD BUSINESS

A. CMS Annual Report (separate handout)
Mr. Citron presented the annual report and explained that CCOs will be required to complete it effective January 2019
B. Prioritization of PA Criteria Implementation
Mr. Citron presented prior authorization (PA) criteria awaiting implementation and bandwidth from DXC with recommendations for implementation prioritization.

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

III. PREFERRED DRUG LIST NEW BUSINESS

A. Biologics Class Update (pages 9 - 59)
Dr. Moretz and Dr. Servid presented the new drug evaluation and class update with the following recommendations:

1. Update PA criteria with updated FDA approved ages and indications as presented.
2. Approve recommended step therapy as presented.
3. Designate brodalumab as non-preferred drug on the PDL.
4. Amend original proposed criteria to include: change the list of drugs requiring PA to "all biologics" and remove the list of indications; change the order of the questions; add to the list of other potent immunosuppressants in question #14; and to add a question requiring a quantiferon gold test to evaluate for tuberculosis before approval of these agents. The Committee also recommended to revise Table 1 of the PA criteria to state brodalumab is indicated for plaque psoriasis.

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

B. Emflaza® (deflazacort) (pages 113-128)
Dr. Servid presented the new drug evaluation and proposed PA criteria with the following recommendations:

1. Adopt proposed PA criteria which restricts use to patients with DMD and documented contraindication or serious intolerance to oral corticosteroids.
2. Refer deflazacort to the Health Evidence Review Commission (HERC) for prioritization consideration as a drug with high cost and marginal benefit compared to currently available low-cost oral corticosteroids.
3. Amend original proposal to include: remove “or other corticosteroid” from question #6; clarify that age restrictions of only apply to deflazacort; and to change the deflazacort approval to 12 months.
4.

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

C. Exondys 51® (eteplirsen) (pages 129-139)

Dr. Servid presented the new drug evaluation and proposed PA criteria with the following recommendations:

1. Adopt proposed PA criteria to limit use to the population studied and continuation of therapy criteria.
2. Refer eteplirsen to the Health Evidence Review Commission (HERC) for prioritization consideration as a medication with high cost and no clinically meaningful benefit.
3. Amend original proposal to: remove the requirement of ambulatory status; revise question #10 to require documentation of a baseline functional assessment and examples of validated functional assessment tools such as the 6-minute walk test or North Star Ambulatory Assessment; and change the wording of the renewal criteria to ask “Has the patient’s baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?”.

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

D. Spinraza® (nusinersen) (pages 98 - 112)

Dr.Moretz presented the new drug evaluation and proposed PA criteria with the following recommendations:

1. Revise PA criteria to insure nusinersen utilization in SMA populations in which the drug has been studied.
2. Refer nusinersen to the Health Evidence Review Commission (HERC) for prioritization consideration as a medication with high cost and marginal clinical benefit.
3. Amend original proposal to include: revising the PA criteria to limit coverage of nusinersen to the SMA populations in which the drug has been studied after amending to: add the Upper Limb Module to the list of functional assessments in question #4; add a note in question #5 to clarify that this criteria does not apply to patients who have ventilator assistance; to change the length of approval to 5 doses within 8 months for initial approvals and 1 year for renewals; and to separate question #7 into renewal criteria and re-order the numbering as appropriate.

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

E. Abbreviated Drug Reviews (pages 202 - 204)
Dr. Servid presented the class update and following recommendation:

1. Trulance™ (plecanatide) (page 202)
    a. Require PA to restrict use to OHP-funded conditions.
    b. Add plecanatide to “drugs for constipation” PA criteria.
2. Symproic® (naldemedine) (page 203-204)
    a. Require PA to restrict use to OHP-funded conditions.
    b. Add naldemedine to “drugs for constipation” PA criteria.

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

VI. EXECUTIVE SESSION

VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Biologics Class Update (pages 9 - 59)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.

VIII. ADJOURN

Drug Use Research & Management Program
DHS - Health Systems Division
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Pharmacy Utilization Summary Report: January 2016 - December 2016

Eligibility	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Total Members (FFS & Encounter)	1,045,449	1,066,593	1,076,454	1,058,671	1,045,530	1,034,285	1,018,479	1,005,560	991,736	990,652	980,593	969,749	1,023,646
FFS Members	132,175	136,513	132,588	150,635	144,444	140,048	145,488	143,283	149,942	155,740	139,906	142,728	142,791
OHP Basic with Medicare	31,349	31,408	31,594	31,864	32,133	32,393	32,597	32,574	32,707	32,844	32,823	32,859	32,262
OHP Basic without Medicare	13,175	12,913	13,091	13,272	13,285	13,242	13,155	13,263	13,490	13,382	12,478	12,602	13,112
ACA	87,651	92,192	87,903	105,499	99,026	94,413	99,736	97,446	103,745	109,514	94,605	97,267	97,416
Encounter Members	913,274	930,080	943,866	908,036	901,086	894,237	872,991	862,277	841,794	834,912	840,687	827,021	880,855
OHP Basic with Medicare	39,907	40,356	40,276	39,984	39,968	40,100	40,186	40,383	40,452	40,531	40,691	40,697	40,294
OHP Basic without Medicare	72,813	72,503	71,622	70,953	70,303	69,870	69,438	68,793	67,857	67,357	67,819	67,277	69,717
ACA	800,554	817,221	831,968	797,099	790,815	784,267	763,367	753,101	733,485	727,024	732,177	719,047	770,844

Gross Cost Figures for Drugs	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	YTD Sum
Total Amount Paid (FFS & Encounter)	$69,254,064	$71,431,240	$76,587,516	$69,797,543	$69,923,087	$71,705,760	$65,483,619	$70,561,316	$67,551,639	$67,803,942	$68,209,607	$69,061,227	$837,370,562
Mental Health Carve-Out Drugs	$11,114,533	$11,446,204	$10,380,072	$8,256,864	$8,406,247	$8,364,462	$7,819,082	$8,456,638	$7,891,022	$7,592,317	$7,803,467	$7,808,889	$105,339,798
OHP Basic with Medicare	$1,137	$427	$367	$639	$737	$407	$820	$373	$753	$571	$263	$1,066	$7,561
OHP Basic without Medicare	$4,792,656	$4,967,180	$4,383,836	$3,409,706	$3,476,409	$3,509,418	$3,258,488	$3,506,583	$3,345,033	$3,146,144	$3,330,447	$3,323,658	$44,449,558
ACA	$6,247,029	$6,404,856	$5,932,417	$4,794,269	$4,870,063	$4,799,286	$4,500,043	$4,876,790	$4,484,863	$4,388,094	$4,407,815	$4,423,103	$60,128,628
FFS Physical Health Drugs	$3,186,490	$3,394,936	$3,603,914	$3,527,399	$3,303,009	$3,599,514	$3,244,602	$3,779,154	$3,653,642	$3,617,317	$3,419,175	$3,374,746	$41,703,899
OHP Basic with Medicare	$217,533	$219,689	$231,250	$195,403	$210,682	$254,144	$206,027	$305,927	$214,459	$277,094	$242,312	$203,910	$2,778,430
OHP Basic without Medicare	$960,245	$991,112	$1,032,076	$961,959	$960,260	$998,234	$942,763	$1,121,523	$1,070,050	$1,041,159	$924,724	$905,462	$11,909,568
ACA	$1,909,651	$2,068,749	$2,236,318	$2,291,136	$2,047,701	$2,249,469	$2,012,598	$2,246,185	$2,262,805	$2,192,881	$2,151,656	$2,179,093	$25,848,242
FFS Physician Administered Drugs	$1,399,606	$1,373,726	$1,500,091	$1,474,500	$1,612,026	$1,908,532	$1,578,710	$1,616,521	$1,860,886	$1,675,169	$1,662,590	$2,281,167	$19,943,524
OHP Basic with Medicare	$309,394	$333,184	$397,368	$397,870	$288,253	$377,332	$302,746	$338,956	$408,751	$325,274	$312,090	$309,716	$4,100,933
OHP Basic without Medicare	$261,443	$300,437	$316,583	$213,651	$314,950	$253,750	$232,455	$213,626	$400,978	$339,573	$228,542	$208,462	$3,284,450
ACA	$583,478	$510,712	$562,489	$649,867	$777,524	$969,820	$749,790	$804,403	$808,084	$795,927	$896,747	$1,022,474	$9,131,316
Encounter Physical Health Drugs	$44,825,870	$46,309,598	$51,213,038	$47,779,089	$47,435,677	$48,404,972	$43,921,731	$46,535,260	$44,738,202	$45,140,020	$46,893,232	$46,101,193	$559,297,882
OHP Basic with Medicare	$127,132	$134,761	$138,671	$135,314	$134,331	$128,990	$122,160	$144,214	$133,979	$140,857	$130,798	$116,292	$1,587,499
OHP Basic without Medicare	$12,110,569	$12,313,201	$13,608,941	$12,650,578	$12,492,038	$12,772,529	$11,807,544	$12,960,715	$12,293,044	$12,371,007	$12,810,511	$12,922,014	$151,112,690
ACA	$32,188,366	$33,483,088	$37,014,061	$34,541,373	$34,350,558	$35,039,428	$31,603,259	$32,950,659	$31,836,807	$32,188,909	$33,430,819	$32,512,258	$401,139,585
Encounter Physician Administered Drugs	$8,727,565	$8,906,776	$9,890,402	$8,759,690	$9,166,129	$9,428,280	$8,919,493	$10,173,743	$9,407,888	$9,779,119	$8,431,143	$9,495,231	$111,085,459
OHP Basic with Medicare	$268,118	$254,079	$265,353	$209,658	$247,875	$215,099	$173,749	$246,347	$192,825	$172,605	$191,730	$200,330	$2,637,770
OHP Basic without Medicare	$2,064,591	$2,444,877	$2,390,221	$2,105,753	$2,211,426	$2,453,772	$2,248,051	$2,333,747	$2,052,079	$2,242,191	$2,084,386	$2,304,362	$26,935,454
ACA	$6,200,431	$6,023,045	$7,057,665	$6,243,801	$6,570,051	$6,615,306	$5,844,307	$6,936,093	$6,808,608	$6,934,053	$5,968,728	$6,753,334	$77,955,423

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: August 28, 2017

Drug Use Research & Management Program
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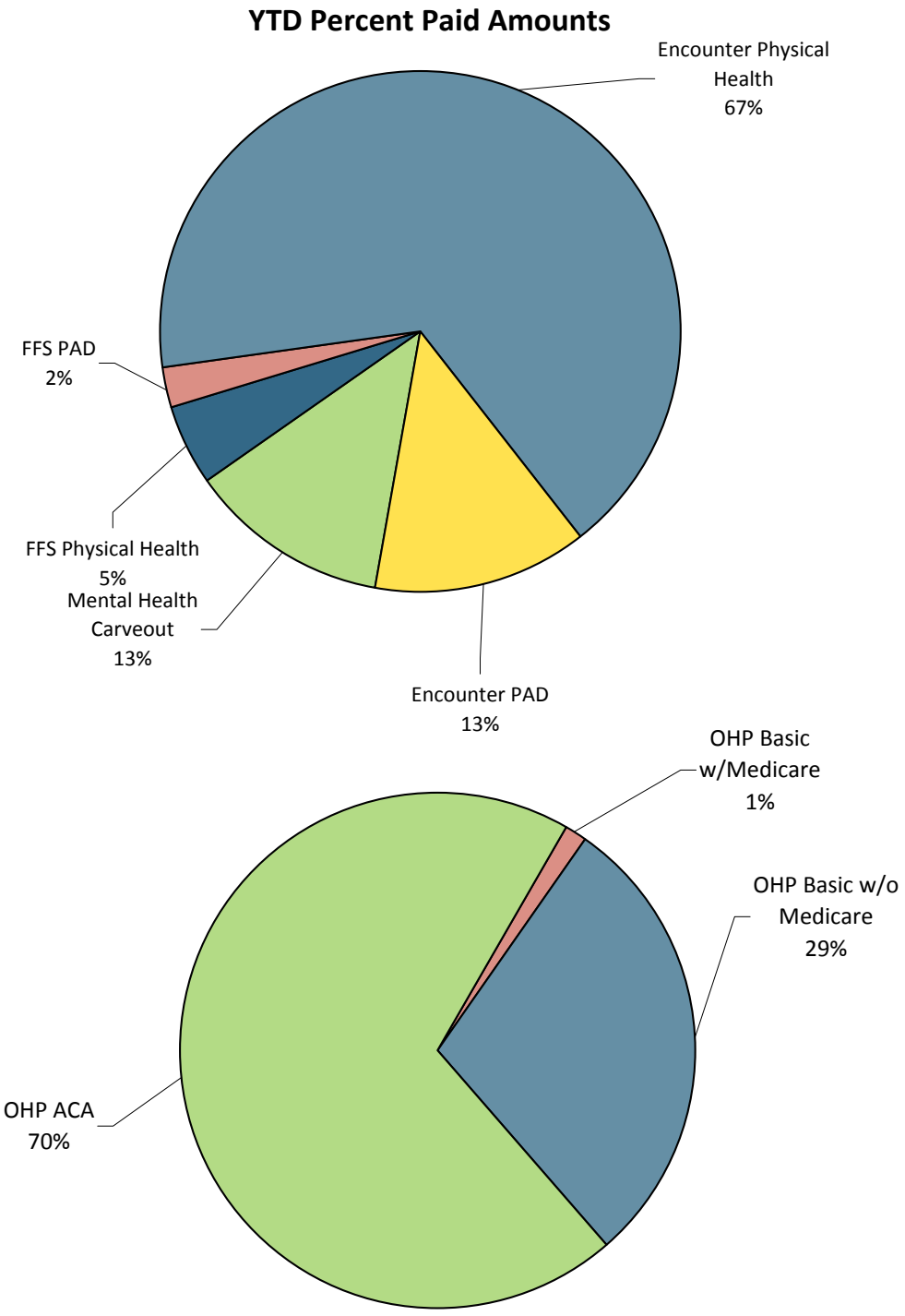
Pharmacy Utilization Summary Report: January 2016 - December 2016



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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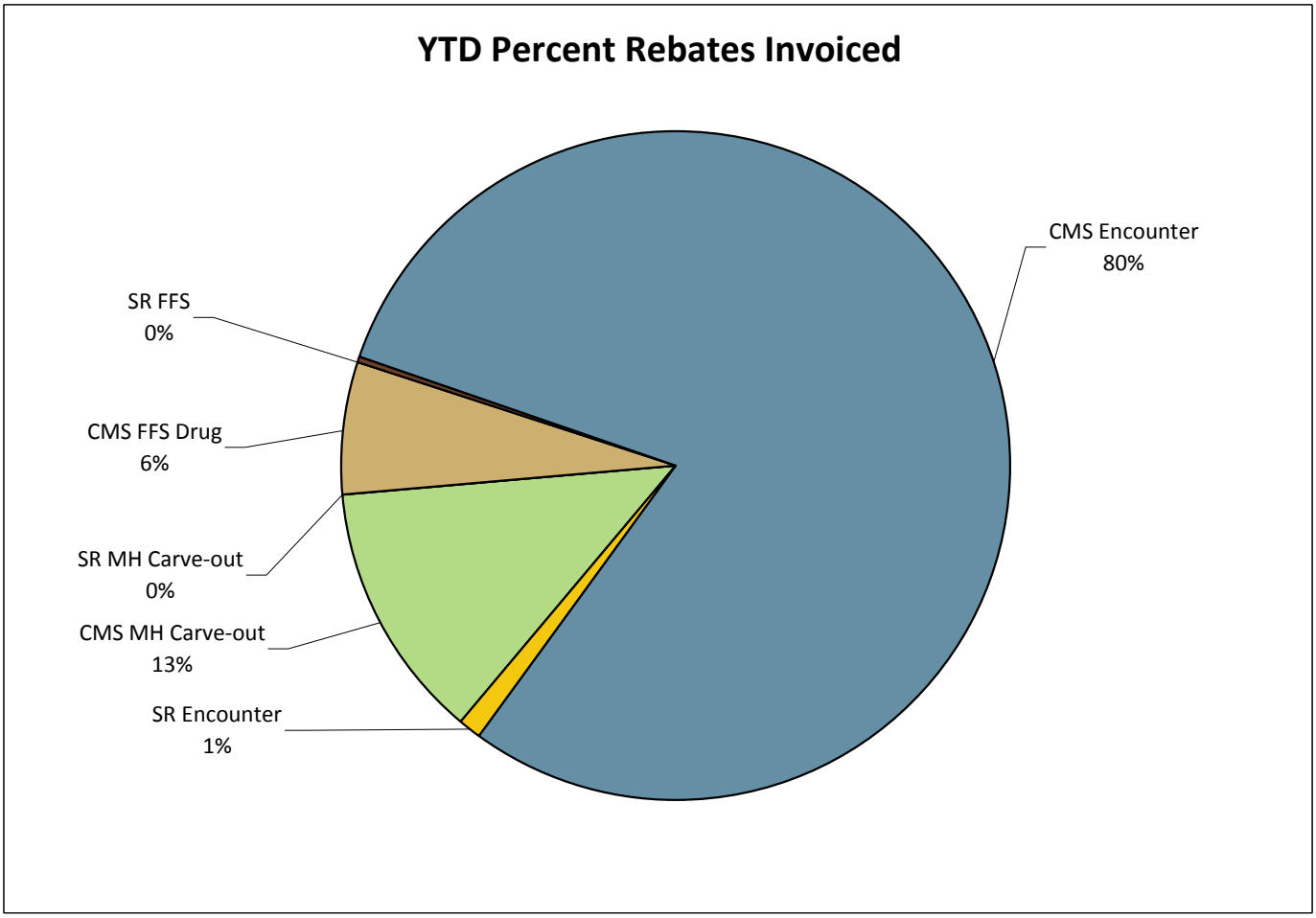
Pharmacy Utilization Summary Report: January 2016 - December 2016

Quarterly Rebates Invoiced	2016-Q1	2016-Q2	2016-Q3	2016-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$107,171,169	$100,918,844	$91,982,322	$102,939,536	$403,011,871
CMS MH Carve-out	$19,024,186	$11,116,538	$10,704,562	$9,528,303	$50,373,589
SR MH Carve-out				$512,730	$512,730
CMS FFS Drug	$6,558,169	$6,770,802	$5,909,929	$6,483,495	$25,722,395
SR FFS	$261,925	$292,296	$311,465	$276,301	$1,141,988
CMS Encounter	$80,743,943	$81,174,410	$73,808,600	$84,635,590	$320,362,543
SR Encounter	$582,946	$1,564,799	$1,247,765	$1,503,117	$4,898,627

Quaterly Net Drug Costs	2016-Q1	2016-Q2	2016-Q3	2016-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$110,101,652	$110,507,547	$111,614,253	$102,135,239	$434,358,690
Mental Health Carve-Out Drugs	$13,916,623	$13,911,036	$13,462,181	$13,163,641	$54,453,480
FFS Phys Health + PAD	$7,638,669	$8,361,883	$9,512,120	$9,270,367	$34,783,039
Encounter Phys Health + PAD	$88,546,360	$88,234,628	$88,639,951	$79,701,231	$345,122,171



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

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Pharmacy Utilization Summary Report: January 2016 - December 2016

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$66.24	$66.97	$71.15	$65.93	$66.88	$69.33	$64.30	$70.17	$68.11	$68.44	$69.56	$71.22	$68.19
Mental Health Carve-Out Drugs	$10.63	$10.73	$9.64	$7.80	$8.04	$8.09	$7.68	$8.41	$7.96	$7.66	$7.96	$8.05	$8.55
FFS Physical Health Drugs	$24.11	$24.87	$27.18	$23.42	$22.87	$25.70	$22.30	$26.38	$24.37	$23.23	$24.44	$23.64	$24.37
FFS Physician Administered Drugs	$10.59	$10.06	$11.31	$9.79	$11.16	$13.63	$10.85	$11.28	$12.41	$10.76	$11.88	$15.98	$11.64
Encounter Physical Health Drugs	$49.08	$49.79	$54.26	$52.62	$52.64	$54.13	$50.31	$53.97	$53.15	$54.07	$55.78	$55.74	$52.96
Encounter Physician Administered Drugs	$9.56	$9.58	$10.48	$9.65	$10.17	$10.54	$10.22	$11.80	$11.18	$11.71	$10.03	$11.48	$10.53

Claim Counts	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Total Claim Count (FFS & Encounter)	1,030,546	1,050,280	1,134,640	1,046,740	1,050,626	1,045,008	969,844	1,031,589	988,331	1,001,645	999,320	986,734	1,027,942
Mental Health Carve-Out Drugs	152,823	153,291	164,505	152,969	154,526	154,813	145,018	156,005	146,050	146,341	146,380	144,462	151,432
FFS Physical Health Drugs	68,123	70,628	74,600	71,711	70,914	68,780	64,247	70,186	67,881	68,287	67,900	71,783	69,587
FFS Physician Administered Drugs	12,373	12,282	13,267	13,798	14,352	15,091	15,711	15,987	15,639	15,994	15,865	16,192	14,713
Encounter Physical Health Drugs	708,978	726,802	787,395	717,624	720,277	708,589	651,835	691,799	665,225	673,718	675,517	659,254	698,918
Encounter Physician Administered Drugs	88,249	87,277	94,873	90,638	90,557	97,735	93,033	97,612	93,536	97,305	93,658	95,043	93,293

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$67.20	$68.01	$67.50	$66.68	$66.55	$68.62	$67.52	$68.40	$68.35	$67.69	$68.26	$69.99	$67.90
Mental Health Carve-Out Drugs	$72.73	$74.67	$63.10	$53.98	$54.40	$54.03	$53.92	$54.21	$54.03	$51.88	$53.31	$54.05	$57.86
FFS Physical Health Drugs	$46.78	$48.07	$48.31	$49.19	$46.58	$52.33	$50.50	$53.84	$53.82	$52.97	$50.36	$47.01	$49.98
FFS Physician Administered Drugs	$113.12	$111.85	$113.07	$106.86	$112.32	$126.47	$100.48	$101.11	$118.99	$104.74	$104.80	$140.88	$112.89
Encounter Physical Health Drugs	$63.23	$63.72	$65.04	$66.58	$65.86	$68.31	$67.38	$67.27	$67.25	$67.00	$69.42	$69.93	$66.75
Encounter Physician Administered Drugs	$98.90	$102.05	$104.25	$96.64	$101.22	$96.47	$95.87	$104.23	$100.58	$100.50	$90.02	$99.90	$99.22

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$29.74	$30.03	$28.20	$26.62	$26.39	$26.33	$26.08	$25.80	$25.24	$24.80	$25.20	$25.54	$26.66
Mental Health Carve-Out Drugs	$59.77	$60.18	$48.25	$39.02	$38.35	$37.78	$37.56	$37.35	$36.53	$33.85	$33.83	$33.93	$41.37
FFS Physical Health Drugs	$22.67	$22.50	$23.38	$23.02	$22.50	$22.18	$23.11	$23.09	$22.35	$21.02	$20.95	$20.83	$22.30
Encounter Physical Health Drugs	$23.61	$24.08	$24.26	$24.20	$24.08	$24.11	$23.69	$23.33	$22.92	$23.10	$23.65	$24.12	$23.76

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$586.32	$590.40	$604.24	$618.75	$612.42	$643.33	$631.30	$625.36	$593.01	$587.08	$628.80	$626.32	$612.28
Mental Health Carve-Out Drugs	$687.19	$723.90	$736.80	$720.59	$730.82	$736.18	$732.37	$746.97	$757.50	$767.60	$785.84	$799.51	$743.77
FFS Physical Health Drugs	$374.17	$393.91	$384.66	$403.47	$367.63	$450.63	$408.83	$447.49	$437.52	$432.87	$416.12	$373.95	$407.61
Encounter Physical Health Drugs	$600.13	$600.58	$616.40	$633.17	$628.22	$655.39	$645.93	$634.49	$597.24	$590.30	$638.32	$640.31	$623.37

Multi-Source Drug Use Percentage	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Multi-Source Drug Use Percentage	93.9%	93.9%	93.9%	93.8%	93.8%	93.8%	93.8%	93.6%	93.2%	93.1%	93.4%	93.4%	93.6%
Mental Health Carve-Out Drugs	97.9%	97.8%	97.8%	97.8%	97.7%	97.7%	97.6%	97.6%	97.6%	97.5%	97.4%	97.4%	97.7%
FFS Physical Health Drugs	93.1%	93.1%	93.1%	93.1%	93.0%	93.0%	92.9%	92.8%	92.4%	92.2%	92.6%	92.6%	92.8%
Encounter Physical Health Drugs	93.1%	93.1%	93.1%	93.0%	93.1%	93.0%	93.0%	92.8%	92.3%	92.3%	92.6%	92.6%	92.8%

Preferred Drug Use Percentage	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Avg Monthly
Preferred Drug Use Percentage	86.65%	86.87%	87.02%	86.56%	86.30%	86.02%	85.98%	85.77%	85.54%	85.45%	85.15%	85.17%	86.0%
Mental Health Carve-Out Drugs	76.26%	75.92%	77.60%	76.15%	75.52%	75.29%	75.18%	75.02%	75.00%	76.23%	76.04%	76.02%	75.9%
FFS Physical Health Drugs	95.45%	95.36%	95.37%	95.22%	95.24%	95.14%	95.34%	95.37%	95.19%	95.26%	95.56%	95.65%	95.3%
Encounter Physical Health Drugs	87.97%	88.30%	88.14%	87.85%	87.71%	87.43%	87.42%	87.18%	86.87%	86.48%	86.11%	86.05%	87.3%

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

Last Updated: August 28, 2017

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$4,776,033	11.8%	4,285	$1,115	Y
2	STRATTERA	ADHD Drugs	$2,092,758	5.2%	4,774	$438	Y
3	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,613,667	4.0%	997	$1,619	V
4	Unclassified Drugs Or Biolog	Physican Administered Drug	$1,498,456	3.7%	15	$99,897	
5	QUETIAPINE FUMARATE ER	Antipsychotics, 2nd Gen	$1,157,473	2.9%	2,759	$420	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$785,794	1.9%	474	$1,658	Y
7	FLUOXETINE HCL	Antidepressants	$628,720	1.6%	31,724	$20	Y
8	SAPHRIS	Antipsychotics, 2nd Gen	$576,880	1.4%	882	$654	Y
9	DULOXETINE HCL	Antidepressants	$566,586	1.4%	27,829	$20	V
10	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$564,890	1.4%	1,441	$392	V
11	REXULTI	Antipsychotics, 2nd Gen	$541,520	1.3%	535	$1,012	V
12	VENLAFAXINE HCL ER	Antidepressants	$515,734	1.3%	2,036	$253	V
13	VRAYLAR	Antipsychotics, 2nd Gen	$469,341	1.2%	423	$1,110	V
14	Factor Viii Recombinant Nos	Physican Administered Drug	$460,476	1.1%	11	$41,861	
15	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$457,568	1.1%	13,181	$35	V
16	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$453,259	1.1%	1,628	$278	V
17	SERTRALINE HCL	Antidepressants	$451,456	1.1%	39,748	$11	Y
18	RISPERDAL CONSTA	Antipsychotics, Parenteral	$445,210	1.1%	568	$784	Y
19	TRAZODONE HCL	Antidepressants	$429,563	1.1%	37,742	$11	
20	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$415,207	1.0%	3,101	$134	
21	BUPROPION XL	Antidepressants	$373,760	0.9%	19,434	$19	V
22	INVEGA TRINZA	Antipsychotics, Parenteral	$362,088	0.9%	73	$4,960	V
23	VIIBRYD	Antidepressants	$339,163	0.8%	1,404	$242	V
24	Infliximab Not Biosimil 10mg	Physican Administered Drug	$332,408	0.8%	167	$1,990	
25	EPCLUSA	Hepatitis C, Direct-Acting Antivirals	$324,086	0.8%	13	$24,930	Y
26	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$289,387	0.7%	101	$2,865	
27	TRINTELLIX	Antidepressants	$288,071	0.7%	827	$348	V
28	Injection, Nivolumab	Physican Administered Drug	$287,708	0.7%	94	$3,061	
29	AMITRIPTYLINE HCL	Antidepressants	$281,787	0.7%	16,342	$17	Y
30	LAMOTRIGINE	Antiepileptics (oral & rectal)	$277,057	0.7%	22,003	$13	Y
31	HUMIRA PEN	Biologics for Autoimmune Conditions	$267,693	0.7%	71	$3,770	Y
32	ENBREL	Biologics for Autoimmune Conditions	$254,522	0.6%	65	$3,916	Y
33	CITALOPRAM HBR	Antidepressants	$251,061	0.6%	26,071	$10	Y
34	SPINRAZA	Oligonucleotides for Muscular Disorders	$250,000	0.6%	2	$125,000	
35	ESCITALOPRAM OXALATE	Antidepressants	$247,933	0.6%	21,189	$12	Y
36	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$245,992	0.6%	15,528	$16	
37	Rituximab Injection	Physican Administered Drug	$233,446	0.6%	105	$2,223	
38	LANTUS	Diabetes, Insulins	$233,342	0.6%	718	$325	Y
39	VENLAFAXINE HCL ER	Antidepressants	$218,545	0.5%	14,537	$15	Y
40	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$200,453	0.5%	562	$357	V
		Top 40 Aggregate:	**$24,459,093**		**313,459**	**$8,145**	
		All FFS Drugs Totals:	**$40,336,173**		**695,195**	**$542**	

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 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Unclassified Drugs Or Biolog	Physican Administered Drug	$1,498,456	9.5%	15	$99,897	
2	Factor Viii Recombinant Nos	Physican Administered Drug	$460,476	2.9%	11	$41,861	
3	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$415,207	2.6%	3,101	$134	
4	Infliximab Not Biosimil 10mg	Physican Administered Drug	$332,408	2.1%	167	$1,990	
5	EPCLUSA	Hepatitis C, Direct-Acting Antivirals	$324,086	2.1%	13	$24,930	Y
6	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$289,387	1.8%	101	$2,865	
7	Injection, Nivolumab	Physican Administered Drug	$287,708	1.8%	94	$3,061	
8	HUMIRA PEN	Biologics for Autoimmune Conditions	$267,693	1.7%	71	$3,770	Y
9	ENBREL	Biologics for Autoimmune Conditions	$254,522	1.6%	65	$3,916	Y
10	SPINRAZA	Oligonucleotides for Muscular Disorders	$250,000	1.6%	2	$125,000	
11	Rituximab Injection	Physican Administered Drug	$233,446	1.5%	105	$2,223	
12	LANTUS	Diabetes, Insulins	$233,342	1.5%	718	$325	Y
13	HARVONI	Hepatitis C, Direct-Acting Antivirals	$183,531	1.2%	6	$30,589	Y
14	METHYLPHENIDATE ER	ADHD Drugs	$175,978	1.1%	1,332	$132	N
15	MAKENA	Progestational Agents	$170,284	1.1%	66	$2,580	Y
16	ADVATE	Antihemophilia Factors	$162,574	1.0%	7	$23,225	
17	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$150,956	1.0%	488	$309	Y
18	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$137,601	0.9%	2,371	$58	Y
19	TRIUMEQ	HIV	$125,572	0.8%	55	$2,283	Y
20	NOVOLOG	Diabetes, Insulins	$123,838	0.8%	344	$360	Y
21	Drugs Unclassified Injection	Physican Administered Drug	$113,651	0.7%	4,164	$27	
22	GENVOYA	HIV	$112,700	0.7%	45	$2,504	Y
23	TRUVADA	HIV	$109,537	0.7%	103	$1,063	Y
24	ZEPATIER	Hepatitis C, Direct-Acting Antivirals	$109,258	0.7%	6	$18,210	Y
25	NUVARING	STC 63 - Oral Contraceptives	$106,356	0.7%	526	$202	
26	VYVANSE	ADHD Drugs	$102,670	0.7%	708	$145	Y
27	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$100,672	0.6%	1,869	$54	Y
28	Mirena, 52 Mg	Physican Administered Drug	$99,256	0.6%	171	$580	
29	Aflibercept Injection	Physican Administered Drug	$98,946	0.6%	226	$438	
30	SPIRIVA	Anticholinergics, Inhaled	$98,141	0.6%	292	$336	Y
31	Factor Viii Recomb Novoeight	Physican Administered Drug	$89,152	0.6%	3	$29,717	
32	HUMIRA	Biologics for Autoimmune Conditions	$87,664	0.6%	24	$3,653	Y
33	PULMOZYME	Cystic Fibrosis	$86,773	0.5%	65	$1,335	Y
34	QVAR	Corticosteroids, Inhaled	$85,494	0.5%	688	$124	Y
35	FLOVENT HFA	Corticosteroids, Inhaled	$84,738	0.5%	467	$181	Y
36	ONFI	Antiepileptics (oral & rectal)	$84,640	0.5%	174	$486	N
37	Pemetrexed Injection	Physican Administered Drug	$83,655	0.5%	15	$5,577	
38	LANTUS SOLOSTAR	Diabetes, Insulins	$81,009	0.5%	255	$318	Y
39	Etonogestrel Implant System	Physican Administered Drug	$80,786	0.5%	141	$573	
40	ORKAMBI	Cystic Fibrosis	$79,681	0.5%	9	$8,853	N
		Top 40 Aggregate:	**$7,971,843**		**19,083**	**$11,097**	
		All FFS Drugs Totals:	**$15,778,367**		**234,147**	**$557**	

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

Last updated: August 28, 2017

ProDUR Report for April through June 2017

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
DA (Drug/Allergy Interaction)	Set alert/Pay claim	21	10	0	11	0.02%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,696	379	2	1,315	1.63%
DD (Drug/Drug Interaction)	Set alert/Pay claim	164	40	0	124	0.10%
ER (Early Refill)	Set alert/Deny claim	69,441	14,162	76	55,188	69.20%
ID (Ingredient Duplication)	Set alert/Pay claim	19,465	5,752	6	13,689	19.37%
LD (Low Dose)	Set alert/Pay claim	664	137	0	526	0.63%
LR (Late Refill/Underutilization)	Set alert/Pay claim	12	8	0	4	0.01%
MC (Drug/Disease Interaction)	Set alert/Pay claim	781	225	1	554	0.70%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,137	356	5	774	1.10%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	97	47	0	50	0.08%
TD (Therapeutic Duplication)	Set alert/Pay claim	6,743	2,101	1	4,635	6.77%
	Totals	**100,221**	**23,217**	**91**	**76,870**	**99.61%**

ProDUR Report for January through March 2017

Top Drugs in Early Refill

DUR Alert	Drug Name	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	Remeron (Mirtazapine)	5	10	20	0	93	0
	Hydrocodone/APAP	1	0	12	0	11	0
	Oxycodone	2	2	21	0	21	0
	Lorazepam	5	2	35	0	73	0
	Alprazolam	5	1	34	0	45	0
	Lamictal (Lamotrigine)	21	33	170	0	281	0
	Abilify (Aripiprazole)	26	14	84	0	199	0
	Seroquel (Quetiapine)	29	56	108	1	281	0
	Risperdal (Risperidone)	9	10	77	1	203	0
	Wellbutrin (Bupropion)	45	46	89	0	278	0
	Zoloft (Sertraline)	58	38	285	0	379	0
	Prozac (Fluoxetine)	28	40	132	2	256	0
	Celexa (Citalopram)	26	24	79	1	193	0
	Trazodone	33	52	200	0	390	0
	Cymbalta (Duloxetine)	19	22	122	0	258	0
	TOTALS =	**312**	**350**	**1,468**	**5**	**2,961**	**0**

		Nov and Dec 2016	Nov and Dec 2016	Nov and Dec 2016		Jan to April 2017	Jan to April 2017	Jan to April 2017		May to July 2017	May to July 2017	May to July 2017
HICL Sequence Number	**Generic Drug Name**	**# ER Alerts**	**# Overridden**	**Percent Overridden**		**# ER Alerts**	**# Overridden**	**Percent Overridden**		**# ER Alerts**	**# Overridden**	**Percent Overridden**
6438	FENTANYL	4	1	25.00%		11	4	36.36%		4	1	25.00%
1730	HYDROCODONE/ACETAMINOPHEN	106	38	35.85%		184	83	45.11%		106	23	21.70%
1695	HYDROMORPHONE HCL	15	3	20.00%		19	11	57.89%		13	2	15.38%
1745	METHADONE HCL	0	0	0.00%		3	1	33.33%		0	0	0.00%
1694	MORPHINE SULFATE	16	7	43.75%		48	11	22.92%		54	21	38.89%
1742	OXYCODONE HCL	125	43	34.40%		250	94	37.60%		160	71	44.38%
1741	OXYCODONE HCL/ACETAMINOPHEN	41	16	39.02%		74	34	45.95%		55	19	34.55%
8317	TRAMADOL HCL	50	5	10.00%		71	15	21.13%		71	16	22.54%
	ALL OPIOIDS =	**357**	**113**	**31.65%**		**660**	**253**	**38.33%**		**463**	**153**	**33.05%**

Opioid daily morphine equivalent quantity limits were reduced from 120 MEQ to 90 MEQ on 1/1/2017

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

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	50	17	16	11
		Total Faxes Successfully Sent	37	7	9	6
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	15	5	2	1
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	7	2	1	1
		Prescriptions Unchanged after 3 Months of Fax Sent	21	7	10	
		Safety Monitoring Profiles Identified	1	1	1	1
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$84,947	$33,763	$3,499	$643

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	21			
		Profiles Sent	5			
		Responses Received	0			
		Response Rate	0%			
		Information Useful or Will Change Practice	0			
		Patient Not With Office	0			
		Already Scheduled	0			
		Will Not Schedule	0			
		Requested No Future Notifications	0			
	Antipsychotic Metabolic Monitoring	Members Identified	658			
		Profiles Sent	649			
		Members With Response	18			
		Response Rate	3%			
		Newly Scheduled	12			
		Provider Contacted	247			
		Provider Responses	11			
		Provider Agreed with Recommendation	5			
		Patient Not With Office	5			

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

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	90	91	92	46
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	18	19	8
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	92	97	119	47
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	14	14	17	13
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		3	2	1
	Lock-In	RetroDUR_Profiles Reviewed	51	26	20	10
		RetroDUR_Letters Sent To Providers	3	2	1	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	13	2	1	0
	Polypharmacy	RetroDUR_Profiles Reviewed		48	40	3
		RetroDUR_Letters Sent To Providers		1		1
		Provider Responses		0		0
		Provider Agreed / Found Info Useful		0		0

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	1	5	21	27
		Disqualified - No Provider Info	1			
		Disqualified - Erroneous denial		5	21	27
		Faxes Sent	5	4	6	2
		Fax Sent - Combination Inhaler	1	3	2	
		Fax Sent - Controller	2	1	2	
		Fax Sent - SABA	1		2	
		No Subsequent Pulmonary Claims	1			2

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May 2017 Volume 7, Issue 4

Updates in the Management of Chronic Obstructive Pulmonary Disease

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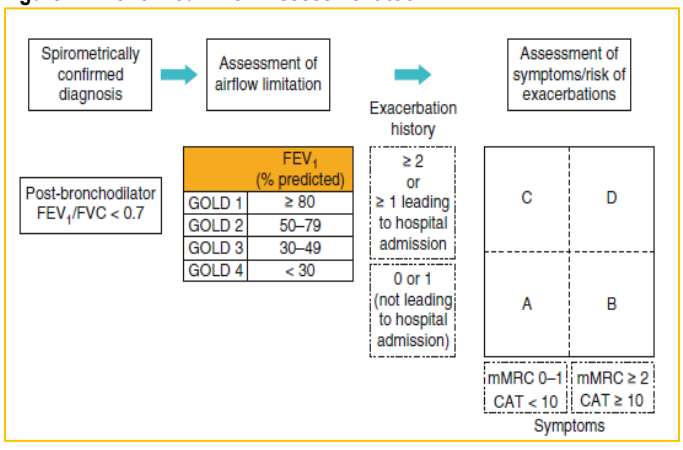
Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by loss of lung function over time. The World Health Organization estimates that by 2030, COPD will be the third leading cause of death worldwide.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report was significantly revised in January 2017.[2] The definition of COPD was broadened to include the impact of chronic respiratory symptoms in addition to persistent airflow limitation. Additional new recommendations include a revised severity assessment of COPD and a shift towards a more personalized treatment approach which includes strategies for both escalating and de-escalating drug therapy when appropriate. This review will highlight pertinent GOLD guideline revisions, and evaluate the evidence supporting the addition of new treatment options.

COPD Severity Assessment

The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on health status, and the risk of future events in order to guide pharmacotherapy.[3] One of the major updates in the GOLD 2017 guidelines is the removal of spirometry from the disease severity assessment. Spirometry remains necessary to make the diagnosis of COPD and is diagnostic for COPD when the post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) ratio is less than 0.7.[3] Early iterations of the GOLD guidelines categorized COPD severity by post-bronchodilator FEV_1 alone. However, there is no strong correlation between FEV_1, symptoms and health status.[2] In 2011 the guidelines included a new severity assessment (ABCD groups) of COPD based upon a combination of clinical symptoms, in particular dyspnea, and staging of spirometry. Groups B and D include patients with a high symptom burden and patients in groups C and D are high risk for exacerbations. This ABCD assessment tool was not based on clear evidence supporting its use and did not perform better for predicting health outcomes or mortality.[4-6] Additionally, group D outcomes were modified by two parameters, lung function and/or exacerbation history, which caused confusion for practitioners.[2]

In the 2017 GOLD report, spirometry is not included in the ABCD groups (Figure 1). Spirometry is still recommended to determine the severity of airflow limitation and prognosis, but it does not impact the ABCD categorization. The ABCD groups and the associated pharmacotherapy treatment recommendations are based solely on patient symptoms and history of exacerbations (Figure 1). This revised assessment is meant to provide more precise treatment recommendations based on the parameters influencing the patient's symptoms at any given time.

Figure 1: The refined ABCD Assessment tool

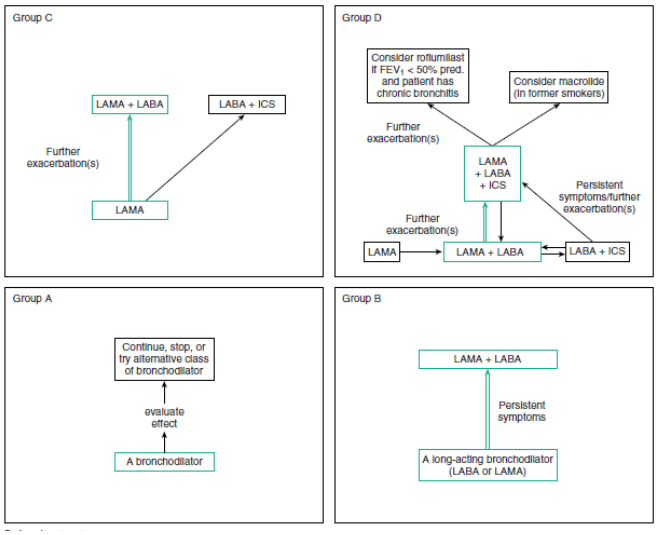


After diagnosis, patients should undergo assessment of dyspnea using the modified British Medical Research Council (mMRC) or symptoms using the COPD Assessment Test (CAT) and their history of exacerbations should be recorded.[3] At each subsequent visit, information on symptoms be collected to help inform necessary changes in pharmacotherapy.

Personalized Treatment Approach

Another advancement in the guidelines is a shift towards a more personalized treatment approach with pharmacological agents. Treatment recommendations are based on the level of symptoms and the individual's risk of exacerbations (ABCD assessment). Previous versions only gave recommendations for initial therapy, while these guidelines include strategies for escalation based on persistent symptoms or de-escalation after resolution of symptoms (Figure 2).

Figure 2: Pharmacologic treatment algorithms by GOLD Grade (highlighted boxes and arrows indicate preferred treatment pathways)



All Group A patients should have a bronchodilator (long acting or short-acting). The previous guidelines recommended only short-acting first line. For Group B patients (high symptom burden but low risk of exacerbation), a long acting bronchodilator is recommended with no preference given to long acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA). For patients with persistent symptoms on one long acting bronchodilator, combination therapy with LABA+LAMA is recommended. There is no direct evidence supporting recommendations for patients in groups C and D.

De-escalation back to one agent is recommended if combination therapy does not improve symptoms. Another change is the recommendation of a LAMA first line for group C patients (high exacerbation risk). This change is based on data from two clinical trials concluding that LAMA is superior to LABA in prevention of exacerbations.[7,8] In patients with a history of at least one exacerbation in the previous 12 months, tiotropium was found to reduce the annualized exacerbation rate compared to indacaterol (0.61 vs. 0.79)[7] and reduce the number of patients who experienced one or more exacerbation compared to salmeterol (34.4% vs. 38.5%; ARR 4.1%; NNT 25).[8] A LABA/LAMA combination is recommended for those with persistent exacerbations over adding inhaled corticosteroid (ICS) due to the risk of developing pneumonia. Finally, in Group D patients (high exacerbation risk/high symptom burden), LABA/LAMA combination is recommended since it was found to be superior to LABA/ICS in preventing exacerbations (RR

0.89; 95% CI 0.83 to 0.96).[9] The FLAME trial was a 52 week randomized, noninferiority trial comparing indacaterol-glycopyrronium (LABA/LAMA) to salmeterol-fluticasone (LABA/ICS) in patients with a history of at least one exacerbation during the previous year. Overall, 77% of patients in the LABA/LAMA arm had at least one exacerbation, compared with 82% of patients in the ICS/LABA (ARR 5%).[9]

Place in therapy of ICS:

In previous GOLD guidelines, therapy with ICS/LABA was recommended as a first line option in both Group C and D patients based on data that ICS treatment decreases the rate of COPD exacerbations.[10] It appears ICS has a more limited place in therapy with the update. The WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) study concluded that discontinuing ICS did not increase the exacerbation rate of patients with both severe disease and an exacerbation history who continued on therapy with LABA/LAMA.[11] Also, the FLAME trial found that patients treated with LABA/LAMA experienced fewer exacerbations than those on LABA/ICS.[9] The guidelines suggest that some patients may still benefit from LABA/ICS as a first choice. This includes those with disease suggestive of asthma-COPD overlap as well as patients with a high blood eosinophil count. Blood eosinophil counts appear to identify acute exacerbations and can predict the effects of ICS on exacerbation prevention.[12] However, currently only post hoc analyses of two clinical trials demonstrate those with a higher blood eosinophil count may respond better to therapy with ICS/LABA.[13] Further prospective randomized controlled trials (RCTs) are needed to determine how best to use eosinophil values in clinical practice.

Prophylactic Antibiotics

The current guidelines include a more ambiguous statement regarding the use of prophylactic, continuous antibiotics. In the previous GOLD update, continuous prophylactic antibiotics were not recommended due to insufficient evidence of benefit (Evidence B).[10] The 2017 version does not definitely recommend against the use and states *"more recent studies have shown that regular use of some antibiotics may reduce exacerbation rate"*.[3] A 2015 meta-analysis identified nine randomized controlled trials evaluating the use of macrolides for prevention of COPD exacerbation.[14] Overall, pooled data demonstrated a reduction in the frequency of exacerbations (RR 0.70; 95% CI 0.56-0.87; p<0.01), but no effect on hospitalizations and all-cause mortality. There was also a trend toward increased adverse events and insufficient data beyond 12 months of therapy.[14] The largest study resulted in a decrease in exacerbations by 0.35 exacerbations per patient-year from 1.83 to 1.48 exacerbation per patient-year. [15] Those with hearing impairment, tachycardia or risk for QT prolongation were often excluded from studies.

The 2017 GOLD report recommends considering adding a macrolide (azithromycin) in former smokers who are still experiencing exacerbations despite being on a LABA/LAMA/ICS (Evidence level B). Uptake of prophylactic antibiotics has been slow in practice, largely due to the unknowns of long term widespread use of antibiotics and the potential effects on macrolide resistance, as well as potential cardiovascular complications. Further research is needed to more precisely determine which patients are most likely to benefit from prophylactic therapy.

Roflumilast

Roflumilast is a phosphodiesterase-4 (PDE4) inhibitor used to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast has been studied in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations. [3] GOLD recommends it as an option in patients treated with LABA/LAMA/ICS with an FEV1<50% and chronic bronchitis who are still being hospitalized for exacerbations.[3] However, roflumilast only modestly reduced exacerbations in clinical trials and intolerable side effects resulting in discontinuation are common and include diarrhea, nausea and weight loss.[16] Due to the strict study criteria showing a benefit and side effect profile, its place in therapy is limited.

Limitations

There are some methodological flaws in the GOLD report to consider when assessing the clinical recommendations. The intent of the GOLD report is a 'strategy document' for health care professionals. Although recommendations include the quality of underlying evidence based on the source (RCT, observational studies, etc.), the strength of each recommendation is not provided. Likewise, very few recommendations are made based on high quality evidence, including RCTs. The GOLD is also funded by the pharmaceutical industry. Lastly, treatment algorithms remain vague and hard to translate into actionable items as it is hard to define 'persistent symptoms' and 'further exacerbation' without any guidance.

Conclusion

Optimal treatment of COPD relies on management of exacerbations and symptoms. Guidance outlined by GOLD should be reinforced with high quality evidence to determine treatment decisions in patients with COPD.

Peer Reviewed By: Louis Libby, MD, Pulmonologist, The Oregon Clinic and Jennifer McElravey, PharmD, BCACP, AE-C, Clinical Pharmacist, Virginia Garcia Memorial Health Center

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June 2017 Volume 7, Issue 5

New Biologics for Treatment of Moderate to Severe Psoriasis

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Plaque psoriasis (PsO) is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[1,2] Men and women are affected equally, with the onset peaking before 40 years of age. PsO affects about 2% of the United States population.[2] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[3] People with psoriasis are at increased risk of psoriatic arthritis, inflammatory bowel disease, cardiovascular disease, diabetes, and depression.[1] The prevalence of depression in patients with psoriasis may be as high as 60%.[4]

The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, history of streptococcal infections, obesity, stress, smoking, and excessive alcohol consumption. Certain medications such as beta-blockers, lithium, chloroquine, and nonsteroidal anti-inflammatory drugs can trigger or exacerbate PsO.[5] Typically, PsO is classified as mild, moderate, or severe. Mild disease involves less than 5% of the body surface area (BSA) with lesions that do not occur on the face, hands or feet. Moderate PsO affects >5% but <10% BSA and severe PsO affects greater than 10% of the patient's body surface area.

Per National Institute for Health and Care Excellence (NICE) guidance, topical medications including corticosteroids, vitamin D analogs, and coal tar are first line agents for treatment of mild PsO.[6] Phototherapy is an option for moderate to severe PsO that has not responded to topical therapy. Systemic non-biologic treatments are recommended for moderate to severe PsO and include cyclosporine, acitretin and methotrexate. Biologics or targeted immunomodulators are also options for moderate to severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include tumor necrosis factor (TNF) inhibitors, (adalimumab, etanercept, infliximab), an interleukin (IL)-12/23 inhibitor (ustekinumab) and IL-17 inhibitors (brodalumab, ixekizumab, secukinumab). A small molecule, apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, is also approved for treatment of moderate to severe PsO. PDE4 is a key enzyme in the degradation of cyclic adenosine monophosphate (cAMP), which plays an important role in controlling pro-inflammatory and anti-inflammatory mediators.[7] Apremilast offers another alternative to patients who do not choose to be on immunosuppressive biologic therapy.

Assessment of Therapy

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI), the Static Physician's Global Assessment Scale (sPGA), or the Psoriasis Symptom Inventory (PSI). The PASI is used most often in clinical trials and is considered the most validated scale.[8] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. A 75% improvement in the PASI score (PASI-75) is widely used to establish the effectiveness of therapies in clinical trials of patients with severe psoriasis. PASI-100 indicates full disease clearance. There is no consensus on the most reliable scale in clinical practice.

New Biologic Agents

TNF inhibitors were the first biologic agents to demonstrate efficacy in treating psoriasis. Recent drug developments have focused on the IL cytokines which have been identified as key pathways involved in the pathogenesis of psoriasis. The IL inhibitors provide an alternative treatment for patients that cannot tolerate or lose response to TNF inhibitors. Ustekinumab was the first IL-12/23 inhibitor approved in 2009, followed by secukinumab, an IL-17 inhibitor in 2015. Ixekizumab and brodalumab are the newest IL-17 inhibitors approved by the Food and Drug Administration (FDA) to treat moderate to severe psoriasis.

In 2016, the FDA approved ixekizumab to treat moderate to severe PsO based on 3 randomized, placebo controlled trials conducted in patients who could not tolerate or did not improve with non-biologic systemic therapy.[9] These phase 3 trials also assessed the superiority of ixekizumab 80 mg subcutaneously every 2 or every 4 weeks over etanercept 50 mg subcutaneously twice weekly. The primary efficacy endpoints for all 3 trials were the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (minimal) with a ≥2-point improvement at Week 12 and a PASI-75 at week 12. Ixekizumab was superior to placebo or etanercept in terms of the proportion of patients achieving a ≥75% reduction from baseline in the PSAI and in those achieving a sPGA score of 0 or 1, after 12 weeks of induction treatment.[9] The pooled results of these trials (UNDERCOVER 2 and 3) are presented in **Table 1**. Adverse events reported during ixekizumab trials included infection (26-38%), injection site reaction (17%), neutropenia (12%), candida infections (3%), and inflammatory bowel disease (1%). Neutropenia was transient and did not result in discontinuation of ixekizumab. The phase 3 trials for ixekizumab were conducted for a total of 60 weeks, and therefore, long-term safety and efficacy data is lacking.

Brodalumab received FDA approval to treat moderate to severe PsO in 2017 on the basis of 3 randomized, multicenter, double-blind, placebo-controlled phase 3 trials.[10] Two trials also included patients randomized to ustekinumab as the active comparator.[10] Primary endpoints for these trials included the proportion of patients with a 75% improvement in PASI and proportion of patients with a sPGA score of 0 or 1. In all phase 3 trials, use of brodalumab 210 mg every 2 weeks demonstrated consistent symptom improvement compared to placebo after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. The results of the AMAGINE 3 trial are summarized in **Table 1**. At a lower dose of 140 mg every 2 weeks, brodalumab did not demonstrate consistent improvement compared to ustekinumab in both trials. Adverse reactions reported during the trials included infections (25%), joint pain (5%), injection site reaction (2%) fatigue (3%), and neutropenia (1%). Suicidal ideation and behavior occurred in patients treated with brodalumab. The relative risk of suicide with brodalumab was approximately 3 times higher than other biologic agents (58 vs. 14 suicides/100,000 patient-years).

However, because analyses were conducted retrospectively, the exact incidence of neuropsychiatric events is unclear.[11] For this reason, brodalumab package insert contains a black boxed warning and the drug is only available under a Risk Evaluation and Mitigation Strategy (REMS) program.

Systematic Review

The Institute for Clinical and Economic Review (ICER) published a systematic evaluation of the biologics for the treatment of moderate to severe PsO in late 2016.[12] A total of 80 references met inclusion criteria including 36 randomized controlled trials (RCTs) and 11 observational studies. Seven studies were head-to-head comparative evaluations of biologic agents for plaque psoriasis in patients with moderate to severe PsO that tried and failed topical and oral systemic therapies. In direct comparative trials, response rates from ustekinumab, secukinumab, and ixekizumab were superior to etanercept, as measured by the PASI 75.[12] Additionally, secukinumab and brodalumab were superior to ustekinumab.[12] The proportion of patients responding to different biologics from the comparative trials are summarized in **Table 1.**

Table 1. Comparative Trials: Proportion of Patient Response Rates at 10-16 Weeks[12]

Treatment	PASI 75	PASI 90	sPGA Score < 2
ACCEPT[13]			
Etanercept 50 mg twice weekly	57%	NR	49%
Ustekinumab 45 mg	68% E vs U45: NNT 9	NR	65% E vs. U45: NNT 7
Ustekinumab 90 mg	74% E vs. U90: NNT 6	NR	71% E vs. U90: NNT 5
FIXTURE[14]			
Etanercept 50 mg twice weekly	44%	NR	NR
Secukinumab 150 mg	67% E vs. S150: NNT 5	NR	NR
Secukinumab 300 mg	77% E vs. S300: NNT 3	NR	NR
UNDERCOVER 2 & 3[15] (data reported as pooled from both studies)			
Etanercept 50 mg twice weekly	42-53%	NR	39%
Ixekizumab 80 mg every 2 weeks	87%	NR	82% E vs. I q2: NNT 3
Ixekizumab 80 mg every 4 weeks	90%	NR	74% E vs. I q4: NNT 3
AMAGINE 3[11]			
Ustekinumab 45 mg or 90 mg*	69%	NR	NR
Brodalumab 210 mg	85% U vs. B: NNT 7	NR	NR
CLEAR[16]			
Ustekinumab 45 mg or 90 mg	NR	58%	NR
Secukinumab 300 mg	NR	79% U vs. S: NNT 5	NR
Abbreviations: NNT = number needed to treat; NR = not reported			

Emerging Therapies

Several IL-23 inhibitors currently under investigation for safety and efficacy include tildrakizumab, risankizumab and guselkumab. Tofacitinib, an oral janus kinase inhibitor, is FDA approved to treat rheumatoid arthritis, and is being studied for efficacy in moderate to severe plaque psoriasis.

Conclusion

In summary, biologic agents offer targeted therapy to patients with moderate to severe psoriasis. NICE guidelines recommend initiating systemic biological therapy for severe PsO defined as a total PASI greater than 10 that has not responded to standard systemic therapy or if the patient is intolerant of, or has a contraindication to these treatments.[6] Adalimumab and etanercept have been on the US market the longest and are generally the least expensive options in this class of drugs. Etanercept is the only biologic approved for use in children aged 4 years and older. Trials assessing the efficacy and safety of other biologics in children are ongoing. Ustekinumab, secukinumab, ixekizumab, and apremilast all have proven efficacy in managing moderate to severe psoriasis and all are reasonable options for patients. Given the black box warning associated with the use of brodalumab, it should be considered for patients that have not responded to other IL inhibitors. Future research directions would include determining which biologic is appropriate for an individual patient, making the treatment individualized as the disease.

Peer Reviewed By: Alex Ortega Loayza, M.D., Assistant Professor of Dermatology, Oregon Health and Science University

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Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses <150 mg/day
- Auto PA approvals for :
    - Patients with a claim for a second generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem and benzodiazepine sedatives are available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339; F3130	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)

Approval Criteria		
2. Is the prescription for quetiapine less than 150 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose <150 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *9/15 (KK); 9/10; 5/10*
Implementation: *10/15; 1/1/11*

Antihistamines

Goals:

- Approve antihistamines only for conditions funded by the OHP.
- Allergic rhinitis treatment is covered by the OHP only when complicated by other diagnoses (e.g. asthma, sleep apnea).
- Promote use that is consistent with Oregon Asthma Guidelines and medical evidence. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx

Length of Authorization:

- 6 months

Requires PA:

- Non-preferred oral antihistamines and combinations

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. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does patient have a diagnosis of allergic rhinitis, allergic conjunctivitis, or chronic rhinitis/pharyngitis/nasopharyngitis?	**Yes:** Go to #4	**No:** Go to #8
4. Does the patient have asthma or reactive airway disease exacerbated by chronic/allergic rhinitis or allergies?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Does the drug profile show an asthma controller medication (e.g. ORAL inhaled corticosteroid, leukotriene antagonist, etc.) and/or inhaled rescue beta-agonist (e.g. albuterol) within the last 6 months? *Keep in mind: albuterol may not need to be used as often if asthma is controlled on other medications.*	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. *Oregon Asthma guidelines recommend all asthma clients have access to rescue inhalers and those with persistent disease should use anti-inflammatory medicines daily (preferably orally inhaled corticosteroids).*
6. Does patient have other co-morbid conditions or complications that are funded? • Acute or chronic inflammation of the orbit • Chronic Sinusitis • Acute Sinusitis • Sleep apnea • Wegener's Granulomatosis	**Yes:** Document ICD-10 codes. Go to #7	**No:** Pass to RPh. Deny; not funded by the OHP
7. Does patient have contraindications (e.g. pregnancy), or had insufficient response to available alternatives? Document.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis COPD or Obstructive Chronic Bronchitis?	**Yes:** Pass to RPh. Deny; medical appropriateness. Antihistamine not indicated.	**No:** Go to #9
9. Is the diagnosis Chronic Bronchitis?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #10
10. RPh only: Is the diagnosis above the line or below the line? • Above: Deny; medical appropriateness • Below: Deny; not funded by the OHP (e.g., acute upper respiratory infections or urticaria).		

P&T Review: *5/15 (AG); 9/10; 9/08; 2/06; 9/04; 5/04; 2/02*
Implementation: *5/1/16; 7/15, 1/11, 7/09, 7/06, 3/06, 10/04, 8/02, 9/06*

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases

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. Approved Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI)	≥18 yo				≥18 yo	≥18 yo	≥18 yo	
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo				
Natalizumab (TYSABRI)		≥18 yo						MS ≥18 yo
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		

Tofacitinib (XELJANZ)						≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥18 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	
Guselkumab (Tremfya)				≥18 yo				

Abbreviations: CLL = Chronic Lymphocytic Leukemia; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MS = Multiple Sclerosis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Relapsing Multiple Sclerosis, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient failed to respond to adalimumab or etanercept after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12

Approval Criteria		
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either adalimumab or etanercept for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Has the patient failed to respond to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: adalimumab or etanercept for at least 3 months?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months.
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months.
16. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #17	**No:** Go to #18
17. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • For Crohn's Disease patients only: has the patient tried and failed a 3 month trial of adalimumab?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment.	**No:** Go to #19
19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *7/17 (DM); 11/16 (AG); 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *9/1/17; 1/1/17; 9/27/14; 2/21/13*

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Class Update: Antidiabetic Agents (excluding insulins)

Month/Year of Review: September 2017 **End date of literature search:** May 22, 2017
Last Review: September 2016
PDL Classes: DPP-4 Inhibitors; GLP-1 Receptor Agonists; Oral Hypoglycemics (sulfonylureas and meglitinides); SGLT-2 Inhibitors; Thiazolidinediones; Miscellaneous Antidiabetic Agents

Current Status of PDL Class:
- See Appendix 2

Purpose of Review:
To evaluate new evidence for each non-insulin antidiabetic drug class on the Preferred Drug List (PDL) and, if appropriate, update current recommendations for placement of specific agents within these drug classes on the Oregon Health Plan (OHP) PDL and current clinical prior authorization (PA) criteria.

Research Questions:
1. Is there any new comparative evidence for non-insulin diabetes treatments on surrogate efficacy outcomes (e.g., hemoglobin A1C [A1C] less than 7%) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for non-insulin diabetes treatments on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, etc.)?
3. Are there subpopulations of patients with diabetes mellitus for which specific therapies may be more effective or associated with less harm?

Conclusions:
There were 3 systematic reviews with meta-analyses[1–3], 6 new clinical practice guidelines (American Diabetes Association [ADA], American College of Physicians [ACP], 3 from the National Institute for Health and Care Excellence [NICE], and one from the American Association of Clinical Endocrinologists/American College of Endocrinology [AACE/ACE])[4–9], 4 new safety alerts[10–13], 4 new drug formulations[14–17] and 3 new randomized controlled studies (RCTs)[18–21] that provide clinically meaningful new evidence for these drugs. The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed. Several systematic reviews and meta-analyses were not included due to poor quality or because the evidence available for the analysis was of poor quality.[22-32]

EFFICACY OUTCOMES

- *Mortality:* Head-to-head RCTs are often underpowered to detect differences in mortality. Many RCTs that have evaluated clinically meaningful effectiveness outcomes (e.g., mortality, macrovascular and microvascular outcomes) lack long-term data, do not report cardiovascular (CV) mortality, have low incidence of mortality overall, and have low or insufficient quality of evidence for these outcomes. Caution is advised in drawing strong conclusions on these outcomes subject to these limitations. **Table 1** describes evidence related to A1C lowering, CV events and harms.
    - There is low quality evidence that there are no differences in CV outcomes or all-cause mortality between antidiabetic treatments for patients with type 2 diabetes mellitus (T2DM) based on mean trial duration of 6 months.[2]
    - There is moderate evidence in patients with T2DM that metformin is associated with less CV-related mortality than sulfonylureas (SU) (absolute difference [AD] -2.9% to -0.1%; 2 RCTs).[1]
    - There is moderate evidence liraglutide lowers the risk for the composite endpoint of CV-related mortality, non-fatal myocardial infarction (MI), or non-fatal stroke compared to placebo at 36 months (Absolute risk reduction [ARR]= 1.9%; number needed to treat [NNT]= 53). Liraglutide reduced the risk of CV-related mortality (ARR= 1.3%; NNT of 77) and all-cause mortality (ARR of 1.4%; NNT 71) versus placebo over 3.5 years.[18] The ADA guideline recommends liraglutide be considered in T2DM patients with established atherosclerotic disease.[5]
    - There is moderate evidence from a double-blind, multi-center randomized controlled trial, in patients with CV disease or at high risk for CV disease, that canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo, 26.9 vs. 31.5/1000 patient-years, respectively (ARR 0.3%/NNT 333 over 3.6 years).[21] None of the component endpoints were statistically different from placebo. There was a higher risk of amputations in patients treated with canagliflozin compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75).
- *Hemoglobin A1c:*
    - There is high quality evidence to recommend metformin first for patients with T2DM requiring antidiabetic treatment to meet glucose targets. [4,5,32]
    - There is moderate to high level of evidence, based on two high quality systematic reviews and meta-analyses, that A1C lowering is similar between monotherapy antidiabetic therapies, except for DPP-4 inhibitors which were found to have less glucose lowering than metformin[1,2] or SU[1].

SAFETY OUTCOMES

- *Hypoglycemia:* There is high quality evidence that the risk of hypoglycemia is higher with SU therapy than metformin, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 RAs.[1,2]
    - Use of SU was associated with a higher incidence of severe hypoglycemia compared to metformin (absolute difference [AD] 0.8% to 14%) and higher rates of mild, moderate or total hyperglycemia when compared to GLP-1 RAs and DPP-4 inhibitors based on moderate evidence (AD 6% to 21% ; $p<0.05$).[1]
- *Heart Failure:* An update from the U.S. Food and Drug Administration (FDA) reports saxagliptin and alogliptin may increase the risk of heart failure (HF), especially in patients with preexisting heart or kidney disease.[12]
- *Weight:* There is moderate to high evidence that metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with weight loss and SUs and thiazolidinediones (TZDs) are associated with weight gain.[1,2]
    - In monotherapy comparisons, metformin was associated with a mean difference of 1.3 kg weight loss compared to a DPP-4 inhibitor ($p<0.05$). Use of a TZD was associated with a mean weight gain of 1.2 kg more than with a SU ($p<0.05$). Use of a SU was associated with a mean weight gain of 2.3 kg more than with a GLP-1 RA ($p<0.05$). Table 1 gives an overview of relative effect of each antidiabetic class on weight when compared to placebo.

- *Bladder Cancer:* The FDA has added a warning to pioglitazone labeling that it may be associated with increased risk for bladder cancer, although the risk is not fully illucidated.[10] However, data analysis shows conflicting results suggested with hazard ratios (HR) that ranged from 1.0 (95% CI, 0.59 to 1.72) to 1.63 (95% CI, 1.22 to 2.19).
- *Amputations:* An FDA black boxed warning has been added to canagliflozin labeling due to the increased risk of amputations.[11] Amputation rates were 5.9 out of every 1,000 patients treated for canagliflozin compared to 2.8 for placebo out of every 1,000 patients treated based on the CANVAS study. A second study, CANVAS-R, found the risk to be 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 patients treated with placebo. The mechanism is unknown and the applicability of this risk to the entire class is still being determined.

PLACE IN THERAPY

- Moderate quality evidence demonstrates that adding a second antidiabetic therapy to metformin results in a similar A1C lowering of 0.9 -1.1%. A SU, DPP-4 inhibitor, or pioglitazone are recommended as second-line agents in combination with metformin by NICE if monotherapy with metformin fails to get patients to their treatment goal.[8] Triple therapy regimens recommended by NICE are: 1) metformin, DPP-4 inhibitor, and a SU; 2) metformin, pioglitazone and a SU 3); metformin, pioglitazone or SU, and an SGLT-2 inhibitor; or 4) insulin-based treatment.[8] GLP-1 RAs are recommended by NICE if patients on metformin and 2 other treatments, fail to meet glucose lowering targets and meet additional criteria as described below.
- Dual therapy treatment options recommended by the ADA, in combination with metformin, are: SU, thiazolidinedione (TZD), DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA or basal insulin.[5] ACP recommends a SU, TZD, SGT-2 inhibitor, or a DPP-4 inhibitor if a second oral agent is required in addition to metformin.[4]
- There is high quality evidence from a report by CADTH that SU should be added to metformin in patients with T2DM and without established CV disease that fail to meet glucose lowering targets.[3] Moderate quality evidence recommends the use of empagliflozin for patients with T2DM and a high risk of CV disease.[3]

Table 1. Non-insulin Glucose Lowering Drugs Effectiveness and Harms Comparisons

Drug Class	Relative A1C lowering[33]	Cardiovascular Data	Safety Warnings	Effect on Weight[1,5]
Biguanides • Metformin	1% to 1.5%	• UKPDS found that metformin may reduce the risk of CV mortality[34]	• 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[1]	• 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[20]	• Pioglitazone may increase the risk of bladder cancer compared to placebo[10] • TZDs increase the risk of HF exacerbations • TZDs increase the risk of bone fractures	• Gain

		• No CV morbidity or mortality benefit when rosiglitazone was added to metformin and SU[35] • 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)[36]		
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.[37,38] • Sitagliptin was found to provide no benefit or harm to CV endpoints[40] • Linagliptin is still being evaluated	• Saxagliptin and alogliptin have been linked to increased risk of heart failure[12] • 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	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 6%/NNT 63) over 3.1 years in patients with underlying CV disease.[39] • 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 (ARR 0.3%/NNT 333 over 3.6 years).[21]	• Canagliflozin increases risk for amputations[11] • 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	• Loss
GLP-1 Receptor Agonists • Exenatide • Exenatide Once-weekly • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide	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[18] • Lixisenatide demonstrated no benefit or harm when compared to placebo for the composite endpoint of death from	• GLP-1 RA class may increase the risk of pancreatitis • An increased risk of thyroid cell cancers was demonstrated in rodent models	• Loss

		CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (HR 1.02; 95% CI, 0.89 to 1.17)[41]		
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

Recommendations:

- New evidence does not require a change to the current policy.
- Add new formulations to existing PA criteria.
- No changes to the PDL are recommended based on the new evidence. Evaluate comparative costs in executive session.

Previous Conclusions

- There is insufficient comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for T2DM
- There is insufficient evidence to compare health outcomes of the newer diabetes medications and combinations.
- There is high quality evidence that monotherapy with either metformin, a TZD or a SU results in similar lowering of A1C based on one systematic review. There is moderate quality evidence that DPP-4 inhibitors lower A1C less than metformin and glimepiride based on two systematic reviews (one for each comparison).
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews. Evidence from a recent systematic review and meta-analysis found glyburide to be associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.
- Moderate quality evidence from one fair and one good quality trial suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Hospitalization rates in patients with heart failure were higher in clinical trials of saxagliptin compared to placebo.
- A systematic review and meta-analysis on SGLT2 inhibitors, including canagliflozin and dapagliflozin, demonstrated A1C lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]). The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90)] and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to7.45]).
- In patients with a history of cardiovascular (CV) disease, there is moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) can decrease risk for CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed

to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99) in patients with high cardiovascular risk. Reduction in risk is primarily driven by a 2.2% reduction in CV death (3.7% vs. 5.9%) and not non-fatal MI or non-fatal stroke.

Previous Recommendations:

- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.
- Prior authorize the GLP-1 agonists and DPP-4 inhibitors to limit use to patients who have tried and failed therapy with metformin and sulfonylureas.
- Prior authorize SGLT-2 inhibitors to limit for patients unable to tolerate or have contraindications to all other therapies proven to be safe and effective (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin).

Background:

Type 2 diabetes mellitus is a prevalent disease affecting an estimated 25.6 million people in the United States, based on 2013 data. In Oregon, it is estimated that 287,000 adults have T2DM, in which 38,000 are estimated to be OHP members.[42] 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.[42] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[43] Despite a variety of treatment options, a significant number of patients fail to meet A1C goals; within 3 years of being diagnosed, 50% of patients require combination therapy to control their disease.[44,45] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with T2DM and the addition of pharmacotherapy for persistent hyperglycemia.[32,33] Guidelines recommend a goal A1C of < 7% for most patients but a range of <6.5% to <8% is reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[5] 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 continue to recommend metformin a first line treatment in most patients with T2DM.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) 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.[32,33] A clinically relevant change in A1C is considered to be ≥0.3%.[1] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most available antidiabetic treatments to control glucose levels long-term and to compare their impact on microvascular and macrovascular complications. However, in 2008 the Food and Drug Administration (FDA) started requiring that CV risk be evaluated. Evidence has demonstrated an increased risk of HF-related hospital admissions with alogliptin (NNH 167) and saxagliptin (NNH 143).[37,38] For GLP-1 RAs, lixisenatide demonstrated no benefit or harm in patients with a recent acute coronary syndrome (ACS).[41] The results of the liraglutide study is included in this update and also showed CV benefits. There is moderate evidence from one trial that the SGLT-2 inhibitor empagliflozin demonstrated a 1.6% absolute reduction in the composite primary endpoint of CV death, non-fatal MI, or non-fatal stroke compared to placebo (10.5% vs. 12.1%, respectively; NNT 63 over 3.1 years).[39] Available evidence suggests that metformin is likely to reduce the incidence of CV disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS).[46] UKPDS data also shows reduced incidence of microvascular risk with SU therapy and insulin.[34]

Current OHP fee-for-service policy for non-insulin antidiabetic treatment allows for metformin use without restriction which is designated as a preferred drug (Appendix 1). Therapeutic options in the SU and TZD class are also available without restriction. DPP-4 inhibitors and GLP-1 RAs are options after trials of metformin and SU or contraindications to these drugs (Appendix 4). 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.

Utilization:
The majority of non-insulin anti-diabetic treatment costs were for metformin, SU, TZDs, DPP-4 inhibitors, GLP-1 RAs and SGLT2 inhibitors. Ninety-nine percent of prescriptions dispensed were for metformin, SU or TZD. Metformin was associated with the highest utilization accounting for 78% of the prescriptions dispensed and 66% of the costs. GLP-1 RAs prescriptions accounted for 34% of the costs but < 1% of the prescriptions dispensed. SU were found to be associated with 12% of the prescriptions dispensed and 14% of the costs. Two percent of the utilization and costs were for TZD therapy. The cost for SGLT-2 class accounted < 1% of prescription volume and cost. DPP-4 inhibitors accounted for < 1% utilization and costs.

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), 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.

Systematic Reviews:

AHRQ – Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes
A systematic review and meta-analysis was performed to determine the comparative effectiveness and safety of antidiabetic treatments used alone or in combination with metformin.[1] Studies were included if they were head-to-head monotherapy comparisons of metformin, TZDs, SU, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs; comparisons to metformin alone with a metformin-based combination; and comparisons of metformin-based combinations where the second medication was one of the monotherapies described above or a basal or premixed insulin. The Jadad scale was used to evaluate the quality of the RCTs and the Downs and Black tool was utilized for non-randomized and observational studies. One-hundred sixteen new studies were included, 81% were RCTs, for a total of 204 studies all together. Funding was provided by Agency for Healthcare Research and Quality (AHRQ) and no authors reported a conflict of interest.

The evidence was graded low or insufficient for all-cause mortality, CV morbidity and microvascular complications. There is insufficient evidence on the study of long-term outcomes.[1]

Cardiovascular mortality: metformin was found to have a lower incidence than SU (moderate evidence).

- Based on evidence from 2 RCTs that found a relative risk of CV mortality of 0.6 to 0.7 favoring metformin over SU, with an absolute difference of 0.1% to 2.9%.[1]

Hemoglobin A1C lowering: reductions were similar across all antidiabetic therapies and metformin-based combinations. The exception was DPP-4 inhibitors which had less lowering compared to metformin and SU (based on moderate to high evidence for all comparisons).[1]

- Analysis of 14 studies found no clinically meaningful difference (≥0.3%) in A1C between antidiabetic therapies.

Body weight: maintenance or reductions were seen with metformin, DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors.[1] Weight was increased with SU, TZDs, and insulin with between group differences of up to 5 kg.

- Results were significant for metformin compared to DPP-4 inhibitors where an analysis of 6 studies found a mean difference of -1.3 kg (95% CI, -1.6 to -1.0 kg; $p<0.05$) favoring metformin (high level of evidence). TZDs caused significantly more weight gain compared to SU by a mean difference of 1.2 kg (95% CI, 0.6 to 1.8 kg; $p < 0.05$) (high level of evidence). SUs increase weight by a mean difference of 2.3 kg (95% CI, 1.2 to 3.3 kg; $p<0.05$) more than GLP-1 RAs based on 4 studies (moderate level of evidence). Comparisons in which meta-analyses were not able to be conducted are presented in **Table 2** below.
- Metformin monotherapy was found to decrease weight by a mean difference of 2.2 kg (95% CI, -2.6 to -1.9 kg; $p<0.05$) when compared to metformin/TZD combination. A mean difference of -3.2 kg (95% CI, -4.6 to -1.6 kg; $p<0.05$) was found between metformin monotherapy and metformin/SU combinations, favoring monotherapy, in patients who weight 90 kg or more based on high strength of evidence. In patients weighing less than 90 kg, metformin monotherapy was associated with a mean difference in weight of -1.2 kg (95% CI, -1.6 to -0.6 kg; $p < 0.05$) based on high strength of evidence from 5 studies.

Table 2. Summary of Moderate to High Strength Evidence on the Comparative Effectiveness of Diabetes Medications as Monotherapy and Metformin-Based Combinations Therapy Where Meta-analyses Could Not Be Conducted for Weight.[1]

Comparison	RCTs (Participants), *n (n)*	Range in Mean Between-Group Differences	Conclusion	Strength of Evidence
SU vs. DPP-4 inhibitors	4 (1659)	0.7 to 1.8 kg	DPP-4 inhibitors favored	Moderate
DPP-4 inhibitors vs. TZD	2 (1475)	−2.3 to −2.5 kg	DPP-4 inhibitors favored	Moderate
GLP-1 receptor agonists vs. TZD	2 (1048)	Both studies: −3.5 kg	GLP-1 receptor agonists favored	Moderate
SGLT-2 inhibitors vs. Met	3 (1903)	−1.3 to −1.4 kg	SGLT-2 inhibitors favored	Moderate
SGLT-2 inhibitor vs. DPP-4 inhibitors	1 (899)	−2.5 to −2.7 kg	SGLT-2 inhibitors favored	Moderate
Met + SGLT-2 inhibitors vs. Met + DPP-4 inhibitors	5 (3423)	−1.8 to −3.6 kg	Met + SGLT-2 inhibitors favored	Moderate
Met + SU vs. Met + premixed or basal insulin	3 (894)	−1.7 to −0.6 kg	Met + SU favored	Moderate
Met + GLP-1 receptor agonists vs. Met + premixed insulin	2 (426)	−1.9 to −5.1 kg	Met + GLP-1 receptor agonists favored	Moderate

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; Met = metformin; RCT = randomized, controlled trial; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylureas; TZD= thiazolidinedione.

Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. [Review]. Annals of Internal Medicine. 2016;164(11):740-751. doi:10.7326/M15-2650.

Hypoglycemia: SUs were most often associated with hypoglycemia as monotherapy and in combination therapy regimens (moderate to high evidence).

- In studies that compared metformin to SU, risk for severe hypoglycemia was 0.8% to 14% higher with SU ($p<0.05$). In comparisons of combination therapy, metformin/SU therapy was associated with an increased risk of severe hypoglycemia compared to metformin/DPP-4 inhibitors (OR 0.2; 95% CI, 0.1 to 0.6; $p<0.05$) (moderate evidence). Metformin/SU were also associated with a 1% to 3% increased risk of severe hypoglycemia compared to metformin/SGLT2 inhibitors.
- SU as monotherapy or in combination therapy was associated with a higher rate of mild, moderate, or total hyperglycemia versus GLP-1 RA, DPP-4 inhibitors, and metformin (OR 2.0 to 3.8; $P < 0.05$).

Gastrointestinal Adverse Events: GI adverse events are defined as diarrhea, nausea and vomiting for this endpoint. There was moderate to high strength of evidence that metformin and GLP-1 RAs, as monotherapy and in combination with other antidiabetic treatments, were associated with the highest incidence of adverse GI events.[1] In comparisons between GLP-1 RAs and SU, GLP-1 RAs were associated with a 3% to 9% increased risk of adverse GI events. Combination therapy of metformin/GLP-1 RA had a 0% to 23% higher risk for adverse GI events compared to metformin/DPP-4 inhibitor ($p<0.05$). Metformin/GLP-1 RA combination were also associated with 8% to 19% more adverse GI events than metformin/TZDs ($p<0.05$). No difference was found in the risk of GI adverse events between TZDs and SU and the combination of metformin/SU and metformin/TZD.

Genital Mycotic Infections: There was moderate to high strength of evidence that risk of genital mycotic infections was higher with SGLT2 inhibitors compared to placebo and active treatments. When metformin was compared to metformin/SGLT2 inhibitor, the risk of genital mycotic infections was up to 9.9% higher for the combination therapy (OR 3.0; 95% CI, 1.2 to 7.2 for women and OR 2.7; 95% CI, 0.8 to 9.0 for men). In a comparison between metformin/GLP-1 RA and metformin/SU combinations, there was a 7.1% to 17.4% P < 0.05) increase in genital mycotic infections with metformin/SGLT2 ($p<0.05$). In a comparison between SGLT2s and metformin, SGLT2s were associated with increased risk of genital mycotic infections by -0.04% to 15.7% ($p<0.05$). A comparison between metformin/SGLT2 inhibitor and metformin/DPP-4 inhibitor combinations found a -2.8% to 8.8% increase in genital mycotic infections with metformin/SGLT2.

In summary, the new evidence that was identified since the 2015 AHRQ review supports the current guideline recommendations. Metformin remains the first-line treatment in patients with T2DM who require therapy to reduce glucose levels. The optimal second-line agent to add to metformin to in most patients is not clear and dependent upon patient specific characteristics. With lack of long-term outcomes, practitioners must balance adverse events, costs, comorbidities and administration concerns when choosing a second antidiabetic agent.

Palmer, et al. – Clinical Outcomes and Adverse Events of Glucose-Lowering Drugs

In a systematic review and meta-analysis, the efficacy and safety of drugs used to treat T2DM were compared. Three-hundred and one RCTs that were at least 24 weeks (median 6 months) in duration that compared two individual glucose lowering therapies were included.[2] Classes included in the review were: metformin, SU, DPP-4 inhibitors, GLP-1 RA, SGLT-2 inhibitors, basal insulin, meglitinide, and alpha-glucosidase inhibitors. Insulin therapies of basal-bolus and prandial insulin were included if they were compared to previous drug classes already mentioned, placebo or standard therapy. Monotherapy (n=177 studies), drugs added to metformin (n=109 studies) and drugs added to metformin and a SU (n=29 studies) were identified. Patients included had a baseline A1C of 8.2%-8.4% and mean duration of diabetes of 5.7 years. The Cochrane risk of bias tool was used to determine study quality. Depending on the domain, the risk of bias ranged from 31.9%-93.4%. Trials were excluded (n=1035) on a methodological basis for non-parallel study design and lack of reporting of meta-analysis outcomes. The primary outcome was CV mortality. Secondary outcomes were all-cause mortality, serious adverse events, MI, stroke, change in A1C, treatment failure, hypoglycemia and body weight. Several authors had received funding from industry. Funding for the analysis was provided by the Royal Society of New Zealand.

The incidence of CV and all-cause mortality outcomes between antidiabetic treatment when compared as monotherapy (n=25 studies), dual therapy (with metformin) (n=26 trials) and triple therapy (with metformin and SU) were not statistically significantly different.[2]

Monotherapy Comparisons: No evidence was available for GLP-1 RAs and basal insulin for monotherapy comparisons. All monotherapy antidiabetic treatment comparisons were more effective than placebo with an A1C standard mean difference (SMD) of -0.66% to -1.11%. In metformin comparisons, metformin resulted in lower A1C than alpha-glucosidase inhibitors, DPP-4 inhibitors, SU and TZDs (SMD 0.16% to 0.35%). SGLT-2 inhibitors, basal insulins, GLP-1 RA and meglitinides were not statistically significantly different from metformin. Treatment failure was highest with placebo (11%; 95% CI, 8 to 14%), followed by meglitinides (5%; 95% CI, 1 to 9%) and DPP-4 inhibitors (3%; 95% CI, 1 to 6%).[2] Compared to metformin SGLT2 inhibitors were associated with the lower risk of treatment failure by a difference of -0.3% (95% CI, -4% to 3%), which is unlikely to be clinically significant. The two treatments most commonly associated with hypoglycemia, based on placebo and active treatment comparisons, were basal insulin (AD 10%; 95% CI 0.08% to 20%) and SU (AD 10%; 95% CI, 7% to 13%). When compared to metformin, GLP-1 RAs were associated with the lower body weight with a SMD of -0.28 kg. SU and TZDs were associated with 0.19 kg to 0.24 kg higher body weight than metformin.[2] Differences in body weight were small suggesting the clinical significance is low.

Dual Therapy Comparisons with Metformin: Metformin/DPP-4 inhibitor combination therapy was associated with lower risk of stroke when compared to metformin/SU (AD -0.2%; 95% CI -0.4% to -0.04%).[2] Differences were small and unlikely to be clinically significant. For all other dual combination therapy comparisons with metformin, the outcomes of serious adverse events, MI or stroke were not significantly different. Similar levels of A1C lowering were seen with all dual combination comparisons; however, there was substantial heterogeneity in the comparison making conclusions difficult. In comparisons of dual combination therapy, metformin/SGLT-2 inhibitor therapy was associated with 3% lower rate of treatment failure compared to metformin/SU (95% CI; -6% to -0.8%).[2] Metformin/alpha-glucosidase inhibitor, followed by metformin/DPP-4 inhibitor, were associated with the highest treatment failure rates compared to other metformin combinations. Hypoglycemia rates were higher with metformin/SU. The difference in risk of hypoglycemia was -4% to -22% lower with other combinations compared to metformin/SU. Metformin combined with a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 RA resulted in a mean weight decrease of -0.58 kg to -1.05 kg when compared to metformin/SU combination therapy.

Triple Combination with Metformin and SU: No differences were found between any comparisons for all-cause mortality or serious adverse event outcomes. There was insufficient evidence for MI and stroke. The combination of metformin/SU plus TZD or basal insulin were associated with greatest A1C reduction. Metformin/SU plus an alpha-glucosidase inhibitor had the least A1C lowering when compared to or metformin/SU plus TZD, GLP-1 RA, or basal insulin.[2] Treatment failure rates were lowest with metformin/SU plus basal insulin and highest with metformin/SU plus DPP-4 inhibitor. A GLP-1 RA added to metformin and SU resulted in the lowest risk of hypoglycemia of all triple therapy studied. The largest difference in hypoglycemia rates were seen when GLP-1 RAs were compared to TZDs combined with metformin and SU which demonstrated a 10% difference between the groups (95% CI, -18 to 2) favoring GLP-1 RAs; however, this was not statistically significant. Changes in body weight were significantly lower for SGLT2 inhibitors (SMD -0.33 kg), which is unlikely to be clinically significant.

In summary, monotherapy comparisons with metformin found DPP-4 inhibitors and alpha-glucosidase inhibitors resulted in 0.33% to 0.35% lower mean A1C values. Compared to metformin, SU and basal insulin had clinically significant increases in hypoglycemia rates. GLP-1 RAs were associated with the least changes in body weight with a mean decrease in body weight of 0.28 kg. For dual therapy comparisons, there is no clear difference in glucose lowering. SU therapy, alone or in combination, is consistently associated with a higher risk of hypoglycemia. TZDs were consistently associated with the most weight gain. There were no significant correlations between the degree of A1C lowering, hypoglycemia and body weight and characteristics at baseline based on a network meta-regression analyses. Cardiovascular and mortality outcomes remain imprecise, primarily due to short trial durations, lack of reporting CV mortality and low incidence of mortality in studies.

<u>CADTH – New Drugs for Type 2 Diabetes: Second-line Therapy</u>

A recently published CADTH report provides recommendations for second-line therapy for patients with T2DM.[3] This report updates a 2013 version and includes evidence on new drugs and new drug classes that have become available since that time. A systematic review of oral and injectable antidiabetic agents was performed which identified 166 RCTs for inclusion in the review. Classes included were the following: SU, SGLT2 inhibitors, DPP-4 inhibitors, TZDs, GLP-1 RAs, alpha-glucosidase inhibitors, meglitinides and biphasic insulin.

The report provides two new recommendations.

1. **In patients with T2DM without established CV disease it is recommended that a SU be added to metformin for adults who are inadequately controlled on metformin alone.[3] Additional evidence is presented in Table 3.**

a. A meta-analysis was preformed to support this recommendation which found A1C lowering of -0.58% to -0.94%.[3] There was no evidence of superiority of other classes to SU for safety or efficacy outcomes. Limitations to the review were a lack of evidence for long-term outcomes (e.g., CV events). Overall the evidence was defined as robust by the authors. Clinically significant hypoglycemia events were rare across all classes studied, including the incidence of severe hypoglycemia. SU were associated with a small increase in weight, approximately 2 kg.
b. Evidence suggests that SU should be used with caution in elderly patients.

Table 3. Evidence Analysis for Recommendation 1[3]

Outcome	Evidence
Body Weight	When compared to metformin basal insulin and SU were associated with the most weight gain ranging from 2.1 kg to 2.8 kg. Statistically significant reductions in weight were found for GLP-1 RAs and SGLT2 inhibitors (-1.4 to -2.2 kg) when compared to metformin. Antidiabetic agents (non-insulin) added to metformin were associated with less weight gain compared to SU with a range of -1.9 to -4.3 kg. Compared to DPP-4 inhibitors both GLP1-RAs and SGLT2 inhibitors were found to reduce weight to a greater extent ($p < 0.05$).
Blood Pressure	When compared to metformin monotherapy all antidiabetic treatments lowered blood pressure diastolic blood pressure compared to baseline values except for SU ($p < 0.05$). The mean difference in diastolic blood pressure lowering was more for SGLT2 inhibitors combined with metformin compared to SU and DPP-4 inhibitors ($p < 0.05$).
Hypoglycemia	Severe hypoglycemia was more common with SU compared to metformin (OR 6.4%; 95% CI, 2.24 to 17.51). Comparisons between the classes demonstrated a reduced risk of severe hypoglycemia with GLP-1 RAs, SGLT2 inhibitors and DDP-4 inhibitors compared to SU. In metformin monotherapy comparisons, all antidiabetic treatments had a lower rate of nonsevere hypoglycemia compared to SU and basal and biphasic insulin. Biphasic insulin was associated with a higher rate of nonsevere hypoglycemia compared to basal insulin.
Mortality	Due to low event rates the meta-analysis for all-cause mortality and CV mortality were not robust. In an analysis of DPP-4 inhibitors compared to SU there was no difference in all-cause mortality (OR 1.19; 95% CI, 0.65 to 2.17) or CV mortality (OR 1.84; 95% CI, 0.66 to 5.12).
Adverse Events	In comparison to metformin no antidiabetic class was associated with a statistically significant increase or decrease in serious adverse events. Withdrawals were higher with SU, DPP-4 inhibitors, basal insulin, GLP-1 RAs when combined with metformin compared to metformin alone ($p < 0.05$). The total number of adverse events were higher with GLP-1 RAs, basal insulin and biphasic insulin compared to metformin.
Cholesterol	SGLT2 inhibitors increased low-density lipoprotein (LDL) cholesterol in comparison to metformin and DPP-4 inhibitors. Combinations of metformin and SGLT2 inhibitors were associated with an increase in high-density lipoprotein (HDL) cholesterol compared to metformin alone, SU, DPP-4 inhibitors, and GLP-1 RAs.
Heart Failure	Low events prevented strong conclusions on HF. Comparison of SU to DPP-4 inhibitors found no difference in HF rates (OR 1.35; 95% CI, 0.48 to 3.82).
Stroke and TIA	Low event rates prevented strong conclusions. No significant differences were found between metformin and SU, SGLT-2 and DPP-4 inhibitors.
Pancreatitis	Meta-analysis results were inconclusive due to low event rates.
Urogenital Adverse Events	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased urogenital adverse events.

Fractures	In comparisons to metformin no combinations of metformin and other classes significantly increased or decreased fracture rates (data not available for GLP-1 RAs).
Unstable Angina	No significant differences were found in comparisons of metformin to combinations of metformin and SU or SGLT2 inhibitors or DPP-4 inhibitors.

2. **In patients with T2DM and CV disease, therapy should be considered which has been has been specifically studied for this indication and recommendations have been previously provided by CADTH.[3] Additional evidence is presented in Table 4.**
    a. There is not enough evidence to support a recommendation for a specific drug class at this time based on 17 RCTs. All trials allowed patients to continue on varying regimens of background therapies.
    b. Previous reviews of the evidence recommend the use of empagliflozin for patients at high risk of CV events.

Table 4. Evidence Analysis for Recommendation 2 (Cardiovascular trials only)[3]

Outcome	Evidence
Major Adverse Cardiovascular Events	Evidence from 5 RCTs provided insufficient data to conclude that any antidiabetic class lowered the risk of MACE (composite endpoint of CV mortality, nonfatal MI, and nonfatal stroke).
Mortality	SGLT2 inhibitors reduced the risk of all-cause mortality when compared to placebo (OR 0.67; 95% CI, 0.47 to 0.95) or DPP-4 inhibitors (OR 0.66; 95% credible interval [CrI], 045 to 99). No other comparisons were available
Cardiovascular Mortality	None of the classes significantly lowered CV mortality when compared to placebo or to other antidiabetic classes.
Hospitalizations Due to Heart Failure	Data was insufficient to draw conclusions.
Adverse Events	None of the classes significantly increased or decreased the risk of adverse events, severe adverse events or withdrawals due to adverse events
Hypoglycemia	In comparisons of TZDs to existing therapies, TZDs were found to have the greatest risk of severe hypoglycemia (OR 2.05; 95% CI, 1.11 to 3.98); however, data was not available for SU or metformin.
Cancer	Compared to placebo TZDs significantly decreased pancreatic cancer based on 3 RCTS. In class comparisons TZDs also decreased the risk of pancreatic cancer when compared to GLP-1 RAs (OR 0.13; 95% CI, 0.01 to 0.75). Placebo and class comparisons found no increase in the risk of bladder cancer.
Pancreatitis	The risk of pancreatitis was not increased with DPP-4 inhibitors (OR 1.60; 95% CI, 0.97 to 2.66) or GLP-1 RAs (OR 0.73; 95% CI, 0.37 to 1.39) when compared to placebo or each other.
Fractures	No classes significantly increased or decreased fracture rates in comparison to each other or placebo based on 3 RCTs.

New Guidelines:

The American Diabetes Association – Standards of Medical Care 2017

The ADA updates their standards of care in diabetes each year.[5] The 2017 standards contain comprehensive recommendations for managing all aspects of patients with diabetes. ADA makes recommendations based on a systematic review or other review of the published literature and grading of the evidence. Recommendations are given a rating of A, B, C and E (**Table 5**). Statement of extensive literature search is included but specific methods are not described. Updates pertaining to the pharmacology of diabetes and treatment goals will be included in this review.

Table 5. ADA Evidence-grading System[5]

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
B	Supportive evidence from well-conducted cohort studies
C	Supportive evidence from poorly controlled or uncontrolled studies
E	Expert consensus or clinical experience

Recommendations:

Hemoglobin A1C goals – A goal of <7% is recommended for most patients based on level A evidence. A lower goal of <6.5% may be appropriate for those that are candidates for more intensive management without experiencing significant hypoglycemia (level C evidence). Patients with limited life expectancy, history of severe hypoglycemia and advanced complications may be more appropriately managed with a higher goal of <8% (level B evidence).[5]

Pharmacological Management of T2DM – Metformin is recommended first-line in patients without contraindications based on level A evidence.[5] Newly diagnosed patients presenting with an A1C of ≥10% or a blood glucose of ≥300 mg/dL should be considered candidates for insulin based on expert opinion (level E evidence). Dual therapy may be considered in patients presenting with A1C levels of ≥9%. If noninsulin monotherapy at maximal tolerated doses fails to control glucose levels to target ranges after 3 months, then an additional oral agent, basal insulin or a GLP-1 RA should be added (evidence level A). The most appropriate treatment to add to metformin is not clearly defined.[5] A meta-analysis found that newer classes of noninsulin therapies lowered A1C to a similar level of approximately 0.9-1.1%. If goal glycemic levels are not obtained with metformin monotherapy, a treatment from one of the following classes should be considered: SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 RA or basal insulin. If after 3 months the goal A1C is still not achieved, a third agent should be initiated. If triple therapy fails to get a patient to target A1C after an additional 3 months, then combination injectable treatment should be considered. The guidelines do not recommend one medication class over another after metformin. Treatments should be determined by patient-specific factors, such as risk for hypoglycemia, weight changes, adverse effects, and cost (evidence level E). Insulin therapy should not be delayed in patients who are not obtaining glycemic treatment goals (evidence level B). Empagliflozin or liraglutide should be considered for patients with a long history of diabetes who are not meeting glucose targets and have established atherosclerotic disease (evidence B) since both agents have shown to decrease cardiovascular and all-cause mortality when added to standard care in patients with preexisting cardiovascular disease.

American College of Physicians – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus

A 2017 update from the ACP evaluated oral treatment options for patients with T2DM and updated recommendations from 2012.[4] The recommendations were based on the AHRQ evidence review of oral agents for the treatment of T2DM (presented above). Evidence from randomized and observational studies were

included. Study quality was assessed and evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Classes included in the review were TZDs, SUs, DPP-4 inhibitors and SGLT2 inhibitors and metformin.

Evidence was low or insufficient for clinical outcomes of mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy and neuropathy, based on data from 65 new studies.[4] Most antidiabetic therapies had similar efficacy in their ability to lower A1C.
ACP updated 2 recommendations:

1. Metformin should be prescribed to patients requiring glucose lowering therapy (strong recommendation; moderate-quality of evidence).[4]
2. If a second oral agent is required then either a SU, TZD, an SGLT2 inhibitor, or a DPP-4 inhibitor should be considered in addition to metformin (weak recommendation; moderate quality of evidence). Treatment selection should be made after a discussion of benefits, adverse effects and costs.[4]

NICE – Type 2 Diabetes in Adults

NICE updated several recommendations to its 2015 guidance on the management of T2DM.[8] Recommendations include a target A1C of 7.0% or less. If target A1C is not met with diet, lifestyle and adherence reinforcement, drug treatment should be considered. Metformin is recommended first-line in adults with T2DM. Metformin is not recommended in patients with an estimate glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2. Alternatives to metformin, if contraindicated or not tolerated, are: DDP-4 inhibitor, pioglitazone or SU. SGLT2 inhibitors are recommended instead of a DPP-4 inhibitors if SU or pioglitazone is not appropriate. Pioglitazone is not recommended in patients with HF, hepatic impairment, diabetic ketoacidosis, current or history of bladder cancer or uninvestigated macroscopic hematuria. In patients with symptoms of hyperglycemia, SU or insulin therapy should be considered.

Drug therapy intensification is also recommended in patients on monotherapy with an A1C above 7.5%.[8] Specific drug treatments should be based on efficacy, safety, comorbidities, polypharmacy, patient's preferences and needs and cost. Recommended combinations are: metformin and DPP-4 inhibitor, metformin and pioglitazone, metformin and a SU, or metformin and a SGLT2 inhibitor. In patients who are unable to take metformin, the following combinations are recommended: DPP-4 inhibitor and pioglitazone, DPP-4 inhibitor and a SU or pioglitazone and a SU.

The following triple therapies are recommended if needed: 1) metformin, DPP-4 inhibitor and SU 2) metformin, pioglitazone and SU 3) metformin, SGLT2 inhibitor, and pioglitazone or SU 4) insulin-based treatment.[8] If metformin and 2 other antidiabetic treatments fail to lower glucose levels to goal, are not tolerated or are contraindicated then metformin, a SU and GLP-1 RA should be considered in patients who have the following characteristics:1) a BMI of 35 kg/m2 or greater and psychological or other medical problems associated with obesity 2) a BMI of less than 35 kg/m^2 and who insulin therapy would have significant occupational implications 3) weight loss would benefit other significant obesity-related comorbidities. Use of GLP-1 RA should be monitored and only continued if there is at least a 1% reduction in A1C and at least a 3% weight loss within 6 months. In patients who are candidates for insulin, metformin therapy should be continued unless contraindicated or not tolerated. NPH insulin is recommended with or without short-acting insulin; however, this practice is less common in the United States (US). Insulin detemir or insulin glargine is recommended in patients who require assistance in insulin administration, experience lifestyle altering hypoglycemia, or the patient would require NPH and additional oral antidiabetic treatments.[8] Pre-mixed (biphasic) insulin analogues are recommended if injecting immediately before a meal, hypoglycemia is an issue or postprandial hyperglycemia is a concern. Patients who start on NPH insulin may need to be switched to insulin detemir or insulin glargine if target A1C levels are not reached due to hypoglycemia, or if the patient experiences significant hypoglycemia, has problems operating the NPH insulin device (not available in the US), or who require assistance in insulin administration.

Suggested intervals for monitoring A1C to assess goal attainment and response to therapy is every 3 months until A1C and treatment is stable, after that every 6 months is sufficient.

NICE – Recommendations for Dapagliflozin Triple Therapy in T2DM

In 2016 NICE updated guidance on the use of dapagliflozin in triple therapy regimens for adult patients with T2DM.[6] The guidance recommends dapagliflozin as one option as a triple therapy regimen in combination with metformin and a sulfonylurea (see below). Previous appraisals focus on the use of dapagliflozin as part of a dual therapy regimen. NICE recommends metformin first-line, followed by combination therapy if glucose targets are not obtained.

NICE – Canagliflozin, Dapagliflozin and Empagliflozin as Monotherapies for Treating Type 2 Diabetes

Based on an evidence review, NICE recently updated guidance for the use of 3 SGLT-2 inhibitors.[7] The guidance recommends canagliflozin, dapagliflozin or empagliflozin as an option in adult patients with T2DM that are unable to take metformin and diet and exercise fail to lower blood glucose levels to target after the following have been met:

- A DDP-4 inhibitor would otherwise be prescribed and
- A SU or pioglitazone is not appropriate

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm

An updated consensus statement was released by the AACE/ACE in 2017.[9] Recommendations are based on evaluating the evidence by giving the evidence a rating and evaluating the risk of bias. They also include a subjective factor impact and two-thirds expert consensus in the overall recommendation grade, which allows for high bias in recommendation development. Several authors have associations with industry that could influence recommendations. The strength of the recommendations were provided in a visual format based on a colored line but were not assigned an alphabetical recommendation grade which limits interpretation of the guidance.

Target A1C values of ≤ 6.5% are recommended if it can be reached safely and affordably. Pharmacotherapy recommendations are based on initial A1C level (**Table 6**).[9] Hemoglobin A1C should be reassessed every 3 months. Patients on monotherapy that are not meeting glucose targets after 3 months should be considered for dual therapy (**Table 6**). Patients who are not at goal using dual therapy are recommended to go to triple therapy (**Table 6**).

Table 6. AACE/ACE Glycemic Control Recommendations[9]

Entry A1C	Recommendations (in order of suggested hierarchy of usage)	
< 7.5%	1. Metformin 3. SGLT2 Inhibitors 5. TZD‡ 7. SU/GLN‡	2. GLP-1 RA 4. DPP-4 inhibitors 6. AGi
Dual Therapy: ≥ 7.5%* * In combination with metformin or other first-line agent	1. GLP-1 RA 3. DPP-4 inhibitors 5. Basal insulin‡ 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. TZD‡ 6. Colesevelam 8. AGi

Triple Therapy: ≥ 7.5%† † In combination with metformin or other first-line agent + second-line agent	1. GLP-1 RA 3. TZD‡ 5. DPP-4 inhibitor 7. Bromocriptine QR 9. SU/GLN‡	2. SGLT2 Inhibitors 4. Basal insulin‡ 6. Colesevelam 8. AGi 10. Add or intensify insulin therapy
< 9%	Symptoms: Insulin ± other agents No symptoms: Dual therapy or triple therapy	
‡ These treatments are recommended to be used with caution due to adverse effects. Abbreviations: AGi = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase 4; GLP-1 RA = glucagon-like peptide receptor agonist; SGLT2 = sodium glucose cotransporter 2; TZD = thiazolidinedione		

Safety Alerts:

The FDA reviewed the risk of heart failure associated with the use of the DPP-4 inhibitors, saxagliptin and alogliptin, in February 2014.[12] In April 2016, they concluded that saxagliptin and alogliptin may increase the risk of heart failure, especially in patients with preexisting heart or kidney disease and. The FDA requested the manufacturers to update warning labeling for these drugs. The recommendation came from review of clinical trial data that demonstrated increased risk of hospitalizations in patients who received saxagliptin or alogliptin compared to placebo. The risk was 35 out of 1,000 patients for saxagliptin compared to 28 out of 1,000 for placebo. The risk was 39 out of 1,000 for alogliptin compared to 33 out of 1,000 for placebo. Therefore, the risk is approximately increased by 6-7 patients per 1000 with saxagliptin and alogliptin compared to placebo.

Pioglitazone may be associated with an increased risk of bladder cancer according to an updated review by the FDA in December of 2016.[10] The possible association of pioglitazone and bladder cancer was first identified in 2010 based on epidemiological data. Since then, additional studies have yielded conflicting results. One study found a trend towards higher risk with increased duration of use but results were not statistically significant (HR 1.06; 95% CI, 0.89 to 1.26). A second study found the risk of bladder cancer with pioglitazone, compared to placebo, was higher during the treatment period (RR 2.83; 95% CI, 1.02 to 7.85); however, during the 12.8 years of follow-up (trial and observational period) there was no increased risk identified (HR 1.0; 95% CI, 0.59 to 1.72). A retrospective cohort trial found the risk of bladder cancer with pioglitazone use was higher compared to no TZD use (HR of 1.63; 95% CI, 1.22 to 2.19). The FDA concluded that pioglitazone may increase the risk of bladder cancer and the label has been updated.

Labeling changes were required by the FDA for metformin-containing products in April of 2016.[13] The changes expanded the use of metformin for patients with diabetes with mild to moderate renal impairment when previously metformin was note recommended to be used in these patients. Recommendations were also added that eGFR be monitored annually. Metformin is still contraindicated in patients with an eGFR of less than 30 mL/min/1.73 m^2 and not recommended in patients with an eGFR of 30-45 mL/min/1.73 m^2.

A 2016 review found interim trial data that suggested canagliflozin may be associated with an increased risk of leg and foot amputations in patients with T2DM.[11] The suggested mechanism for this risk is unknown and the risk with other SGLT2 inhibitors has not been determined. Recent data released in May 2017 found that canagliflozin was associated with an increased risk of amputations based on analyses of two large clinical trials, the Canagliflozin Cardiovascular

Assessment Study (CANVAS) and A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R). The incidence of amputations was 2-times higher in patients treated with canagliflozin compared to placebo. In the CANVAS study, the risk was 5.9 out of every 1,000 patients treated with canagliflozin compared to 2.8 out of every 1,000 patients treated with placebo. In the CANVAS-R study, the risk was 7.5 out of every 1,000 patients treated with canagliflozin compared to 4.2 out of every 1,000 treated with placebo. Amputations were most common in the toe and middle of the foot. More extensive amputations involving the leg, below and above the knee have also occurred. Canagliflozin labeling has been updated with a black box warning to this effect.

New Formulations:

Insulin glargine/lixisenatide (Soliqua™ 100/33)

A combination formulation of the previously reviewed lixisenatide and insulin glargine was approved in 2016 as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM who are not controlled on basal insulin (less than 60 units daily) or lixisenatide.[14] The starting dose for patients that remain uncontrolled on 30 units or less of basal insulin or on lixisenatide is 15 units of the combination product (15 units of glargine/5 mcg lixisenatide) subcutaneously (SC) once daily. For patients using 30-60 units of basal insulin daily, who remain uncontrolled, the starting dose is 30 units (30 units of insulin glargine/10 mcg lixisenatide) given SC once daily. The maximum daily dose is 60 units (60 units of insulin glargine/20 mcg lixisenatide) SC daily. Injection should be administered one hour prior to the first meal of the day.

Insulin glargine/lixisenatide was approved based on one open-label, 30-week, active-controlled, multicenter, RCT in patients with T2DM.[14] Insulin glargine/lixisenatide 100/33 was compared to insulin glargine 100 units/mL in 736 patients. Patients with a 12-year history of diabetes were followed for 30 weeks after a 6-week run-in and stabilization phase. Insulin glargine/lixisenatide treated patients had lower A1C levels compared to insulin glargine alone (6.9% vs. 7.5%, respectively; MD -0.5%; 95% CI, -0.6 to -0.4%: p<0.01). The dose of insulin glargine was capped at 60 units to determine the efficacy of the GLP-1 RA component. The doses of insulin glargine at the end of the trial were similar between groups.

Dapagliflozin/saxagliptin (Qtern®)

The combination product of the SGLT-2 inhibitor, dapagliflozin, and the DPP-4 inhibitor, saxagliptin, was approved for the treatment of patients with T2DM as an adjunct to diet and exercise who have inadequate glycemic control with dapagliflozin or are already being treated with dapagliflozin and saxagliptin.[15] The combination tablet of dapagliflozin 10 mg and saxagliptin 5 mg should be taken once daily in the morning.

The dapagliflozin/saxagliptin combination was approved based on one 24-week, double-blind, placebo-controlled trial in 315 patients with T2DM. Patients who were on dapagliflozin and metformin and remained uncontrolled were randomized to saxagliptin or placebo.[15] At week 24, patients receiving dapagliflozin, metformin and saxagliptin had greater A1c lowering compared to patients taking dapagliflozin, metformin and placebo (MD -0.4%; 95% CI, -0.4 to -0.2; p<0.0001).

Insulin degludec/liraglutide (Xultophy® 100/3.6)

A combination formulation insulin degludec, a long-acting insulin, and liraglutide, a GLP-1 RA, was approved in 2016.[16] The combination product is approved as an adjunct to diet and exercise in patients with T2DM who have hyperglycemia despite basal insulin (less than 50 units a day) or liraglutide (less than or equal to 1.8 mg daily). The recommended starting dose is 16 units (16 units of insulin degludec and 0.58 mg of liraglutide) given SC once daily with a maximal dose of 50 units (50 units insulin degludec and 1.8 mg liraglutide).

Three RCTs were used for the approval of insulin degludec/liraglutide. All trials had a duration of 26 weeks in a total of 1393 patients with T2DM.[16] In an open-label comparison between insulin degludec/liraglutide versus liraglutide 1.8 mg in patients on stable oral antidiabetic treatments, insulin degludec/liraglutide resulted in an A1C reduction of -1.31% compared to -0.36% in the liraglutide group (MD -0.95%, 95% CI, -1.15 to -0.75%; p<0.001). A second double-blind trial evaluated insulin degludec/liraglutide compared to insulin degludec once daily in patients taking metformin. Insulin degludec/liraglutide decreased A1C by 1.95% compared to a decrease of 1.05% for insulin degludec at week 26 (MD -0.89% (95% CI, -1.10 to -0.68%). Insulin degludec doses were kept to a similar level to determine contribution of liraglutide to the combination; therefore, the clinical effect of insulin degludec may have been diminished by titration restrictions. The last trial was an open-label comparison of insulin degludec/liraglutide versus insulin glargine in patients with T2DM who were on metformin. At 26 weeks, A1C decreased by 1.67% in patients taking insulin degludec/liraglutide compared to 1.16% in patients taking insulin glargine. Insulin degludec/liraglutide was found to be non-inferior to insulin glargine (MD -0.51%, 95% CI, -0.67 to -0.34; p<0.01).[16]

Canagliflozin/metformin ER (Invokamet XR)

A new combination product of canagliflozin and metformin ER was approved in 2016 for the treatment of patients with T2DM as an adjunct to diet and exercise in adults with T2DM.[17] Canagliflozin/metformin ER is available 4 different strengths: canagliflozin 50 mg with metformin ER 500 mg or 1000 mg and canagliflozin 150 mg with metformin ER 500 mg or 1000 mg. Maximum recommended dose is canagliflozin 300 mg daily/metformin ER 2000 mg daily. Approval of canagliflozin/metformin ER was based on previous study data that compared canagliflozin and metformin to other active treatments.

New Indications:

In August of this year liraglutide (Victoza®) labeling was changed to include the indication for reduction in the risk of major adverse CV events in adults with T2DM and established CV disease. The evidence was based on the results of the study by Marso, et al (Table 7) which found a reduction in the composite endpoint of CV death, non-fatal MI and non-fatal stroke at 36 months in patients taking liraglutide compared to placebo for an average of 3.5 years (ARR 1.9%/NNT 53).

Randomized Controlled Trials:

One thousand fifty-two potentially relevant clinical trials were evaluated from the literature search. After further review, only 4 trials were included (**Table 7**). Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trials are briefly described in the table below. The full abstracts are included in Appendix 2.

Table 7. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Outcomes	ARR/NNT	Quality Rating
1. Marso, et al (LEADER)[18] RCT, DB, MC, Phase 3	1. Liraglutide 1.8 mg SC (L)* ‡ 2. Placebo SC (P)* * In addition to standard care	Demographics: Age: 64 years Male: 64% A1C: 8.7% DM duration: 13 yrs. Established CV disease: 81.3% CKD: 72.4%	ITT: 1.4668 2.4672 PP: 1. 4529 2. 4513 Attrition:	**Composite of CV death, non-fatal MI, and non-fatal stroke at 36 months:** L: 608 (13.0%) P: 694 (14.9%) HR 0.87 (95% CI, 0.78 to 0.97; P<0.001 for noninferiority and P=0.01 for superiority)	ARR 1.9/53	**Internal Validity (Risk of Bias)**: Selection: (low) Patients were randomized in a 1:1 ratio by interactive voice/web response system. Performance: (unclear) Trial was double-blind design but no details on blinding were provided. Detection: (low) Outcome assessment was adjudicated in a blinded fashion by an external, independent, event-adjudication committee. Attrition: (low) Overall attrition was low and similar between groups. ITT analysis was used for all data. Discontinuations without an outcome

	‡ or the maximum tolerated dose 3.5 years	Any antidiabetic mediations: 88% Metformin use: 76% SU use: 50% <u>Key Inclusion Criteria</u>: - T2DM - A1C ≥ 7% - Currently on DM therapy or naïve to treatment - ≥ 50 yo + ≥1 CV coexisting condition or ≥ 60 years + ≥1 CV risk factor <u>Key Exclusion Criteria</u>: - T1DM - Use of GLP-1 RA, DPP-4 inhibitor, pramlintide, or rapid-acting insulin - MEC or medullary thyroid cancer - Acute coronary event or CV event within 14 days of screening and randomization	1. 139 (3.0%) 2. 159 (3.4%)	**Death from CV causes:** L: 219 (4.7%) vs. P: 278 (6.0%) HR 0.78 (95% CI, 0.66 to 0.93; P=0.007) **Death from any cause:** L: 381 (8.2%) vs. P: 447 (9.6%) HR 0.85 (95% CI, 0.74 to 0.97; P=0.02) **<u>Secondary Outcomes</u>** **Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, hospitalization for unstable angina pectoris or heart failure:** L: 948 (20.3%) vs. P: 1062 (22.7%) HR 0.88 (0.81 to 0.96; P=0.005) **Renal and retinal microvascular outcome:** L: 355 (7.6%) vs. P: 416 (8.9%) HR 0.84 (95% CI, 0.73 to 0.97; P= 0.02)	ARR 1.3/77 ARR 1.4/71 ARR 2.4/42 ARR 1.3/77	were censored from the day of last visit and any future outcomes were not included. <u>Publication:</u> (high) The study was funded by Novo Nordisk, the manufacturer of liraglutide, and the National Institutes of Health. **Applicability**: <u>Patients</u>: Patients were well matched at baseline for most characteristics. There were more patients in the placebo group that received SU, TZDs and insulin which may negatively influence cardiac effects which may bias results in favor of liraglutide. Patients were most likely older than the majority of patients with Medicaid. <u>Intervention</u>: FDA approved dose of liraglutide. Median daily study dose was 1.78 mg. <u>Comparator</u>: Matched placebo. <u>Outcomes</u>: composite of major cardiac events is an accepted outcome and required by the FDA to ensure antidiabetic therapy is not associated with unacceptable levels of cardiac risk. <u>Setting</u>: Thirty-two countries and 410 centers. Thirty percent of patients were enrolled in North American treatment centers. **Analysis**: In patients with T2DM liraglutide was more effective at reducing the risk of death and death from CV causes in patients on standard therapy and had a history of CV disease. Subgroup analysis found that patients with an eGFR of < 60 ml/min/1.73 m^2 may be most likely to benefit from liraglutide.
2. Gadde, et al (DURATION-NEO-2)[19] RCT, OL, MC, Phase 3	1. Exenatide QWS-AI 2 mg SC (E) 2. sitagliptin 100 mg PO daily (S) 3. Placebo SC (P) 28 weeks	<u>Demographics</u>: Age: 53 years Male: 55% A1C: 8.5% DM duration: 8.4 yrs. White: 81% Body mass index: 31.7 kg/m2 <u>Key Inclusion Criteria</u>: - T2DM - A1C ≥ 7.1 -11.0%	<u>mITT</u> E: 181 S: 122 P: 61 Attrition: E: 26 (14%) S: 13 (11%) P: 14 (23%)	**Change in A1C at 28 weeks:** E: -1.13% S: -0.75% P: -0.40% E vs. S: LSM -0.38 (95% CI, -0.70 to -0.06) P = 0.021 E vs. P:	NA NA	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized in a 3:2:1 ratio by interactive web response system and stratified by A1C level. <u>Performance</u>: (high) Trial was open-label design. All staff, providers and patients were blinded to placebo or sitagliptin randomization. <u>Detection</u>: (low) Outcome assessment performed in a blinded manner. <u>Attrition</u>: (high) Attrition varied between groups and was substantial in the placebo group. <u>Publication:</u> Study funded by the manufacturer. **Applicability**:

		- FPG < 280 mg/dL - Currently on metformin ≥ 1500 mg for at least 2 months - BMI ≤ 45 kg/m2 <u>Key Exclusion Criteria</u>: - eGFR < 30 mL/min/1.73 m^2 - Use of GLP-1 RA, DPP-4 inhibitor, SU, TZD or weight loss medications within 3 months of screening - ≥ 2 episodes of severe hypoglycemia within previous 6 months		LSM -0.72 (95% CI, -1.15 to -0.30) P = 0.001 **<u>Secondary Outcomes</u>** **A1C < 7%:** E: 43.1% S: 32% P: 24.6% P < 0.05 for both comparisons (no CI provided) **Body weight:** E: -1.12 kg S: -1.19 kg P: 0.15 kg E vs. S: LSM 0.1 kg (95% CI, -0.70 to 0.9) P = 0.863 E vs. P: LSM -1.3 (95% CI, -2.3 to -0.2) P = 0.20	 E vs. S: ARR 11.1/9 E vs. P: ARR 18.5/5 NS NS	<u>Patients</u>: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. <u>Intervention</u>: FDA approved dose of exenatide weekly. <u>Comparator</u>: Sitagliptin 100 mg and placebo comparison appropriate. <u>Outcomes</u>: A1C is an accepted surrogate end point used for evaluating the efficacy of glucose lower therapy. Health outcomes, such as mortality, macrovascular and microvascular effects would be more helpful. <u>Setting</u>: Eighty-one treatment centers in the US. **Analysis**: In patients with T2DM exenatide used once weekly was more effective than sitagliptin and placebo w/ similar effect on weight. A majority of patients experienced anti-exenatide antibodies which reduced effect on A1C in patients w/ high levels.
3. Kernan, et al (IRIS)[20] RCT, DB, MC, Phase 3	1. Pioglitazone 45 mg daily (PZ) 2. Placebo (P) 4.8 years	<u>Demographics</u>: Age: 63 years Male: 66% Fasting glucose: 98 mg/dL (pre-diabetic) Stroke: 87% HTN: 71% <u>Key Inclusion Criteria</u>: - ≥ 40 years	<u>ITT</u> PZ: 1939 P: 1937 Attrition: PZ: 175 (9%) P: 151 (8%)	**Fatal or non-fatal stroke or MI:** PZ: 175 (9.0%) P: 228 (11.8%) HR 0.76; 95% CI, 0.62 to 0.93 P = 0.007 **<u>Secondary Outcomes</u>**	 ARR 2.8/36	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized in a 1:1 ratio by random permuted block design. <u>Performance</u>: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. <u>Detection</u>: (unclear) Endpoints will be assessed and adjudicated by three separate review committees for stroke, MI/CV and diabetes. Blinding was not described. <u>Attrition</u>: (low) Attrition was low in both groups. ITT was used for data analysis. <u>Publication:</u> (high) Authors had ties to industry. Funding provided by a grant from the National Institute of Neurological Disorders and Stroke.

		- Ischemic stroke or TIA - HOMA IR ≥3.0 <u>Key Exclusion Criteria</u>: - Diabetes diagnosis - NYHA Class III or IV - Liver disease - Pitting edema - Risk of bladder cancer		**All-cause mortality:** PZ: 136 (7%) P: 146 (7.5%) HR 0.93; 95% CI, 0.73 to 1.17 P = 0.53 **Fractures:** PZ: 99 (5.1%) P: 62 (3.2%) P = 0.003 **Diabetes Developed:** PZ: 73 (3.8%) P: 149 (7.7%) HR 0.48; 95% CI 0.33 to 0.69 P < 0.001	NS ARR 1.9/53 ARR 3.9/26	**Applicability**: <u>Patients</u>: Patients in the placebo group had 11% more males compared to the exenatide group. Other baseline characteristics were well matched. <u>Intervention</u>: FDA approved dose of pioglitazone. <u>Comparator</u>: Placebo comparison appropriate in this population. <u>Outcomes</u>: Stroke is an important health outcome. <u>Setting</u>: Sixty-seven percent were from treatment centers in the US. **Analysis**: The results of this study shows a reduced risk of stroke in patients with pre-diabetes and history of stroke or TIA. The incidence of patients developing diabetes was low so applicability to patients with a diabetes diagnosis is low; however, due to lack of data in this area, the findings are still of clinical value.
3. Neal, et al (CANVAS Program)[21] RCT, DB, MC, Phase 3	1. Canagliflozin 100 mg and 300 mg daily*ł (C) 3. Placebo* (P) * Background antidiabetic therapy was permitted ł Results are a combination of two trials 188 weeks follow-up	<u>Demographics</u>: Age: 63 years Male: 64% Diabetes history: 13.5 years CV disease: 65.6% White: 78% Baseline A1C: 8.2% <u>Key Inclusion Criteria</u>: - Type 2 diabetes - A1C ≥ 7% or ≤ 10.5% - ≥ 30 years with symptomatic atherosclerotic CV disease OR ≥ 50 years with 2 or more CV risk factors - eGFR of > 30 ml/min/1.73 m^2 <u>Key Exclusion Criteria</u>: - T1DM - Fasting glucose > 270 mg/dL	<u>ITT</u> C: 5795 P: 4347 Attrition: C: 224 (3.9%) P: 184 (4.2%)	**Composite of CV death, non-fatal MI, and non-fatal stroke:** C: 585 (10.1%) P: 426 (9.8%) HR 0.86; 95% CI, 0.75 to 0.97 P < 0.001 for non-inferiority P=0.0158 for superiority **<u>Secondary Outcomes</u>** **All-cause mortality:** C: 400 (6.9%) P: 281 (6.5%) HR 0.87 (95% CI, 0.74 to 1.01) P = 0.24 **Death from CV causes:** C: 268 (4.6%) P: 185 (4.3%) HR 0.87 (95% CI, 0.72 to 1.06) P = NS	ARR 0.3%/333 NS NS	**Internal Validity (Risk of Bias)**: <u>Selection</u>: (low) Patients were randomized thru an interactive web-based response system with the use of a computer-generated randomization schedule. <u>Performance</u>: (low) Trial was double-blind. All staff, providers and patients were blinded and methods were put in place to ensure blinding. <u>Detection</u>: (low) Endpoints were assessed and adjudicated by separate review committees for all major cardiac evens, hospitalizations for heart failure, renal outcomes, and death who were blinded to treatment assignment. <u>Attrition</u>: (low) Attrition was low in both groups. ITT was used for data analysis. <u>Publication:</u> (low) Industry funded study. Endpoints were reported as prespecified. **Applicability**: <u>Patients</u>: A majority (71.4%) of patients took canagliflozin 300 mg in CANVAS-R and 55% in CANVAS Program were randomized to 300 mg of canagliflozin. Sixty-five percent of patients had a history of symptomatic atherosclerotic CV disease and 35% had a least 2 risk factors for CV disease. A majority of patients were on other antidiabetic and cardioprotective treatments at baseline. <u>Intervention</u>: FDA approved dose of canagliflozin. <u>Comparator</u>: Placebo comparison appropriate in this population. <u>Outcomes</u>: CV outcomes are more common in this population compared to patients without diabetes therefore, the CV impact of antidiabetic treatments are of particular importance. <u>Setting</u>: Thirty countries and 667 centers.

		- Fasting glucose <110 mg/dL and taking insulin or a SU at baseline - History of ≥1 severe hypoglycemia episode in the last 6 months - eGFR < 30 mL/min/1.73 m^2 -NYHA Class IV cardiac disease, MI, unstable angina or planned revascularization		**Progression to albuminuria:** C: 1341 (26%) P: 1114 (29.0%) (HR 0.73; 95% CI, 0.67 to 0.79)	NS	Safety Warning: A higher number of patients who received canagliflozin had amputations compared to placebo (HR 1.97; 95% CI, 1.41 to 2.75) (ARR not provided). **Analysis**: In patients with CV disease or who are high risk of CV disease, canagliflozin reduced the composite of CV endpoints. Patients at high risk of CV disease who are also on cardioprotective medications (e.g., ACE inhibitors) may receive cardiovascular benefit from canagliflozin but also have a higher risk of amputations.
Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; CKD = chronic kidney disease; CV = cardiovascular; DB = double-blind; DD = double-dummy; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; FAS = full analysis set; FPG = fasting plasma glucose; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance index; HR = hazard ratio; HTN = hypertension; ITT = intention to treat; kg = kilogram; LSMD = least-squares mean difference; MEC = multiple endocrine neoplasia; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; NYHA = New York Heart Association; PO = by mouth; PP = per protocol; QWS-AI = once-weekly suspension for autoinjection; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; yo = years old.						

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Appendix 1: Current Status on Preferred Drug List

Diabetes, Dipeptidyl Peptidase-4 Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**JANUMET**	**SITAGLIPTIN PHOS/METFORMIN HCL**	**Y**
ORAL	**TABLET**	**JANUVIA**	**SITAGLIPTIN PHOSPHATE**	**Y**
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN /METFORMIN HCL	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN MONOHYDRATE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N

Diabetes, GLP-1 Receptor Agonists & Amylin Analogs

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN INJCTR	SYMLINPEN 120	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	SYMLINPEN 60	PRAMLINTIDE ACETATE	N
SUB-Q	PEN INJCTR	BYETTA	EXENATIDE	N
SUB-Q	PEN INJCTR	VICTOZA 2-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	XULTROPHY	INSULIN DEGLUDEC/LIRAGLUTIDE	N
SUB-Q	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-Q	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-Q	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-Q	PEN INJCTR	TRULICITY	DULAGLUTIDE	N
SUB-Q	PEN INJCTR	ADLYXIN	LIXISENATIDE	N
SUB-Q	PEN INJCTR	SOLIQUA	INSULIN GLARGINE/LIXISENATIDE	N

Diabetes, Oral Hypoglycemic

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**DIABETA**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLYBURIDE**	**GLYBURIDE**	**Y**
ORAL	**TABLET**	**GLIPIZIDE**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**GLUCOTROL**	**GLIPIZIDE**	**Y**
ORAL	**TABLET**	**AMARYL**	**GLIMEPIRIDE**	**Y**
ORAL	**TABLET**	**GLIMEPIRIDE**	**GLIMEPIRIDE**	**Y**
ORAL	**TAB ER 24H**	**GLUCOPHAGE XR**	**METFORMIN HCL**	**Y**
ORAL	**TAB ER 24H**	**METFORMIN HCL ER**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**GLUCOPHAGE**	**METFORMIN HCL**	**Y**
ORAL	**TABLET**	**METFORMIN HCL**	**METFORMIN HCL**	**Y**
ORAL	TABLET	TOLBUTAMIDE	TOLBUTAMIDE	N
ORAL	TABLET	CHLORPROPAMIDE	CHLORPROPAMIDE	N
ORAL	TABLET	TOLAZAMIDE	TOLAZAMIDE	N
ORAL	TAB ER 24	GLIPIZIDE ER	GLIPIZIDE	N
ORAL	TAB ER 24	GLIPIZIDE XL	GLIPIZIDE	N
ORAL	TAB ER 24	GLUCOTROL XL	GLIPIZIDE	N
ORAL	TABLET	GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	GLYNASE	GLYBURIDE,MICRONIZED	N
ORAL	TABLET	PRANDIN	REPAGLINIDE	N
ORAL	TABLET	REPAGLINIDE	REPAGLINIDE	N
ORAL	TABLET	NATEGLINIDE	NATEGLINIDE	N
ORAL	TABLET	STARLIX	NATEGLINIDE	N
ORAL	SOLUTION	RIOMET	METFORMIN HCL	N
ORAL	TAB ER 24	FORTAMET	METFORMIN HCL	N
ORAL	TAB ER 24	METFORMIN HCL ER	METFORMIN HCL	N
ORAL	TABERGR24H	GLUMETZA	METFORMIN HCL	N
ORAL	TABLET	ACARBOSE	ACARBOSE	N
ORAL	TABLET	PRECOSE	ACARBOSE	N
ORAL	TABLET	GLYSET	MIGLITOL	N
ORAL	TABLET	GLUCOVANCE	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLYBURIDE-METFORMIN	GLYBURIDE/METFORMIN HCL	N
ORAL	TABLET	GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	N
ORAL	TABLET	PRANDIMET	REPAGLINIDE/METFORMIN HCL	N

Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	QTERN	DAPAGLIFLOZIN/SAXAGLIPTIN	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKAMET XR	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY	EMPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	SYNJARDY XR	EMPAGLIFLOZIN/METFORMIN HCL	N

Diabetes, Thiazolidinediones

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	**TABLET**	**PIOGLITAZONE HCL**	**PIOGLITAZONE HCL**	**Y**
ORAL	TABLET	AVANDIA	ROSIGLITAZONE MALEATE	N
ORAL	TABLET	AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	N
ORAL	TABLET	DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	N
ORAL	TABLET	AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	N
ORAL	TABLET	PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	N
ORAL	TBMP 24HR	ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	N

Appendix 2: Abstracts of Clinical Trials

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators.

BACKGROUND:

The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS:

In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS:

A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS:

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.).

Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study.

Gadde KM, Vetter ML, Iqbal N, Hardy E, Öhman P; DURATION-NEO-2 study investigators.

AIMS:

Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors treat type 2 diabetes through incretin-signaling pathways. This study compared the efficacy and safety of the glucagon-like peptide-1 receptor agonist exenatide once-weekly (Miglyol) suspension for autoinjection (QWS-AI) with the dipeptidyl peptidase-4 inhibitor sitagliptin or placebo.

MATERIALS AND METHODS:

In this open-label, multicentre study of patients with type 2 diabetes who had suboptimal glycaemic control on metformin monotherapy, 365 patients were randomized to receive exenatide 2.0 mg QWS-AI, sitagliptin 100 mg once daily or oral placebo (3:2:1 ratio). The primary endpoint was change in glycated hemoglobin (HbA1c) from baseline to 28 weeks.

RESULTS:
At 28 weeks, exenatide QWS-AI significantly reduced HbA1c from baseline compared to sitagliptin (-1.13% vs -0.75% [baseline values, 8.42% and 8.50%, respectively]; P = .02) and placebo (-0.40% [baseline value, 8.50%]; P = .001). More exenatide QWS-AI-treated patients achieved HbA1c <7.0% than did sitagliptin- or placebo-treated patients (43.1% vs 32.0% and 24.6%; both P < .05). Exenatide QWS-AI and sitagliptin reduced fasting plasma glucose from baseline to 28 weeks (-21.3 and -11.3 mg/dL) vs placebo (+9.6 mg/dL), with no significant difference between the 2 active treatments. Body weight decreased with both active treatments (-1.12 and -1.19 kg), but not with placebo (+0.15 kg). No improvement in blood pressure was observed in any group. The most common adverse events with exenatide QWS-AI were gastrointestinal events and injection-site reactions.
CONCLUSIONS:
This study demonstrated that exenatide QWS-AI reduced HbA1c more than sitagliptin or placebo and was well tolerated.

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack.
Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR; IRIS Trial Investigators.
Abstract
BACKGROUND:
Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.
METHODS:
In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.
RESULTS:
By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).
CONCLUSIONS:
In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2017
Search Strategy:

#	Searches	Results
1	Sitagliptin Phosphate/	970
2	alogliptin.mp.	264
3	saxagliptin.mp.	380
4	linagliptin.mp. or Linagliptin/	342
5	pramlintide.mp.	303
6	exenatide.mp.	2168
7	liraglutide.mp. or Liraglutide/	1214
8	albiglutide.mp.	68
9	dulaglutide.mp.	79
10	glyburide.mp. or Glyburide/	4041
11	glipizide.mp. or Glipizide/	602
12	glimepiride.mp.	964
13	Metformin/ or metformin.mp.	12206
14	tolbutamide.mp. or Tolbutamide/	1662
15	chlorpropamide.mp. or Chlorpropamide/	218
16	tolazamide.mp. or Tolazamide/	22
17	repaglinide.mp.	633
18	nateglinide.mp.	473
19	acarbose.mp. or Acarbose/	1595
20	miglitol.mp.	195
21	dapagliflozin.mp.	285
22	canagliflozin.mp. or Canagliflozin/	286
23	empagliflozin.mp.	277
24	pioglitazone.mp.	4165
25	rosiglitazone.mp.	5289
26	lixisenatide.mp.	133
27	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	31226

28	limit 27 to (english language and humans and yr="2015 -Current")	3214
29	limit 28 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	1052

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:
- Preferred alternatives 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: *7/17 (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:
- Preferred alternatives 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 patient currently taking insulin?	Yes: Go to #6	No: Approve for up to 12 months
6. Is the patient requesting exenatide, liraglutide, ~~or~~ albiglutide, dulaglutide or lixisenatide (including combination products) and using basal insulin?	Yes: Approve for up to 12 months	No: Go to #7
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 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: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *2/15; 1/14*

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT-2 Inhibitors)

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

Length of Authorization:
- Up to 12 months

Requires PA:
- All SGLT-2 inhibitors

Covered Alternatives:
- Preferred alternatives 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 Type 2 diabetes mellitus?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
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 and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
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	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #6
6. Has the patient tried and failed all of the following drugs, or have contraindications to these drugs? • Insulin • Thiazolidinedione • DPP-4 inhibitor • GLP-1 agonist • 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		
1. 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	Yes: Pass to RPh. Deny; medical appropriateness	No: Approve for up to 6 months.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day 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: *7/17 (KS), 9/15 (KS); 1/15; 9/14; 9/13*
Implementation: *2/15*

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Insulin Drug Class Update

Date of Review: September 2017 **End Date of Literature Search:** June 2017

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

Purpose of Review:
To evaluate new evidence for insulin products on the Preferred Drug List (PDL) and, if appropriate, update current recommendations for placement of specific insulin formulations on the Oregon Health Plan (OHP) PDL and update current clinical prior authorization (PA) criteria if appropriate.

Research Questions:
1. Is there any new comparative evidence for insulin treatments on surrogate efficacy endpoints (e.g., hemoglobin A1C [A1C] less than 7%) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for insulin treatments on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, weight gain, etc.)?
3. Are there subpopulations of patients with diabetes mellitus for which specific insulin formulations may be more effective or associated with less harm?

Conclusions:
One high quality systematic review[1], four clinical practice guidelines[2–5], one new randomized clinical trial[6] (RCT) and one new formulation[7] were identified in this review. Subgroup analyses specific to Medicaid patients were not conducted; however, the evidence is applicable to Oregon's Medicaid patients. Several systematic reviews and meta-analyses were not included due to poor quality or because the evidence available for the analysis was of poor quality.[8–15]
CLINICAL EFFICACY
- There is insufficient comparative evidence in specific subgroup populations, and between insulins for clinically meaningful health outcomes. In addition, there is insufficient comparative evidence between different formulations of the same insulin (i.e., pens versus vials).
- There is low quality evidence in patients with type 1 diabetes mellitus (T1DM) of no difference in A1C lowering for the following comparisons: insulin degludec and insulin detemir; insulin glargine and insulin degludec; insulin detemir and insulin glargine; follow-on (F-O) insulin glargine (Basaglar) and insulin glargine U100 (Lantus); insulin glargine U100 and insulin glargine U300; fixed-dose combination product (FDCP) insulin degludec/aspart and insulin detemir.
- In patients with type 2 diabetes mellitus (T2DM), there is moderate quality evidence that daily insulin degludec and daily insulin glargine were similar in the number of patients achieving an A1C less than 7% (pooled risk ration [RR] 0.96; 95% CI, 0.90 to 1.03).[1] There was low quality evidence of no difference in A1C lowering in patients with T2DM between the following comparisons: insulin detemir and insulin glargine; F-O insulin glargine and insulin glargine U100; FDCP insulin degludec/aspart and insulin glargine U100.[1]

- A new 100 units/mL formulation of insulin glargine, Basaglar KwikPen, was found to be non-inferior to another formulation of insulin glargine 100u/mL (formulation not provided) when studied in patients with T1DM and T2DM (low quality evidence).[7] A 24-week randomized controlled trial (RCT) in patients with T1DM found Basaglar and a comparator insulin glargine 100u/mL formulation to lower A1C, -0.35% and -0.46%, respectively. In T2DM patients, Basaglar was non-inferior to a comparator insulin glargine 100u/mL formulation with A1C lowering of -1.3% in both groups.[7]
- In patients with T2DM at high risk for CV events, there was an 8.5% incidence of the first occurrence of an adjudicated major cardiovascular (CV) event (death from CV causes, nonfatal myocardial infarction [MI] or nonfatal stroke) in patients treated with insulin degludec versus 9.3% for insulin glargine (HR 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[6]

SAFETY

- There is low quality evidence that insulin degludec has less risk of nocturnal hypoglycemia than insulin glargine U100 in patients with T1DM based on three studies (rate ratio 0.61; 95% CI, 0.46 to 0.82).[1,16–18] Due to reporting methods absolute risk reductions (ARR) could not be calculated for two of the three studies. In the third study, nocturnal hypoglycemia in patients with T1DM treated with insulin degludec was less than with insulin glargine at 52 weeks (ARR 2.0%/NNT 50).[16]
- Data from six studies found moderate quality evidence in patients with T2DM than insulin degludec had a reduced incidence of nocturnal hypoglycemia compared to insulin glargine (rate ratio 0.71; 95% CI, 0.59 to 0.85).[1] Results were statistically significant for two studies lasting 52 weeks and no differences were found in four studies lasting 26 weeks.[19–24] The two studies showing differences found a 1.4 -7% less risk of nocturnal hypoglycemia with insulin degludec compared to insulin glargine (NNT 14-71).[20,21]
- There is moderate quality evidence that severe hypoglycemia rates were not clinically different between basal insulin therapies.[3]
- Withdrawals due to adverse events were found to be higher, based on moderate quality evidence, in patients with T2DM treated with insulin detemir compared to insulin glargine U100 in trials lasting up to 52 weeks (RR 2.1; 95% CI, 1.4 to 3.3). In two of the six studies the withdrawal rates were statistically significantly higher with insulin detemir compared to insulin glargine resulting in an ARR of 3-4% and number needed to harm (NNH) of 25-33.[25,26]

Recommendations:

- No changes are recommended to the PDL based on new evidence.
- Remove requirement that patients must use 40 units or less per day of insulin to be candidates for an insulin pen. Removal of this restriction will allow patients who use large amounts of insulin to have access to concentrated insulin products (insulin glargine 300 units/mL [Toujeo], insulin lispro 200 units/mL [Humalog], insulin degludec [Tresiba] and combination products) as these products are not available in vials. This recommendation does not affect the PDL status of these insulin products.
- Evaluate comparative costs in executive session.

Previous Conclusions and Recommendations:

- In adults with T1DM or T2DM, there is no difference between insulin detemir and glargine in absolute reduction of A1C or proportion with A1C of 7.0% or less between 12 to 52 weeks based on low quality evidence.
- In adults with T1DM or T2DM, there is no difference between insulin glargine U100 and U300 in absolute reduction in A1C or proportion with A1C of 7.0% or less between 4 to 6 months based on low to moderate quality evidence.

- There is low quality evidence that there are no differences in rates of severe hypoglycemia or serious adverse events between insulin detemir and glargine in adults enrolled in studies up to 1 year in length; however, there may be increased risk of drug discontinuation with insulin detemir due to adverse events (pooled RR 2.1; 95% CI, 1.4 to 3.3).
- In adults with T1DM or T2DM, glargine concentration (U100 vs. U300) did not affect rates of severe hypoglycemia or serious adverse events based on low quality evidence in studies up to 6 months in length. However, there is moderate quality evidence that rates of nocturnal hypoglycemia may be less with U300 in adults with T2DM, but not T1DM, over 6 months (38% vs. 51%; pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%).
- In adults with T1DM and T2DM, insulin degludec was found to be non-inferior to insulin glargine U100, insulin detemir and sitagliptin based on moderate evidence. Risk of hypoglycemia was found to be less with insulin degludec compared to insulin glargine in patients with T1DM and T2DM; however, differences were small suggesting additional long-term evidence is needed to clarify clinical significance.
- Make insulin glargine U300 and insulin degludec non-preferred and subject to current PA criteria for insulin pens.

Background:

More than 29 million people in the United States are thought to be living with diabetes.[27] In Oregon, it is estimated that 287,000 adults have diabetes, in which 38,000 are thought to be OHP members. There are over 7,000 patients in the Oregon Medicaid fee-for-service population alone that have T2DM and almost 1,000 have T1DM.[28] Caring for patients with diabetes enrolled in OHP accounted for $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.[28]

Insulin is used to mimic endogenous insulin release in patients with T1DM and is often necessary to obtain glucose targets in patients with T2DM. Adjustments in insulin doses are made to obtain target fasting and prandial glucose levels while minimizing the risk of hypoglycemia. Insulins are categorized by onset and duration of action. Most T1DM patients use multiple daily injections of basal and prandial insulins. Patients with T2DM who require insulin therapy are usually initiated on a basal insulin product. Basal insulins include NPH and recombinant analog formulations glargine, detemir, and degludec. Prandial insulins include formulations of regular insulin, and recombinant analogs lispro, aspart and glulisine. Evidence suggests no clinical differences in A1C lowering between the different basal insulins products in patients with T1DM or T2DM.[3] Hemoglobin A1C lowering has been shown to be similar between the different prandial insulins. Common insulin adverse reactions are hypoglycemia, injection site reactions, and weight gain. Basal insulin analogs and rapid-acting insulin analogs may have a reduced risk of hypoglycemia.[5]

Clinically meaningful outcomes in patients with diabetes include microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular complications (i.e., stroke, myocardial infarction), mortality, and severe hypoglycemia. Because hyperglycemia is associated with increased microvascular complications and possibly macrovascular outcomes, A1C changes are often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies.[4] The Diabetes Control and Complication Trial (DCCT), which was a large prospective trial in patients with T1DM, provided evidence that intensive insulin therapy led to improved glucose control and reductions in microvascular outcomes.[29] A study in T2DM patients reiterated the DCCT findings, that maintenance of glucose lowering targets minimized microvascular complications in this population.[30] Due to the increased risk of CV disease in patients with diabetes, the effect of insulin on CV outcomes is of high importance. Evidence has shown that intensive glucose control produced a trend towards less risk of CV events in patients with T1DM.[29] In patients with T2DM intensive glucose control reduced CV outcomes based on the United Kingdom Prospective Diabetes Study (UKPDS) study; however, this was not shown in subsequent studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD], The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] and Veterans Affairs Diabetes Trial [VADT]]).[4] There is a paucity of evidence on the risk or benefit of insulin use on CV outcomes in patients with diabetes from RCTs specifically designed to assess CV events. One study compared insulin glargine to standard of care and n-3 fatty acids or placebo in patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. The study

found similar rates of CV outcomes (nonfatal MI, nonfatal stroke, or death from CV causes) in both groups: 2.94 and 2.85 per 100 person-years in patients with a median follow-up of 6.2 years (HR 1.02; 95% CI, 0.94 to 1.11).[31]

Utilization:
The highest insulin utilization is for the preferred product insulin glargine (Lantus) with 43% of the insulin market share. For short-acting insulin, insulin lispro (16%) and insulin apart (18%) have the highest utilization. The number of non-preferred insulins prescription claims comprises 7% of insulin utilization and 49% of net costs for the class. Overall preferred insulin products account for 51% of the insulin class costs. The concentrated insulin products account for 4% of the market share and 17% of the net costs for 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), 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.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer for new drug approval included in this review, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Systematic Reviews:

DERP – Long-Acting Insulins for Type 1 and Type 2 Diabetes
The Drug Effectiveness Review Project (DERP) released a report on long-acting insulins used for the treatment of T1DM and T2DM in adults and children in May of 2017.[1] The review included the following: insulin glargine U100 or U300 (Basaglar U100, Lantus U100, Toujeo U300), insulin detemir (Levemir), insulin degludec (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30) and insulin glargine biosimilar, which they describe as F-O glargine (Basaglar). Sixty-one studies comparing insulin products were included in the review with a search date lasting till November 2016. Efficacy and harms data was insufficient for long-acting insulin use in children with diabetes.

Insulin Degludec and Insulin Detemir
Type 1 Diabetes

- There is low quality evidence of no difference in glycemic control between insulin degludec and insulin detemir in children and adolescents or adults with T1DM based on two fair-quality trials. There was insufficient evidence available to evaluate differences in risk of nocturnal or severe hypoglycemia.[1]

Insulin Degludec versus Insulin Glargine U100

Type 1 Diabetes

- Insulin degludec and insulin glargine demonstrated similar A1C lowering in patients with T1DM based on three fair to good quality trials lasting up to 52 weeks (low strength of evidence).
- Nocturnal hypoglycemia was lower with insulin degludec than insulin glargine U100 with a pooled rate ratio of 0.61 (95% CI, 0.46 to 0.82; I^2 = 55%) based on low quality evidence.[1] Data from one of the original trials that lasted 52 weeks found nocturnal hypoglycemia occurred in 72% of insulin degludec treated patients and 74% of glargine treated patients (ARR 2.0%/NNT 50; P=0.021).[16] In a second study the incidence of nocturnal hypoglycemia was 5.1 events per patient/year with insulin degludec compared to 12.3 events per patient/year with insulin glargine (p<0.01).[17] In a third study, the incidence of nocturnal hypoglycemia was 3 events/patient for insulin degludec compared to 4.5 events/patient for insulin glargine when patients were treatment for 24 weeks (p=0.001).[18] Data was insufficient to compare outcomes of severe hypoglycemia or withdrawals due to adverse events.

Type 2 Diabetes

- Six (n= 4,434) trials provided moderate-strength evidence that there was no difference in glycemic efficacy between insulin degludec and insulin glargine based on the number of patients achieving an A1C less than 7% (RR 0.96; 95% CI, 0.90 to 1.03; I^2= 0%) and the number of patients meeting this A1C goal with no episodes of confirmed hypoglycemia (RR 1.0; 95% CI, 0.88 to 1.1; I^2=17%).[1]
- Low-strength evidence found insulin degludec given three times weekly had less glucose lowering efficacy than insulin glargine U100 given daily. Fewer patients in the insulin degludec group achieved an A1C less than 7% compared to insulin degludec, 47% versus 56%, respectively (ARR 0.09; RR 0.84; 95% CI, 0.74 to 0.95; I^2=0%).[1] Nocturnal hypoglycemia was more common in patients treated with insulin degludec 3 times weekly (given before breakfast) compared to daily insulin glargine based on low-strength evidence (rate ratio 2.1; 95% CI, 1.1 to 4.2).[1] Insulin degludec is only approved for daily use.
- There was no difference between daily insulin degludec and daily insulin glargine in the number of patients with severe hypoglycemia. Moderate-strength evidence found fewer episodes of nocturnal hypoglycemia with daily insulin degludec compared to daily insulin glargine U100 based on evidence from six trials (rate ratio 0.71; 95% CI, 0.59 to 0.85; I^2=0%).[1] Two studies, lasting 52 weeks, found statistically significantly less nocturnal hypoglycemia with insulin degludec compared to insulin glargine. In one study insulin degludec was found to have a 40% incidence of nocturnal hypoglycemia compared to 47% in the insulin glargine group (ARR 7%/NNT 14; P=0.0399).[20] In the second study the incidence of nocturnal hypoglycemia was 13.8% for insulin degludec compared to 15.2% for insulin glargine (ARR 1.4%/NNT 71: P=0.038).[21] There were no statistically significant differences found in nocturnal hypoglycemia rates between insulin degludec and insulin glargine in studies lasting 26 weeks.
- There was no difference in withdrawal rates due to adverse events in comparisons of daily insulin degludec and daily insulin glargine.

Insulin Detemir versus Insulin Glargine

Type 1 Diabetes

- No difference in A1C or plasma glucose was found between insulin detemir and insulin glargine U100 based on low-strength evidence from two studies lasting 26 or 52 weeks.[1] Low-strength evidence found no difference in severe hypoglycemia or withdrawals related to adverse events between insulin detemir and insulin glargine based on two RCTs and two observational studies.
- Rates of severe hypoglycemia and withdrawal rates between insulin detemir and insulin glargine were found to be similar based on low-strength of evidence.[1]

Type 2 Diabetes

- In patients with T2DM, there was no difference in A1C reduction or achievement in A1C goals between insulin detemir and insulin glargine U100 based on low-strength of evidence.[1] Low-strength of evidence from four cohort studies found of no difference in risk of cancer between insulin detemir and insulin glargine when compared to no insulin exposure.
- Severe and nocturnal hypoglycemia rates were similar between insulin detemir and insulin glargine U100 based on low-strength of evidence.
- Patients treated with insulin detemir had significantly more withdrawal rates due to adverse events compared to insulin glargine U100 (RR 2.1; 95% CI, 1.4 to 3.3; I^2=0%) based on moderate-strength of evidence (6 studies).[1,25,26,32–35] The withdrawal rates due to adverse events was consistently higher in all six studies and statistically significant in two studies (ARR 3-4%/NNT 25-33).[25,26]

F-O Glargine vs. Glargine U100

Type 1 Diabetes

- Hemoglobin A1C lowering was similar between F-O glargine and glargine U100 in patients with T1DM based on low-strength of evidence. Evidence was insufficient to determine risk differences between F-O glargine and glargine U100 for severe hypoglycemia, nocturnal hypoglycemia and withdrawals due to adverse events.

Type 2 Diabetes

- F-O glargine was similar to glargine U100 in A1C lowering in patients with T2DM based on low-strength of evidence. Evidence was insufficient for comparisons of nocturnal hypoglycemia, severe hypoglycemia or withdrawals due to adverse events between the two products.[1]

Insulin Glargine U300 vs. Insulin Glargine U100

Type 1 Diabetes

- Hemoglobin A1C lowering was similar between insulin glargine U300 and insulin glargine U100 based on low-strength of evidence from four trials.[1] Severe hypoglycemia and withdrawals due to adverse events were not different between the groups. There was moderate strength of evidence that there was no difference in the risk of nocturnal hypoglycemia between insulin glargine U300 and insulin glargine U100 (RR 0.91; 95% CI, 0.80 to 1.05; I^2=39.1%).[1]

Type 2 Diabetes

- Low-strength of evidence from seven observational trials found the incidence of severe hypoglycemia was 5.4% with insulin glargine administered via a pen compared to 7.5% with insulin glargine administered via vial and syringe (RR 0.72; 95% CI, 0.65 to 0.79; I^2=0%).[1]

Fixed-dose Combination Products (FDCP) Degludec/Aspart vs. Detemir

Type 1 Diabetes

- Low-strength of evidence found similar A1C lowering between the FDCP insulin degludec/aspart and insulin detemir based on one study. Evidence was insufficient to determine differences for severe or nocturnal hypoglycemia or withdrawals due to adverse events for this comparison.[1]

Fixed-dose Combination Products (FDCP) Degludec/Aspart vs. Glargine

Type 2 Diabetes

- Hemoglobin A1C reductions were similar between insulin degludec/aspart and insulin glargine based on one trial providing low-strength of evidence. Insufficient evidence prevented comparative risk of episodes of nocturnal hypoglycemia, severe hypoglycemia and withdrawals due to adverse events.[1]

New Guidelines:

NICE – Diabetes in Children and Young People

In a 2015 update, National Institute for Health and Care Excellence (NICE) provided guidance for the management of children and young people with T1DM and T2DM.[2] The recommended target to minimize complications is an A1C is 6.5% or less. The use of multiple daily basal-bolus insulin regimens are recommended for all T1DM patients. If multiple daily injections are not feasible, then continuous subcutaneous insulin infusion is recommended. NICE recommends the use of metformin monotherapy for children and young people with T2DM. No other treatments were mentioned for the management of T2DM in children and young people.

NICE – Type 1 Diabetes in Adults

NICE guidance was issued on management of adults with T1DM.[3] Twenty-eight studies were identified that compared the following long-acting insulins: insulin glargine, insulin detemir, insulin degludec and NPH insulin. Twenty-six studies were identified that compared rapid-acting insulins. Evidence for insulin aspart, lispro, glulisine, and regular insulin were identified. Evidence graded as low or very low quality was not included. After review of the evidence, nine recommendations were made for managing adults with T1DM (Table 1).

Table 1. NICE Recommendations for Adults with T1DM[3]

1. Offer multiple daily injection basal-bolus regimens, rather than twice-daily mixed insulin regimens.
2. Newly diagnosed adults should not be offered non-basal-bolus insulin regimens (i.e., twice-daily mixed, basal only or bolus only).
3. Offer insulin detemir given twice daily as basal insulin therapy.
4. If twice daily injections are not desired, offer once daily insulin glargine or once daily insulin detemir.
5. Offer rapid-acting insulin analogs injected before meals rather than regular insulin.
6. Do not use rapid-acting insulins after meals on a routine basis.
7. Consider twice-daily regular mixed insulin regimens if a multiple daily injection of basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen.
8. Consider a twice-daily analogs mixed insulin regimen if use of twice-daily regular insulin causes hypoglycemia that affects quality of life.
9. Consider the addition of metformin to insulin therapy in patients with a BMI of 25 kg/m^2 or more who wish to minimize insulin doses.

Review of the Evidence

Long-Acting Insulins

NICE found moderate quality evidence of no clinically significant differences between insulin glargine and insulin degludec for changes in A1C, weight, quality of life and nocturnal hypoglycemia.[3] In studies with less than or equal to 6 months follow-up, the mean difference in A1C was only -0.13% (-0.25 to- 0.01%) favoring insulin degludec. Studies with greater than 6 months follow-up there was no clinically meaningful difference in A1C.[3] Body weight gain was 0.2 kg (0.51 to 0.91 kg) higher with insulin degludec compared to insulin glargine. Depending on the study duration nocturnal hypoglycemia was either more common or less common with insulin degludec compared to insulin glargine. In trials 6 months or less degludec was found to have 7 more nocturnal hypoglycemia episodes (87 fewer to 109 more), per 1000 people, than insulin glargine and in studies of more than 6 months duration insulin degludec had 7 less hypoglycemia episodes (80 fewer to 80 more), per 1000 people, than insulin glargine.[3]

In comparisons between insulin detemir and insulin glargine, there was moderate quality evidence of more injection site reactions with insulin detemir (66 more per 1000 patients).[3] No clinically important differences were found between insulin detemir and insulin glargine for outcomes of A1C, severe hypoglycemia and body weight gain. A comparison between insulin detemir and NPH found 40 fewer nocturnal hypoglycemia events (per 1000 patients treated) with insulin detemir based on moderate quality of evidence and trials lasting greater than 6 months.[3]

In patients with T1DM, NPH and insulin glargine had similar rates of severe hypoglycemia based on high quality evidence and similar rates of nocturnal hypoglycemia based on moderate quality evidence.[3] No clinically meaningful differences in weight changes were found between insulin glargine and NPH based on moderate quality evidence. For the outcomes of severe hypoglycemia, adverse events and severe adverse events, insulin detemir and insulin degludec were found to be clinically similar (0 events for each outcome in both groups) based on moderate quality evidence. A study of insulin detemir dosed once daily versus twice daily found no clinical difference between the dosing regimens on A1C changes or hypoglycemia rates based on high quality evidence. In addition, no clinically meaningful differences were found for NPH dosed once daily compared to twice daily. Meta-analysis of A1C data and risk for severe hypoglycemia between long-acting basal insulin analogs and NPH do not show clinically meaningful differences in A1C and imprecise results for severe hypoglycemia (Table 2).[3]

Table 2. Comparison of Long-Acting Insulins based on Meta-analysis data.[3]

Insulin	Mean Change (95% CrI)	A1C Lowering Compared to NPH (twice daily) (95% CrI)	Severe Hypoglycemia†
NPH (twice daily)	-0.32 (-0.49 to -0.15)	NA	
Insulin detemir (once or twice-daily)	-0.53 (-0.92 to -0.11)	-0.21 (-0.57 to 0.17)	NR
Insulin detemir (twice-daily)	-0.48 (-0.69 to -0.29)	-0.16 (-0.27 to -0.05)[a]	OR 0.92 (95% CI, 0.63 to 1.43)
Insulin glargine (once-daily)	-0.42 (-0.71 to -0.13)	-0.10 (-0.34 to 0.14)	OR 0.99 (95% CI, 0.02 to 47.97)*
Insulin detemir (once-daily)	-0.40 (-0.66 to -0.13)	-0.08 (-0.27 to 0.13)	OR 0.95 (95% CI, 0.01 to 57.39)*
Insulin degludec (once-daily)	-0.35 (-0.68 to -0.02)	-0.03 (-0.31 to 0.26)	OR 1.02 (95% CI, 0.01 to 52.8)*
NPH (once-daily)	-0.28 (-0.61 to 0.06)	0.04 (-0.25 to 0.33)	OR 0.85 (95% CI, 0.01 to 45.68)*

[a] Results were statistically significant (p-value not provided)
* Results should be interpreted with caution due to wide confidence intervals which suggests uncertainty in the results.
† No comparisons were statistically significant.
Abbreviations: CI = confidence interval; OR = odds ratio; NPH = neutral protamine Hagedorn; NR = not reported

Rapid-Acting Insulins

Evidence evaluating insulin lispro and insulin glulisine found no clinically meaningful differences for the outcomes of A1C (MD 0.01% lower with lispro), severe hypoglycemia (MD 0), hypoglycemia (MD 0.07 [episodes/patient-month] higher with lispro in studies ≤ 6 months and MD 0.01[episodes/patient-month) lower with lispro in studies lasting > 6 months), and nocturnal hypoglycemia (MD 0.2 episodes lower with lispro) based on moderate quality evidence.[3] Moderate quality evidence found conflicting results for quality of life assessments in studies comparing insulin aspart to regular human insulin dependent upon type of assessment used. The investigators found moderate quality evidence of no clinically significant differences between insulin glulisine and regular insulin for A1C (MD 0.03% lower with glulisine), severe hypoglycemia (MD 0.08 [episodes/patient-month) lower with insulin glulisine), hypoglycemia (16 more events per 1000

for insulin glulisine), and nocturnal hypoglycemia (MD 0).[3] There was no clinical difference in A1C lowering between Insulin lispro and regular insulin (MD of 0.03% favoring insulin lispro), severe hypoglycemia or nocturnal hypoglycemia. A reduction in nocturnal hypoglycemia was found with insulin aspart compared to regular insulin with a MD -1.1 (episodes/month) in studies of 6 months or less. There were no clinically meaningful differences between insulin lispro and insulin glulisine for outcomes of A1C, hypoglycemia (severe, minor, and nocturnal) or injection site reactions.[3]

Studies that compared pramlintide with insulin to insulin alone in T1DM found less risk of severe hypoglycemia and weight gain with the combination regimen but also increased risk of nausea, vomiting and anorexia based on moderate quality of evidence.[3] Studies of adjunctive metformin added to insulin therapy in patients with T1DM found moderate to high quality evidence that the addition of metformin reduces the dose of insulin required to maintain glucose control. No differences between adjunctive metformin and insulin versus insulin alone were found in outcomes of A1C, hypoglycemia, weight change or gastrointestinal (GI) discomfort. One study found no benefit on A1C, dose of insulin or weight change when liraglutide was added to insulin in patients with T1DM.[3]

NICE – Type 2 Diabetes in Adults

NICE updated several recommendations to its 2015 guidance on the management of T2DM.[36] Recommendations include a target A1C of 7.0% or less for most patients. If target A1C is not met with diet, lifestyle and adherence reinforcement, drug treatment should be considered. Insulin is usually recommended after failure of optimization of oral antidiabetic therapies and in patients with symptoms of hyperglycemia.

In patients who are candidates for insulin, metformin therapy should be continued unless contraindicated or not tolerated. NPH insulin is recommended with or without short-acting insulin; however, this practice is less common in the United States (US). Insulin detemir or insulin glargine is recommended in patients who require assistance in insulin administration, experience lifestyle altering hypoglycemia, or the patient would require NPH and additional oral antidiabetic treatments.[36] Pre-mixed (biphasic) insulin analogues are recommended if injecting immediately before a meal, hypoglycemia is an issue or postprandial hyperglycemia is a concern. Patients who start on NPH insulin may need to be switched to insulin detemir or insulin glargine if target A1C levels are not reached due to hypoglycemia, or if the patient experiences significant hypoglycemia, has problems operating the NPH insulin device (not available in the US), or who require assistance in insulin administration.

The American Diabetes Association – Standards of Medical Care 2017

The ADA updates their standards of care in diabetes on an annual basis.[4] The 2017 standards contain comprehensive recommendations for managing all aspects of patients with diabetes. ADA makes recommendations based on review and grading of the evidence. Recommendations are given a rating ranging of A, B, C and E (Table 3). Statement of extensive literature search is included but specific methods are not described. Updates pertaining to the pharmacology of T1DM and treatment goals are included in this review.

Table 3. ADA Evidence-grading System.[4]

Leve of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
B	Supportive evidence from well-conducted cohort studies
C	Supportive evidence from poorly controlled or uncontrolled studies
E	Expert consensus or clinical experience

Hemoglobin A1C goals – A goal of less than 7% is recommended for most patients based on level A evidence.[4] A lower goal of less than 6.5% may be appropriate for those that are candidates for more intensive management without experiencing significant hypoglycemia (level C evidence). Patients with limited life expectancy, history of severe hypoglycemia and advanced complications may be more appropriately managed with a higher goal of less than 8% (level B evidence).[4]

Pharmacological Management of T1DM – ADA recommends that most patients with T1DM should be managed with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion (Level A evidence).[4] In an effort to minimize hypoglycemia, most patients should use rapid-acting insulin analogs (Level A evidence).

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm

An updated consensus statement was released by the AACE/ACE in 2017.[5] Recommendations are based on evaluation and rating of the evidence. The AACE/ACE also include a subjective factor impact and two-thirds "expert consensus" in the overall recommendation grade, which may permit risk of bias in their final recommendations. Several authors have associations with industry that can also influence recommendations. The strength of the recommendations were provided in a visual format but were not assigned a GRADE recommendation which can also limit interpretation of the recommendations.

Target A1C values of 6.5% or less are recommended for patients with T2DM if they can be reached safely and affordably.[5] Recommendations from the AACE/ACE are based on entry level A1C (level of A1C at time of diagnosis).[5] Basal insulin is recommended, in patients with an A1C of ≥ 7.5%, in dual therapy and triple therapy regimens, as an option with metformin. A basal insulin is recommended in patients already on dual therapy with an A1C of 8% or higher and/or patients with a long history of diabetes who may not be able to reach glucose lowering targets with a third oral agent. A GLP-1 RA can also be tried but most likely the patient will still require insulin to control hyperglycemia.[5] Though efficacy of NPH and basal insulin analogs has been shown to be similar, basal insulin analogs are recommended due to reduced risk of hypoglycemia. Patients may require rapid-acting insulin to cover postprandial hyperglycemia in T2DM patients. In this scenario, rapid-acting insulin analogs are recommended over regular insulin because they have reduced risk of hypoglycemia.[4]

Safety Alerts:

No new safety alerts identified.

New Formulations:

A new formulation of insulin glargine, called Basaglar, was approved to improve glycemic control in adult and pediatric patients with T1DM and in adults with T2DM.[7] Basaglar is a long-acting insulin to be injected once daily at a dose based on individual patient needs. Basaglar is available in a 100 units/mL KwikPen device. Approval of Basaglar was partially based on clinical efficacy and safety data from studies of another insulin glargine product that was not specifically named. Two additional studies compared Basaglar to another type of insulin glargine 100u/mL (exact formulation not stated). An open-label study in adult patients with T1DM compared Basaglar to insulin glargine 100u/mL, both in combination with mealtime insulin lispro. Patients (n=535) were a mean age of 41 years, had a 16-year history of T1DM and baseline A1C of 7.7%. After 24-weeks, Basaglar was non-inferior to insulin glargine 100u/mL with an A1C decreases of -0.35% and -0.46%, respectively.[7] A second double-blind, 24-week study compared Basaglar to another insulin glargine product 100u/mL in patients with T2DM also taking at least 2 oral antidiabetic medications. The mean age was 59 years and the baseline A1C was 8.33%. Basaglar was non-inferior to the other insulin glargine 100u/mL formulation with both groups achieving an A1C reduction of -1.3%.[7]

Randomized Controlled Trials:

One thousand 95 potentially relevant clinical trials were evaluated from the literature search. After further review, only 1 trial was included (**Table 4**). Trials were excluded because they offered no new additional information from sources already included in the review. The remaining trials are briefly described in the table below. The full abstracts are included in Appendix 2.

Table 4. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Marso, et al[6] (DEVOTE)	1. Insulin Degludec* 2. Insulin Glargine U100* * Treat-to-target	Patients (n=7637) with T2DM at high risk of CV disease, chronic kidney disease or both	First occurrence of an adjudicated major CV event (death from CV causes, non-fatal MI or nonfatal stroke)	Insulin Degludec: 325 (8.5%) Insulin Glargine: 356 (9.3%) HR 0.91; 95% CI 0.78 to 1.06 P <0.001 for noninferiority

Abbreviations: RCT = randomized clinical trial; etc.

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Appendix 1: Current Status of PDL Class.

Insulins (long-acting insulins bolded)

ROUTE	FORMULATION	BRAND	GENERIC	PDL	PA
SUB-Q	**VIAL**	**LANTUS**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LANTUS SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LEVEMIR FLEXTOUCH**	**INSULIN DETEMIR**	**Y**	Y
SUB-Q	CARTRIDGE	NOVOLOG	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	HUMULIN 70/30 KWIKPEN	INSULIN NPH HUM/REG INSULIN HM	Y	Y
SUB-Q	INSULN PEN	NOVOLOG FLEXPEN	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	NOVOLOG MIX 70-30 FLEXPEN	INSULIN ASPART PROTAM & ASPART	Y	Y
SUB-Q	VIAL	HUMALOG	INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 50-50	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 75-25	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMULIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	HUMULIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	HUMULIN R U-500	INSULIN REGULAR, HUMAN	Y	
SUB-Q	VIAL	NOVOLIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	NOVOLIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	NOVOLOG	INSULIN ASPART	Y	
SUB-Q	VIAL	NOVOLOG MIX 70-30	INSULIN ASPART PROTAM & ASPART	Y	
INJECTION	VIAL	HUMULIN R	INSULIN REGULAR, HUMAN	Y	
INJECTION	VIAL	NOVOLIN R	INSULIN REGULAR, HUMAN	Y	
SUB-Q	**INSULN PEN**	**TOUJEO SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**N**	Y
SUB-Q	**VIAL**	**LEVEMIR**	**INSULIN DETEMIR**	**N**	
SUB-Q	**INSULIN PEN**	**BASAGLAR KWIKPEN**	**INSULIN GLARGINE**	**N**	
SUB-Q	**INSULIN PEN**	**TRESIBA FLEXTOUCH**	**INSULIN DEGLUDEC**	**N**	
SUB-Q	**INSULIN PEN**	**RYZODEG FLEXTOUCH**	**INSULIN DEGLUDEC/ASPART**	**N**	
INHALATION	CART W/DEV	AFREZZA	INSULIN REGULAR, HUMAN	N	
SUB-Q	CARTRIDGE	HUMALOG	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	APIDRA SOLOSTAR	INSULIN GLULISINE	N	Y
SUB-Q	INSULN PEN	HUMALOG KWIKPEN	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 50-50 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 75-25 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMULIN N KWIKPEN	INSULIN NPH HUMAN ISOPHANE	N	Y
SUB-Q	VIAL	APIDRA	INSULIN GLULISINE	N	

Appendix 2: Abstracts of Comparative Clinical Trials

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes.

Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB; DEVOTE Study Group.

Background Degludec is an ultralong-acting, once-daily basal insulin that is approved for use in adults, adolescents, and children with diabetes. Previous open-label studies have shown lower day-to-day variability in the glucose-lowering effect and lower rates of hypoglycemia among patients who received degludec than among those who received basal insulin glargine. However, data are lacking on the cardiovascular safety of degludec. Methods We randomly assigned 7637 patients with type 2 diabetes to receive either insulin degludec (3818 patients) or insulin glargine U100 (3819 patients) once daily between dinner and bedtime in a double-blind, treat-to-target, event-driven cardiovascular outcomes trial. The primary composite outcome in the time-to-event analysis was the first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3. Adjudicated severe hypoglycemia, as defined by the American Diabetes Association, was the prespecified, multiplicity-adjusted secondary outcome. Results Of the patients who underwent randomization, 6509 (85.2%) had established cardiovascular disease, chronic kidney disease, or both. At baseline, the mean age was 65.0 years, the mean duration of diabetes was 16.4 years, and the mean (±SD) glycated hemoglobin level was 8.4±1.7%; 83.9% of the patients were receiving insulin. The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06; P<0.001 for noninferiority). At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001). Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an absolute difference of 1.7 percentage points (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). Rates of adverse events did not differ between the two groups. Conclusions Among patients with type 2 diabetes at high risk for cardiovascular events, degludec was noninferior to glargine with respect to the incidence of major cardiovascular events. (Funded by Novo Nordisk and others; DEVOTE ClinicalTrials.gov number, NCT01959529 .).

Appendix 3: Highlights of Prescribing Information

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

BASAGLAR (insulin glargine injection), for subcutaneous use
Initial U.S. Approval: 2000

---------- INDICATIONS AND USAGE ----------
BASAGLAR® is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (1)

Limitations of Use:
Not recommended for treating diabetic ketoacidosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use. (2.2, 2.3, 2.4)
- Administer subcutaneously once daily at any time of day, but at the same time every day. (2.2)
- Rotate injection sites to reduce the risk of lipodystrophy. (2.1)
- Closely monitor glucose when converting to BASAGLAR and during initial weeks thereafter. (2.2)
- Do not dilute or mix with any other insulin or solution. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 100 units/mL (U-100) in 3 mL prefilled BASAGLAR® KwikPen® delivery device. (3)

---------- CONTRAINDICATIONS ----------
- During episodes of hypoglycemia. (4)
- Hypersensitivity to BASAGLAR or one of its excipients. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Never share* a BASAGLAR KwikPen between patients, even if the needle is changed. (5.1)
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision. (5.2)
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. (5.3, 6.1)
- *Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue BASAGLAR, monitor and treat if indicated. (5.5, 6.1)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
- *Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)

----------ADVERSE REACTIONS----------
Adverse reactions commonly associated with insulin glargine products (5% or greater incidence) are:
- Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose. (7)
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent. (7)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

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

Revised: 12/2015

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2017
Search Strategy:

#	Searches	Results
1	Insulin Glargine/	1411
2	Insulin Aspart/	575
3	insulin NPH.mp. or Insulin, Isophane/	742
4	Insulin Detemir/	482
5	Insulin Lispro/	783
6	Insulin/ad [Administration & Dosage]	10799
7	insulin glulisine.mp.	187
8	1 or 2 or 3 or 4 or 5 or 6 or 7	12780
9	limit 8 to (english language and humans and yr="2015 -Current")	1106
10	limit 9 to (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or systematic reviews)	94

Insulins

Goal:

- Restrict certain insulin products to specific patient populations to ensure appropriate use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred insulin vials
- All pre-filled insulin pens, cartridges and syringes

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Is the request for an insulin pen or cartridge?	Yes: Go to #4	No: Go to # 5
4. Will the insulin be administered by the patient or a non-professional caregiver AND do any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • ~~The patient is on 40 units or less of insulin per day~~ • The patient is a child less than 18 years of age?	Yes: Go to #5	No: Pass to RPh; deny for medical appropriateness

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	Yes: Inform prescriber of covered alternatives	No: Approve for up to 12 months

P&T / DUR Review: *9/17 (KS), 3/16 (KS); 11/15 (AG); 9/10*
Implementation: *10/13/16; 1/1/11*

ELLEN F. ROSENBLUM
Attorney General

FREDERICK M. BOSS
Deputy Attorney General

DEPARTMENT OF JUSTICE
TRIAL DIVISION

MEMORANDUM

DATE: January 6, 2017

TO: Beth Englander
Marisa Samuelson
Stephen S. Walters
Oregon Law Center

Kevin Costello
Center for Health Law & Policy Innovation
Harvard Law School

FROM: Renee Stineman, Attorney-in-Charge
Special Litigation Section

SUBJECT: Updated Memorandum of Understanding between Oregon Health Authority (OHA) and Oregon Law Center and Center for Health Law & Policy Innovation (collectively, OLC)

OHA is committed to prioritizing essential services and considers expansion of coverage for Hepatitis C (HCV) treatment to be an important priority for Oregonians. Currently, OHA's coverage criteria for Oregon Health Plan (OHP) authorizes treatment of stage F3 and F4 HCV disease, with limited coverage of some stage F2 disease (such as patients who are also HIV-positive or have had a liver transplant). Newly developed, direct acting anti-viral medications (DAAs) have significantly increased the cost of HCV treatment. OHA has spent over $95.5 million on treating HCV at this coverage level since release of the DAAs. The agency's and the Governor's proposed budgets reflect the desire to expand HCV treatment to all Oregon Health Plan (OHP) members with stage F2 stage of the disease by January 1, 2018, if the budgets are funded to the requested levels.

The OLC and CHLPI have threatened to file a lawsuit against OHA alleging that the agency's current coverage criteria for OHP for HCV treatment violates federal Medicaid law. OHA admits no liability relating to the proposed lawsuit.

The agency has a process for establishing prioritization of essential services, and in accordance with that process, the agency plans to expand coverage of HCV, as outlined in this Memorandum of Understanding.

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In furtherance of OHA's plan for expanding OHP coverage for HCV treatment, OHA will:

1. Expand coverage to all OHP members for HCV treatment with HCV stage F-2 by January 1, 2018, conditioned on funding by the Oregon legislature in the 2017 legislative session;

2. Not seek re-prioritization of HCV treatment by F-scores on the Prioritized List;

3. Advocate for legislative approval of funding in the 2017 legislative session in line with OHA's Policy Option Package;

4. Continue to ensure its Coordinated Care Organization (CCO) coverage criteria are properly aligned with Oregon's Fee for Service (FFS) criteria for HCV/DAA coverage. For example, OHA has developed and included within the current CCO contracts a risk corridor that requires CCOs to use the exact FFS criteria. The risk corridor incentivizes CCOs to comply with this requirement through funding agreements.

5. Increase communication with HCV advocates and OLC by providing quarterly summaries of reported data on the number of DAA treatments provided to any OHP member reporting during the immediately prior quarter, broken down between CCO and FFS, in a form to be developed by OHA. The reporting will begin 30 days after the close of the second quarter of 2017 and the first report will cover the first quarter of 2017. In addition, OHA will agree to explore ways to develop a system to efficiently and accurately collect data on denial of DAA treatment coverage and to implement such a system within one year;

6. OHA agrees to receive bi-monthly quarterly updates from OLC on OHP members who are denied HCV treatment and take action when appropriate, as determined by OHA. Reports should be provided by email to Heather Johnson, at heather.n.johnson@dhsoha.state.or.us and Rhonda Busek, at rhonda.j.busek@state.or.us ;

7. Continue to take reasonable steps to ensure CCOs comply with contractual and legal obligations to avoid inappropriate barriers to treatment, including but not limited to, monitoring CCO denials for DAA treatment upon completion of the denial data collection system described in paragraph 5 above;

8. Perform a mid-2017 review of expenditures for HCV treatment to inform OHA in considering possible reinvesting funding previously allocated for HCV treatment but not spent for further expansion of HCV coverage in 2018 and, upon completion, report to OLC any decisions by OHA resulting from that review;

9. Modify its prior authorization criteria to conform to the MOU in not more than 90 days per paragraph 9 and again in not more than 9 months per paragraph 10 (draft attached hereto as Appendix A) as soon as reasonably practicable (providing a copy of these modifications to OLC) as follows, which is anticipated to take 60 to 90 days, but no more than 90 days, from execution of this MOU to implement through rule changes:

a. Reduce required proof of life expectancy from 5 years or more to 1 year or more;

b. Remove specialists restriction for F0, F1, F2 and F3 DAA prescribing. For F3 only, specialist restriction will be removed only for that period from when the member has sought treatment by a specialist and when the member begins receiving treatment by a specialist, so as not to delay DAA treatment while a member is waiting for a specialist to become available;

c. Implement a standard for members with test results that show an F score range (ie: between F2 and F-3) that either (1) requires application of the highest F score in the range for determining coverage (for example, if a member's test result shows an F score of between F-2 and F-3, the member will be considered to have stage F-3 for purposes of coverage) or (2) require one additional, more specific, testing of an individual, if the higher stage is not applied for lack of specificity, however, additional testing may not be limited to biopsy (e.g. coverage cannot be contingent on member consenting to biopsy) and must include the option of noninvasive testing, such as elastography. Any resulting additional testing will not count against limits on number of covered testing per year. After one additional test, if a range still exists, the highest F score in the range will apply for determining coverage; and

d. OHA will distribute educational materials or other training to providers on HVC treatment and prior authorization criteria upon implementation of these modifications.

10. Expand the prior authorization criteria for HCV treatment as follows, which is anticipated to take approximately 6 to 9 months, but no more than 9 months, from execution of this MOU to implement:

a. To apply criteria currently in place for stage F-2 disease to stage F-1 and F-0 disease for OHP members who are co-infected with HIV,

b. To include coverage for members able to provide sufficient documentation of labs or biopsy showing fast progressing fibrosis that would require treatment earlier than the approved fibrosis stage. Determination of the definition of fast progressing fibrosis will be made consistent with guidance by the Health Evidence Review Commission or Pharmacy and Therapeutics Committee, whichever OHA determines is the appropriate forum to consider the matter. In this process, OHA agrees to obtain and consider input from experts in the area of HCV treatment, including

Dr. Benner. OHA will have this matter considered by the appropriate forum during the calendar year 2017 and will implement the changes during the 2018 calendar year, contingent on adequate funding; and

c. To provide coverage for additional extrahepatic manifestations and/or comorbidities consistent with guidance by the Health Evidence Review Commission or Pharmacy and Therapeutics Committee, whichever OHA determines is the appropriate forum to consider the matter. In this process, OHA agrees to obtain and consider input from experts in the area of HCV treatment, including Dr. Benner. OHA intends to have this matter considered by the appropriate forum during the calendar year 2017 with the goal of implementation during the 2018 calendar year, contingent on adequate funding.

11. Perform a mid-2018 review of expenditures for HCV treatment to inform OHA in considering the possibility of expanding to F-0 in the next biennium budget request and, upon completion, report to OLC any decisions by OHA resulting from that review.

OHA commits to make good faith efforts to accomplish the above-described changes and results. However, this memorandum shall not be enforceable in court and does not constitute a contract or other enforceable promise.

OHA's commitment to these aims includes a commitment to take reasonable steps to obtain funding, where needed, from the Oregon Legislative Assembly to accomplish this plan. If adequate funding is not authorized, OHA will assess which of these goals, if any, it will pursue. While OHA welcomes comment and cooperation from OLC, OHA maintains that it has ultimate discretion to determine the time and the manner in which the above-described changes and results are pursued.

OLC understands this memorandum to reflect OHA's intent. In support of that intent, OLC and CHLPI's current clients intend to refrain from filing a lawsuit pending the outcome of the 2017 legislative process and OHA's compliance with this MOU. OLC's clients may pursue litigation if the agency does not receive the funding it has requested on which the above commitments are predicated, or at any time before or after the conclusion of the 2017 session if the commitments expressed in this MOU are not followed.

The provisions of this memorandum are understood to apply from January 10, 2017, to the end of the next biennium (June 30, 2019).

Oregon Law Center and CHLPI Clients

[redacted]
Named Plaintiff 1
Date: March 3, 17

[redacted]
Named Plaintiff 2
Date: 3-13-17

Oregon Health Authority

Lynne Saxton
Lynne Saxton, Director
Date: 3-14-17

7970366-v12/RS7/rh2

Hepatitis C Direct-Acting Antivirals

Goals:

- ☐ Approve use of cost-effective treatments supported by the medical evidence.
- ☐ Provide consistent patient evaluations across all hepatitis C treatments.
- ☐ Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- ☐ 8-12 weeks

Requires PA:

- ☐ All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has all of the following pre-treatment testing been performed: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; and f. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis.	**Yes:** Record results of each test and go to #5	**No:** Pass to RPh. Request updated testing.

Approval Criteria		
5. Has the patient failed treatment with <u>any</u> of the following HCV NS5A inhibitors: a) Daclatasvir plus sofosubvir; b) Ledipasvir/sofosbuvir; c) Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d) Elbasvir/grazoprevir; <u>or</u> e) sofosbuvir/velpatasvir)? <u>Note</u>: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (see table below).	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. Refer to medical director for review.	**No:** Go to #6
6. Which regimen is requested?	Document and go to #7	
7. Does the patient have HIV coinfection and is under treatment by a specialist with experience in HIV?	**Yes:** -If patient has Metavir fibrosis stage F0-F2: Go to #9 -If patient has Metavir fibrosis stage F3-F4 or evidence of cirrhosis: Go to #13	**No:** Go to #8

Approval Criteria		
8. Does the patient have: Liver biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]), or serum test if the above are not available (enhanced liver fibrosis [ELF]; Fibrometer; FIBROSpect II) to indicate fibrosis (METAVIR F2)?	**Yes:** Go to #9 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy For elastography results falling in a range (e.g. F2 to F3), fibrosis stage should be rounded up and categorized as the higher F stage for the purpose of treatment. If elastography is not available, and serum test results fall in a range, additional testing should be obtained to determine more specifically the stage of fibrosis..	**No:** Go to #10
9. **Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C? OR** A provider knowledgeable in treating Hepatitis C?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); or b) Clinical, radiologic or laboratory evidence of complications of advanced cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)?	**Yes:** Go to #13 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy For elastography results falling in a range (e.g. F2 to F3), fibrosis stage should be rounded up and categorized as the higher F stage for the purpose of treatment. If elastography is not available and serum test results fall in a range, additional testing should be obtained to determine more specifically the stage of fibrosis.	**No:** Go to #11
11. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a) Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda	**Yes:** Go to #13	**No:** Go to #12
12. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.
14. In the previous 6 months: ☐ Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR ☐ Has the patient been diagnosed with a substance use disorder; OR ☐ Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #15	**No:** Go to #16
15. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness.
16. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
17. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes:** Go to #18	**No:** Go to #19
18. Has the patient had a baseline NS5a resistance test show a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #16

Approval Criteria		
19. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-12 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Use Research & Management Program
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Class Update with New Drug Evaluations: Hepatitis C Direct-acting Antivirals

Date of Review: September 2017
Generic Name: sofosbuvir/velpatasvir/voxilaprevir
Generic Name: glecaprevir/pibrentasvir

End Date of Literature Search: Week 1, August 2017
Brand Name (Manufacturer): Vosevi® (Gilead)
Brand Name (Manufacturer): Mavyret® (Abbvie)
Dossier Received: Yes (Mavyret), Pending (Vosevi)

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

Purpose for Class Update:
To evaluate new comparative evidence of the benefits and harms of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC) and define place in therapy for 2 new DAAs recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of CHC infection. Additionally, costs associated with the various regimens to the Oregon Medicaid program will be compared in executive session.

Research Questions:
1. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
2. Are there specific subpopulations based on severity of disease, extrahepatic manifestations, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA or benefit from immediate treatment?
3. Is there new evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?
4. Is there evidence that sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX; Vosevi) or glecaprevir/pibrentasvir (G/P; Mavyret) are efficacious for the treatment of CHC and are they more effective/efficacious than other DAAs for the treatment of CHC?
5. IS SOF/VEL/VOX or G/P safer than other DAAs for the treatment of CHC?
6. Are there specific subpopulations based on severity of disease, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA?

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Conclusions:

- There is low quality evidence from a Cochrane systematic review that DAAs reduce the risk of no sustained virologic response (SVR) (higher likelihood of achieving SVR) compared to control (54.1% vs. 23.8%; relative risk [RR] 0.44; 95% CI 0.37 to 0.52; p<0.000001, absolute risk reduction [ARR] 30.3%; number needed to treat [NNT] 4).[1] This is consistent with previous literature. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on SVR. There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants.[1]
- Low-quality evidence from a Cochrane systematic review showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (odds ratio [OR] 0.93; 95% CI 0.75 to 1.15; p=0.52).[1]
- Low quality evidence from a Cochrane systematic review found no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18). There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity.[1]
- A recent study evaluating sofosbuvir/velpatasvir (SOF/VEL) with a new NS3/NS4A protease inhibitor (voxilaprevir [VOX]) demonstrated an SVR of 96% (253/263) in patients previously treated with an NS5A inhibitor.[2]
- There is insufficient evidence that treatment of CHC with any of the DAA-containing regimens improves quality of life or other clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or hepatocellular carcinoma (HCC).
- Limited data are available according to severity of fibrosis. Studies define patients by cirrhosis status. There is insufficient evidence from clinical trials that patients with early stages of disease (F0-F2) achieve higher SVR rates than those with more advanced disease, or whether delayed treatment leads to poorer long-term clinical outcomes. However, an assessment of the patient's readiness to treat and education on the importance of compliance and follow-up are vital for successful treatment. Factors to consider before deciding to treat early fibrosis stages (F0-F1) include: 1) the slow progression of disease to cirrhosis, and 2) possibility of superior DAA regimens in the pipeline.
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), human immunodeficiency virus (HIV), cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
    - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality. Clinical trials use SVR as the primary outcome, which remains a non-validated surrogate outcome.
    - Clinical trials do not analyze results based on Medicaid or other insurance type. However, based on age of participants, comorbidities, and nature of CHC, applicability to Medicaid patients is moderate.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

SOF/VEL/VOX NDE:

- There is low quality evidence that 8 weeks of SOF/VEL/VOX is not noninferior to 12 weeks of SOF/VEL in achieving SVR (95% vs. 98%, respectively) in patients with GT 1-6 CHC without cirrhosis or compensated cirrhosis. There is insufficient evidence that 8 weeks of SOF/VEL results in a similar SVR as 12 weeks of SOF/VEL (96%; 95% CI 91-99) in patients with GT 3 and cirrhosis but the study was not designed to directly compare SVRs between these two regimens.
- There is low quality evidence that 12 weeks of SOF/VEL/VOX achieves a SVR12 rate (96%; 95% CI 93 to 98) that is superior to a performance goal of 85% in patients with GT 1-6 without cirrhosis or compensated cirrhosis who have previously failed (relapse or virologic breakthrough) with a DAA regimen containing a NS5A inhibitor. This performance goal is arbitrary; nonetheless, the magnitude of benefit in SVR rates remains substantial.
- There is low quality evidence that 12 weeks of SOF/VEL/VOX is effective in achieving SVR12 in GTs 1-4 in those who have failed a DAA regimen not containing a NS5A inhibitor (98%; 95% CI 95 to 99). There is insufficient evidence that SOF/VEL/VOX provides a benefit over SOF/VEL for 12 weeks in achieving SVR12 in those with GT 1a (98% vs. 89%) and GT 3 (96% vs. 85%). However, the study was not designed to directly compare these regimens in these subpopulations.
- Limitations in the data evaluating SOF/VEL/VOX include:
    - Significant industry funding and conflicts of interest
    - Extensive exclusion criteria limits generalizability to the general population (renal insufficiency [CrCl < 50mL/min], psychiatric disease, significant alcohol or drug abuse in previous 12 months, significant cardiac disease, HIV, HBV, or chronic liver disease of a non-HCV etiology).
    - There were small numbers of patients with GT 3 and cirrhosis. SOF/VEL/VOX should not be used in decompensated cirrhosis.
    - There is insufficient data for SOF/VEL/VOX in patients who have failed previous therapy due to non-adherence.

G/P NDE:

- There is insufficient evidence that G/P is effective and safe in the treatment of DAA-treatment experienced patients due to small numbers and poor quality trials. Data in this population comes from one published, open-label phase 2 study with a high risk of bias in GT 1 patients without cirrhosis (64% F0-F1) demonstrating an overall SVR12 rate of 92% (46/50; 95% CI 81 to 97). There was not a clear dose response, and the sample size was not large enough to determine the impact of adding RBV to therapy. Additionally, part 2 of this study compared G/P for 12 weeks (n=44) to 16 weeks (n=47) in patients with GT 1 or 4 and prior DAA treatment failure, including those with compensated cirrhosis (n=60). However, this is only available in abstract form and cannot be assessed for quality.
- Overall, there is insufficient evidence that G/P is effective and safe in the treatment of DAA-treatment naïve patients with GT 1-6. G/P was approved based on two phase 2 trials and six phase 3 trials in treatment naïve patients. However, only one of phase 3 trials has been published, and the remaining five are only available in poster abstract form. Additionally, only two of the trials were controlled and the others were open-label, single arm trials. Therefore, it is not possible to assess the quality of the evidence or overall safety and further review is necessary once the FDA documents are available and more data is published.
    - However, SVR12 rates were high in GT 1-6 with and without compensated cirrhosis. The data suggests that 8 weeks of therapy with G/P is non-inferior to 12 weeks of therapy in treatment naïve GT 1, 2, or 3. Data in GT 3 patients with compensated cirrhosis is lacking and the preferred duration remains unclear.

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- There is low quality evidence that G/P for 12 weeks results in SVR12 rates of 99% (145/146) in GT 1, 2, 4, 5 or 6 with compensated cirrhosis from an open-label trial, single arm trial with many limitations. The trial excluded those with GT 3 which is a more difficult patient population to treat.
- There is insufficient evidence that G/P is safe in patients with stage 4 and 5 CKD and results in SVR 12 rates of 98% (102/104).
- Limitations in the data evaluating G/P include:
    - Significant industry funding and conflicts of interest. Increased risk of reporting bias as multiple trials remain unpublished.
    - Extensive exclusion criteria limits generalizability to the general population (psychiatric disease, significant alcohol or drug abuse in previous 12 months, significant cardiac disease, HIV, HBV, or chronic liver disease of a non-HCV etiology).
    - There were small numbers of patients with GT 3 and cirrhosis. G/P should not be used in decompensated cirrhosis.
    - There is insufficient data for G/P in patients who have failed previous therapy due to non-adherence.

Recommendations:

- In accordance with the Memorandum of Understanding (MOU) between the Oregon Health Authority and Oregon Law Center:
    - Expand coverage for HCV treatment with HCV stage F-2 with no requirement to be prescribed by a specialist.
    - Expand coverage for HCV treatment for all individuals with HCV co-infected with HIV.
    - Include additional extrahepatic manifestations into coverage criteria.
- Due to recent FDA safety alert, include baseline HBV monitoring into PA criteria (**Appendix 7**).
- Amend the PA criteria to allow for the re-treatment of HCV in those who have failed therapy with a NS5A inhibitor (Appendix 7) for reasons other than noncompliance.
- Evaluate comparative costs of DAA regimens in executive session for decisions regarding preferred regimens.

Previous Conclusions:

- There is low quality evidence that the DAA regimens are effective in achieving a SVR rate of ≥ 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other alternative treatment regimens approved for GT2 and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.

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- Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
- There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.

- Given the high sensitivity and specificity of image tests to stage fibrosis (specifically, transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], shear wave elastography [SWE]) and potential harms of liver biopsy, these less invasive options are favored for prescribers considering CHC treatment with a DAA.

Previous Recommendations:

- Continue to prioritize treatment for persons with advanced liver disease (METAVIR stage F3 or F4), as well as those at greatest risk of developing complications of liver disease, including:
  - All patients awaiting a liver transplantation
  - All patients post solid organ transplant
  - HIV coinfection with METAVIR stage F2 or greater
  - Patients with extrahepatic manifestations
- Due to extensive drug-drug interactions and safety concerns, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- For those with METAVIR stage F2 or lower, DAA regimens do not need to be prescribed by or in consultation with a specialist.

Background:

Chronic hepatitis C (CHC) infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in the Western world.[3] The global prevalence is 1.6%, and in the United States (U.S.) approximately 50% of affected individuals remain unaware of their diagnosis.[1] The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes or health related quality of life are not available. In addition, only about 10-20% of people with CHC go on to develop cirrhosis (8-16% of all people infected with HCV) and the time to progress to cirrhosis varies at an average of 40 years.[1] Approximately 20% of individuals infected with HCV will clear the virus. HCV is divided into seven major genotypes with variable geographical distribution and prevalence. In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients.[3] Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT 1a and 1b infection may differ depending on the treatment regimen. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.[4]

The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials. There is some evidence based on only on observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[3] However, the results of these observational studies

should be interpreted with great caution. SVR is still a non-validated, surrogate outcome and it is not clear that SVR is a 'cure' for HCV. Many of the observational studies compared two groups that were both treated making it difficult to attribute different outcomes to treatment.[1] SVR has previously been shown as an invalid surrogate for clinical outcomes for the efficacy of interferons.[1] Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. More recent studies use SVR rate at 12 weeks (SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.[5]

The two major predictors of SVR are viral genotype and pre-treatment viral load.[6] Other factors associated with an increased likelihood of SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.[7]

Patients at greatest risk for progression to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[8] However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-term if adverse events are avoided from cure.[9] Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis. Those with stage 3 to 4 disease develop end stage liver disease at a rate of 1 to 2% per year after achieving SVR.[1]

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.[10] Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.[11] Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance.[11] Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs has been reported in the range from 1% to 23% and can significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS5A RAV (SVR rates of 54% vs. 92%, respectively).[12] Another review of 35 clinical trials in patients with HCV GT1 found that pretreatment NS5A RAVs were detected in 13% of GT 1a and 18% with GT 1b and had an impact on SVR in some patients, particularly treatment-experienced patients with GT 1a HCV.[13] There remains debate on which patients should be screened for the presence of RAVs at baseline.

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Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR with this regimen. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.[14] The DAAs target specific proteins of the virus, causing disruption of viral replication. There are currently four classes of DAAs, defined by their mechanism of action and therapeutic target (NS3/4A inhibitors, protease inhibitors [PIs], NS5B inhibitors and NS5A inhibitors). Due to adverse events, high rates of resistance and long duration of treatments, telaprevir was removed from the market and boceprevir is no longer a recommended therapy. Since then, a variety of second generation DAAs have been approved by the FDA resulting in many interferon-free options, fewer adverse events, and SVR12 rates that exceed 90% (Table 1). However, newer DAAs are associated with substantial cost and unknown effects on long-term clinical outcomes. A significant challenge is to identify patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.[15] Additionally, the lack of head-to-head trials, and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available. Studies do not measure long-term morbidity or mortality.

A major gap in the evidence remains the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population. Current guidelines recommend deferral of treatment in this population, pending additional data, or if retreatment is urgent, tailoring the regimen based on resistance testing, using a treatment duration of 24 weeks and adding ribavirin (RBV).[4] Additionally, for genotype 3 (GT3) sofosbuvir (SOF) treatment-experienced patients, deferral of treatment is also recommended unless urgent retreatment is required. However, two additional pangenotypic medications have been studied in those who have failed an NS5A inhibitor. One is a triple drug combination including SOF, VEL and a new NS3/4A inhibitor, voxilaprevir (VOX).[16] The second is a combination of a NS3/4A inhibitor, glecaprevir (GLE) and a NS5A inhibitor, pibrentasvir (PIB). Glecaprevir/pibrentasvir (G/P) is approved for treatment-naïve patients with GT 1-6 for 8 weeks without cirrhosis and 12 weeks with compensated cirrhosis. It is also approved for patients who have failed treatment with a NS5A inhibitor (16 weeks) or NS3/4A protease inhibitor (12 weeks) but not both. SOF/VEL/VOX is only approved for NS5A treatment experienced patients (GT 1-6) and sofosbuvir treatment experienced for GT 1a and GT 3 (Table 1).

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 3 or 4, or patients with extrahepatic manifestations at any stage of fibrosis, patients in the setting of solid organ transplant, and in patients with fibrosis Metavir stage 2 or greater coinfected with HIV. In January 2016, a Memorandum of Understanding (MOU) was signed between the Oregon Health Authority and Oregon Law Center to commit to prioritize essential health services and expand coverage for HCV to treat members with stage F2 disease by January 1, 2018, if the budgets are funded to the requested levels.

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Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza® and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6;	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8, 12, or 24 weeks
Mavyret®	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A inhibitor or an NS3/4a protease inhibitor	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks
Olysio®	Simeprevir	CHC GT 1 in combination with sofosbuvir	Not approved	NS3/4A protease inhibitor	12 -24 weeks
Sovaldi®	Sofosbuvir	CHC GT 1; GT 2; GT 3; GT 4 Used in combination with other antivirals	Not approved	Nucleotide analog NS5B polymerase inhibitor	12 weeks
Technivie®	Ombitasvir/paritaprevir/ritonavir + ribavirin	CHC GT 4	Contraindicated	NS5A inhibitor/NS3/4A protease inhibitor	12 weeks
Viekira Pak®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks
Viekira XR®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 treatment experienced with NS5A inhibitor; GT 1a or 3 treatment experienced with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks

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Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin					

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 through week 1, August 2017. The Medline search strategy used for this review is available in **Appendix 2**, which includes 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. Randomized controlled trials and abstracts are in **Appendix 3 and 4.** Due to the evolving nature of this class and urgency to review the newly approved drugs, additional data will be evaluated as needed to meet the needs of the Oregon Health Authority.

Systematic Reviews:

Cochrane Collaboration
A systematic review and meta-analysis was conducted by the Cochrane Collaboration to assess the benefits and harms of all DAAs in the treatment of CHC.[1] The three pre-specified primary outcomes were a composite of hepatitis C-related morbidity (cirrhosis, ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or HCC) or all-cause mortality, serious adverse events, and health-related quality of life. The proportion of participants without SVR 12 or 24 weeks after completion of treatment was a secondary outcome. A comprehensive search for RCTs comparing DAAs versus no intervention or placebo or any medication intervention except for a DAA (pegylated interferon) through October 2016 identified 138 trials including 51 different DAAs, including both discontinued DAAs and those still under development. Many trials used for FDA approval of currently available DAAs were excluded from this analysis due to wrong control or study design. Eighty five of the 138 trials assessed DAAs on the market or currently under development. All trials had a high risk of bias due to inadequate allocation concealment, unclear blinding or unblinding, incomplete outcome data or unclear selective reporting. Trials included treatment-naïve participants (95 trials), treatment-experienced participants (17), or both (24 trials). The majority of trials were in GT1 (119 trials); trials with genotypes 2-6 were extremely limited. In addition to traditional meta-analysis, Trial Sequential Analysis was performed to better control for random errors due to sparse data. HIV was an exclusion criteria in 102 trials. In all but 1 trial, the funding source was either not reported in sufficient detail or the trial was financially supported by an organization with a financial interest in the trial results.[1]

Overall, the review found very low quality evidence of no difference in CHC morbidity or all-cause mortality from the DAAs compared to placebo or no intervention (OR 3.72; 95% CI 0.53 to 26.18).[1] There were very few data on mortality with DAAs (15/2377; 0.63%) compared to control (1/617; 0.16%) from 11 trials. There was no data on hepatitis C-related morbidity. Very low-quality evidence showed no difference in serious adverse events with DAAs (2.77%) compared to control (5.6%) (OR 0.93; 95% CI 0.75 to 1.15; p=0.52). Simeprevir was the only DAA showing a significantly lower risk of serious adverse events (OR 0.62; 95% CI 0.45 to 0.86). However, when one trial with an extreme result was excluded, the meta-analysis showed no difference. There was very low quality evidence from 32 trials that DAAs reduce the risk of no SVR compared to control (17.6% vs. 69.7%, respectively; RR 0.44; 95% CI 0.37 to 0.52; p<0.000001, ARR 52.1%; NNT 2). This was confirmed by Trial Sequential Analysis and the tests for statistical heterogeneity indicated significant heterogeneity, with a high risk of bias. There did not seem to be a difference between the different DAAs based on subgroup analysis and all subclasses of DAAs showed evidence of a significant effect on no SVR. The subgroup analysis comparing the DAAs in different genotypes did show evidence of a difference between the subgroups (p=0.002; I^2 = 73.6%). There was no difference in SVR between treatment-experienced (RR 0.50; 95% CI 0.36 to 0.69) and treatment-naïve (RR 0.48; 95% CI 0.41 to 0.56) participants. There is insufficient evidence to make conclusions on quality of life. Only one trial assessed quality of life and found no difference.

None of the trials measured the effects of DAAs on clinically important outcomes including ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy or HCC.

The authors concluded that there was insufficient evidence to confirm or reject that DAAs have any clinical effects, but they do seem to reduce the risk of no SVR, which is a non-validated surrogate outcome and the clinical significance of these effects on a non-validated surrogate outcome is unclear.

Criticism from experts in this field have argued that many clinical trials on DAA therapy were excluded from this review since they did not have an untreated control group but instead used the historical control response rates. Additionally, it is unlikely to have data supporting a benefit on HCV related morbidity and all-cause mortality because of the natural history of HCV infection; clinical outcomes may take years to become apparent.[17] Furthermore, experts cite data that SVR is associated with health benefits including a decrease in liver inflammation, rate of progression of liver fibrosis, HCC, and liver transplantation.[17]

CADTH:
Three CADTH reports addressing resistance-associated variants (RAVs) in HCV treatment were identified. However, they were all Rapid Response Reports with little detail or synthesis of included studies.

1) A CADTH Rapid Response Report reviewed the comparative clinical effectiveness of NS3 or NS5B inhibitors in DAA-naïve and DAA-experienced patients with RAVs of HCV.[18] Thirteen publications met inclusion criteria and were included in the report. Many of the studies were post-hoc analyses of previously conducted studies and included only patients for whom sequencing data was available. The prevalence of baseline polymorphisms were often low and impact on outcomes is hard to determine based on this data. The included studies were limited due to small sample sizes, industry funding, and inclusion of four pooled analyses with unknown quality assessment of the included trials. The report concluded the following:
    a. In GT1 HCV treatment-naïve patients, the SVR rates (92% - 100%) with SOF (n=38) and PTV +/- DAS (n=7) containing treatment regimens were comparable between patients with and without NS5B RAVs.

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b. In GT1 treatment-experienced patients (prior SOF or SOF/LDV), SVR rates with SOF containing regimens (n=23) were comparable with and without NS5B RAVs (78%).
c. In HCV GT1 treatment-naïve patients, SVR rates with GZR-containing regimens were comparable between patients with and without NS3 RAVs
d. In HCV GT1 treatment-naïve patients, SVR rates with PTV or simeprevir containing regimens varied depending on the other drugs used in combination.

2) Another CADTH Rapid Response Report reviewed the clinical effectiveness of re-treatment in patients with NS5A RAVs who have failed on treatment with NS5A inhibitors.[19] Only three publications met the inclusion criteria and were included in the report. All of these were non-randomized, open-label, and non-comparative studies. One was a 'real world' study, another study reported outcomes of one single arm from an eight-arm phase 2a study, and the third study was a sub-study of ION-4. They all had a high risk of bias and were low quality. Therefore, a literature search through June 2016 did not identify data to determine if patients who fail other NS5A inhibitors could be successfully retreated using the same intervention strategies. Retreatment strategies included SOF plus SIM after failure with a DCV-based regimen, retreatment with LDV/SOF after failure with LDV/SOF, and LDV/SOF for 24 weeks after failure with 12 weeks. SVR12 was 87.5%, 91% and 89%, respectively suggesting that these regimens are effective.[19] However, the small sample sizes and low quality preclude a definitive conclusion.

3) A third CADTH Rapid Response Report reviewed the clinical effectiveness of HCV therapies containing NS5A inhibitors in DAA-naïve patients with HCV GT1 and with NS5A RAVs at baseline.[20] Current NS5A inhibitors include daclatasvir (DCV), velptasvir (VEL), ledipasvir (LDV), elbasvir (EBR), and ombitasvir (OMB). A total of 16 publications were included in the report (eight secondary analyses of RCTs, five observational, one review article and two guidelines). However, the majority of studies were with DCV + asunaprevir, which the manufacturer is no longer seeking FDA approval for. The proportion of patients with NS5A RAVs at baseline with GT 1b HCV achieved a lower SVR (38-42%) than those without (88-99%). There were limited studies identified on other treatment regimens in patients with NS5A RAVs at baseline. One study found that in patients with HCV1b treated with DCV+SMV, the proportion of patients who achieved SVR12 was 50% for patients with NS5A RAVs and 91% for those without. One study evaluated treatment with LDV/SOF and found that SVR12 was not different for those with GT1 and baseline NS5A RAVs compared to those without (99% for both groups). Lastly, a study showed a decreased SVR12 for treatment with EBR/GZR in those with RAVs (58%) compared to without (96%). There were no studies on the cost-effectiveness of screening for NS5A RAVs at baseline. There is variability in the guidelines regarding recommendations for baseline testing, and recommendations are based on low quality evidence. Due to the poor quality and limited data, definitive conclusions cannot be made.

Clinical Practice Guidelines:

The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016.[21] The Veterans Affairs (VA) National Hepatitis C Resource Center updated treatment guidelines in March 2016,[22] and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in April 2017.[4] The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[4] The AASLD/IDSA guideline has many limitations with poor methodological quality. The panel lacks non-specialist members and there is no assessment of risk of bias for individual studies. In addition, the authors and

sponsors of the guideline have multiple conflicts of interest. The AASLD guidelines have not been updated since approval of the latest DAA regimens (SOF/VEL/VOX and G/P).

The AASLD/IDSA guidelines were updated in April 2017 with the following changes:

1. Initial Treatment of CHC:
    a. Modified the duration of LDV/SOF in patients without cirrhosis to 8 weeks for non-black, HIV-uninfected, and whose HCV RNA is less than 6 million IU/ml. Previous recommendation was 8 weeks for those without cirrhosis and whose HCV RNA is less than 6 million IU/ml. The reasoning for this change was that the analysis on duration was not randomized and baseline characteristics may have varied between 8- and 12-week groups so the guidelines no longer recommend shortening treatment duration to less than 12 weeks for HIV-infected patients and African-American patients.
        i. The original 8 week recommendation came from the ION-3 study which resulted in 8 weeks of LDV/SOF achieving non-inferiority to 12 weeks in SVR12 (94% vs. 96%). There was no significant difference based on age, sex, race, ethnicity, or GT1 subtype. Based on a post-hoc multivariate analysis conducted with the FDA, baseline viral load < 6 million IU/mL was identified as the best predictor of response. A paper by O'Brien and colleagues re-analyzed the data from ION-3 reporting missing outcome data as achieving SVR instead of treatment failures which was done in the original study.[23] The authors suggested that SVR varied by gender and IL28B genotype and found that black patients had a lower SVR rate than other racial groups (91.3% vs. 96.2%, respectively); however this association did not reach statistical significance and it is consistent with lower SVR rates seen with 12 weeks (92.6% vs. 97.2%).
    b. Updated grading of SOF/VEL for GT5 and 6
    c. Language added related to recent data regarding 8 weeks of OMB/PTV-R + DAS for GT 1b with early stage fibrosis. A single phase b, single-arm study (n=163) showed a 98% SVR with 8 weeks of OMB/PTV-R + DAS.
2. Retreatment:
    a. For GT3, PEG/RBV treatment-experienced patients without cirrhosis, DCV/SOF or SOF/VEL for 12 weeks is recommended. For those with cirrhosis, EBR/GZR plus SOF or SOF/VEL plus RBV for 12 weeks is recommended. EBR/GZR plus SOF is recommended based on an unpublished study (n=100) with 53 patients who failed treatment with PEG/RBV. SVR12 was 100% with this regimen. This data is only available as a poster presentation.[24]
3. Decompensated:
    a. Recommendations (SOF/VEL or LDV/SOF) for those with decompensated cirrhosis and GT 5 or 6 were made based on an extrapolation of data from trials in patients with compensated cirrhosis and GT 5 or 6. It is unclear if these results can be generalized to those with decompensated cirrhosis and there remains very limited data with DAAs in patients with CHC GT 5 and 6 with decompensated cirrhosis.[24]

A further update from the AASLD/IDSA guidelines on treatment of adolescents with CHC is in progress.[24]

Publication of both the WHO and VA guidelines preceded the approval of SOF/VEL and this agent is only included in the AASLD/IDSA guidelines. The following recommendations are included in these guidelines:

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When to Treat:
AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.[4] Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient's understanding of treatment goals and provision of education on adherence and follow-up.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.[21]

VA: All patients with CHC who did not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[22] The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion).[22] However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

Fast Progressing:
Progression of fibrosis from stage 0 (no fibrosis) to stage 4 (cirrhosis) is variable but takes place at approximately 0.10-0.15 fibrosis units per decade.[25] The AASLD/IDSA guidelines includes the following patient populations to be at greater risk for rapidly progressive fibrosis and cirrhosis:

- HIV coinfection
- HBV coinfection and other coexistent liver disease (nonalcoholic steatohepatitis [NASH]): Several observational studies have found coinfected patients have more severe liver disease than those with monoinfection.[26] However, there are no longitudinal studies to evaluate the rate of fibrosis progression in coinfected subjects and most data comes from studies with a small sample size and retrospective design.[27] Additional studies with similar limitations have conflicting results. There are no published studies evaluating DAA regimens in patients with HBV/HCV coinfection.

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Extrahepatic Manifestations:
The literature has linked HCV to a number of extrahepatic symptoms involving the skin, musculoskeletal, renal, cardiovascular and nervous systems.[28] There are no studies evaluating the effects of DAA-based regimens on progression of extrahepatic complications and most of the literature consists of observational studies demonstrating an association which are at risk for selection bias. The quality of the evidence for these associations is extremely variable, and it is difficult to make definitive conclusions regarding the effect of DAAs on progression of extrahepatic manifestations. The following extrahepatic manifestations have been identified:

- Cryoglobulinemia and lymphoproliferative disorder
- Dermatologic manifestations: leukocytoclastic vasculitis, porphyria cutanea tarda, lichen planus
- Insulin Resistance and Type 2 Diabetes: There is growing observational evidence that HCV increases the risk of T2DM through induction of insulin resistance and that T2DM can accelerate the course of CHC.[29]
- Lymphomas (B-cell non-Hodgkin lymphoma)

Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection. Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate.[4]

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.[21]

VA: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp).[22] Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.[22]

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Testing for Liver Cirrhosis:
AASLD/IDSA: The use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis should be considered in HCV patients planning on treatment (Class I, Level A).[4] Guidelines also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

WHO: In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence).[21] FibroScan, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.[21]

VA: Testing recommendations include clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [ARFI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.[22]

Decompensated Cirrhosis:
All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

Recommendations for performing pre-treatment resistant testing:
The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT 1a-infected patients who are being treated with EBR/GZR and for GT3 patients who are being treated with DCV.[22] Patients who fail DAA treatment usually have RAVs to one or more classes of DAAs and should have testing done for each of the drug classes before being considered for re-treatment.

Retreatment:
The AASLD/IDSA guidelines have retreatment recommendations for those who have failed treatment with PEG/RBV or PEG/RBV + a NS3 PI (telaprevir, boceprevir, or simeprevir) that are similar to initial treatment recommendations for GT1 (Table 2). For those who have failed sofosbuvir plus RBV, LDV/SOF is the recommended therapy for GT1 based on limited data. At the time of this update, there were no published data on retreatment of SOF-based failure with non-sofosbuvir regimens. For NS5A treatment-experienced patients, the guidelines recommend deferral of treatment, pending additional data. If urgent treatment is necessary, it is recommended that the retreatment regimen be tailored based on resistance testing, a treatment duration of 24 weeks should be used and ribavirin should be added. No recommendations are provided for this NS5A treatment failures for GT 2-6. Additionally, for GT3 SOF treatment-experienced patients, deferral of treatment is also recommended unless urgent retreatment is required.[24]

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Recommended Treatment Options:
Treatment options based on genotype and treatment history are included in the following table:

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[22]	AASLD/IDSA Guidelines[4]	WHO Guidelines[21]
1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks OMB/PTV-R + DAS + RBV x 12 weeks SOF/VEL x 12 weeks DCV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF + RBV x 8-12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 12 weeks SOF/VEL x 12 weeks OMB/PTV-R + DAS x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks	LDV/SOF + RBV x 12 week SOF/VEL + RBV x 12 week DCV/SOF + RBV x 12 week	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or cirrhosis***	EBR/GZR x 12 weeks +/- RBV	LDV/SOF + RBV x 12 weeks – 24 weeks	N/A
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic (or cirrhotic CTP A)***	EBR/GZR + RBV x 12 weeks	LDV/SOF X 12 weeks SOF/VEL x 12 weeks DCV/SOF x 12 weeks EBR/GZR + RBV x 12 weeks	N/A
1	***Experienced (prior NS5A-containing regimen or SMV)***		Test for RAPs to NS5A prior to re-treatment. Consult with an expert based on results.	Deferral of treatment, pending more data. Testing for RAVs should be done.	N/A
2	***Naïve***	***Non-cirrhotic***	SOF + RBV x 12 weeks	SOF/VEL x 12 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	SOF + RBV x 16 weeks
2		***Decompensated***	SOF + RBV x 16 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (prior PEG-IFN/RBV)***	***Non-cirrhotic or Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal DAA-based therapy for this patient population is not known. Consult with an expert	DCV/SOF x 24 weeks SOF/VEL + RBV x 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	LDV/SOF + RBV x 12 weeks*	DCV/SOF x 12 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks
3		***Cirrhotic***	DCV/SOF + RBV x 12 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF +- RBV x 24 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	DCV/SOF + RBV x 12-24 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	N/A
3	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic***	LDV/SOF + RBV X 12 weeks*	SOF/VEL x 12 weeks EBR/GZR + SOF x 12 weeks	N/A
3		***Cirrhotic***	DCV/SOF + RBV X 12 weeks- 24 weeks	SOF/VEL x 12 weeks	DCV/SOF + RBV x 24 weeks

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				DCV/SOF x 24 weeks	
3	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal therapy for this patient population is based on expert opinion and NS5A resistance testing.	Deferral if retreatment is not urgent	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks
4		***Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	N/A	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	OMB/PTV-R + RBV x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	N/A
5/6	***Naïve or Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks	LDV/SOF X 12 weeks

**No baseline NS5A RAVs. Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir; LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RAP = resistance-associated polymorphisms; RAV = resistance-associated variant; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir

National Institute for Health and Care Excellence (NICE)

A technology appraisal guidance was published in January 2017 regarding SOF/VEL for treating CHC.[30] NICE recommended SOF/VEL as an option for treating CHC in adults, only if the company provides the drug with the agreed upon discount. It was recommended for HCV GT 1-6 with or without compensated cirrhosis as well as for those with decompensated cirrhosis (with ribavirin), except for untreated GT2 without cirrhosis. This recommendation was based on review of the four key randomized controlled phase III trials evaluating SOF/VEL on SVR. The committee concluded that the trials showed high SVRs (89% to 100%) regardless of HCV genotype, cirrhosis stage or treatment history. However, there was a high risk of bias in the open-label trials. The committee also concluded that the adverse events associated with SOF/VEL are generally tolerable. Additionally, they concluded there is insufficient evidence to consider those with drug-resistant mutations separately to the overall population.[30]

New FDA Safety Alerts:

In October 2016, the FDA warned about the risk of hepatitis B virus (HBV) reactivation in any patient with a current or previous infection with HBV undergoing treatment with DAAs.[31] This HBV reactivation can result in serious liver problems or death. Twenty four cases of HBV reactivation while receiving DAAs were found in the literature. HBV occurred an average of 52 days (range of 4-8 weeks) after starting treatment. Three patients progressed to decompensated liver disease and 2 of the patients died. The mechanism of HBV reactivation is not known.[31] Since patients with HBV co-infection were excluded from all phase III trials of DAAs, HBV reactivation was not identified in clinical trials.

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The FDA recommends that all patients should be screened for evidence of current or prior HBV infection prior to starting treatment with DAAs; monitor is recommended for HBV reactivation during treatment and following treatment.[31] Clinical guidelines were updated to recommend that all patients be tested for HBsAG, HBsAb, and HBcAb status.[32] In patients with serologic evidence of HBV, baseline HBV DNA should be measured prior to DAA treatment and monitored during therapy and for several weeks after.[31] Antiviral therapy for HBV infection should be given if criteria for treatment are met.

New Indications:
In April 2017, the FDA approved SOF (Sovaldi) and LDV/SOF (Harvoni) to treat HCV in children ages 12 to 17 weighing at least 35 kilograms.[33] These are the only two DAAs approved for children with HCV. It is estimated that there are 23,000 to 46,000 children in the U.S. with HCV.[34]

Sofosbuvir was approved in combination with ribavirin for those with GT 2 or 3 without cirrhosis or with compensated cirrhosis based on an ongoing unpublished, open-label study in 13 adolescents with GT2 (12 weeks) and 37 adolescents with GT3 (24 weeks).[35] Results are not available on clinicaltrials.gov. According to the FDA, 100% of patients with GT2 and 97% of patients with GT3 achieved SVR12.

SOF/LDV was approved for HCV GT 1, 4, 5 or 6 without cirrhosis or mild cirrhosis based on an ongoing, unpublished and open-label study (n=100). Results are not available on clinicaltrials.gov.[36] According to the FDA, 98% of patients achieved SVR12.

Children with GT 1 or 4 are currently being studied in a trial of OMB/PTV-R +/- DAS.

An update from the AASLD/IDSA guidelines regarding treatment of CHC in adolescent patients is in process.

NEW DRUG EVALUATIONS:
Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)

SOF/VEL/VOX is approved for 1) genotype 1, 2, 3, 4, 5 or 6 CHC in those who have previously been treated with an HCV regimen containing an NS5A inhibitor and 2) genotype 1a or 3 infection in those who have previously been treated with an HCV regimen containing SOF without an NS5A inhibitor.[16] See **Appendix 5** 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:
SOF/VEL/VOX was studied four phase 3 studies (Table 3) in both DAA treatment naïve and DAA-treatment experienced patients.[2,37] Since VOX is a protease inhibitor, those with decompensated cirrhosis are not eligible for treatment and were excluded from all clinical trials. Only those with Child-Pugh A compensated cirrhosis were included.

Table 3: Summary of Phase 3 Clinical Trials of SOF/VEL/VOX

	DAA-Treatment Experienced		DAA-Treatment Naïve	
	POLARIS-1	POLARIS-4	POLARIS-2	POLARIS-3
Genotypes included	1, 2, 3, 4, 5, 6	1, 2, 3, 4	1, 2, 3, 4, 5, 6	3
Cirrhosis Inclusion	Non-cirrhosis or compensated cirrhosis	Non-cirrhosis or compensated cirrhosis	Non-cirrhosis or compensated cirrhosis	Cirrhosis only
Duration of SOF/VEL/VOX	12 weeks	12 weeks	8 weeks	8 weeks

DAA-Treatment Naive

POLARIS 2 (n=943) and 3 (n=220) are 2 open-label trials in DAA-treatment naïve patients that compared SOF/VEL/VOX for 8 weeks of therapy to SOF/VEL for 12 weeks. POLARIS 2 included those with GT 1-6 either without cirrhosis or compensated cirrhosis (~18%) and POLARIS 3 included patients with GT 3 and cirrhosis only. In the POLARIS-2 trial, the SVR rate was 95% (95% CI 93 to 97) for those receiving 8 weeks of SOF/VEL/VOX and 98% (95% CI 96-99) among those receiving 12 weeks of SOF/VEL. The 8 week therapy did not meet the pre-specified criteria for noninferiority to 12 weeks of SOF/VEL. There was a higher rate of relapse among patients with GT1a (n=14) who received 8 weeks of SOF/VEL/VOX compared to 1 patient in the SOF/VEL group. Overall, the SVR rates were 94% in those who had baseline RAVs but was only 89% among those with baseline RAV with HCV GT 1a. Among patients with cirrhosis, 91% (82/90) of patients receiving SOF/VEL/VOX had SVR, as compared with 99% (83/84) of patients receiving SOF/VEL. In POLARIS-3, the SVR rate was 96% (95% CI 91-99) in both the SOF/VEL/VOX for 8 week group and the SOF/VEL for 12 week group in GT3 patients with cirrhosis. There were very few discontinuations due to adverse events. There were more slightly more adverse events in the SOF/VEL/VOX group compared to SOF/VEL including diarrhea and nausea due to the presence of a protease inhibitor. All patients with baseline RAVs achieved a SVR. Major limitations of these trials include its open-label design, exclusion criteria including HBV, HIV, decompensated cirrhosis, few non-white patients or those with genotypes 4, 5, and 6, industry funding and conflicts of interest, and lack of long term clinical outcomes. SOF/VEL/VOX currently does not have FDA approval for treatment-naïve patients and would not be an ideal choice of therapy since it was not found to have a significant benefit over SOF/VEL and there are currently no treatment options available for those who fail therapy with SOF/VEL/VOX. Therefore, these trials are not included in the evidence table below.

DAA-Treatment Experienced

Approval of SOF/VEL/VOX for treatment-experienced subjects was approved based on two phase 3 trials in patients who had been previously treated with a DAA-containing regimen.[2] POLARIS-1 was in GT 1-6 infection in those who had previously received a regimen with a NS5A inhibitor and POLARIS-4 was in those who had previously received a DAA but not an NS5A inhibitor. Both trials excluded patients with decompensated cirrhosis.

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POLARIS-1 was double-blinded to investigators and patients for those with GT 1 only.[2] Patients were randomized to SOF/VEL/VOX for 12 weeks or placebo. Although the trial included GTs 1-6, only those with GT 1 were randomized to a deferred treatment, placebo group and there were limited numbers of patients with other GTs (5 with GT 2, 78 with GT 3, 22 with GT 4, and 7 with GT 5 or 6). This was lower than what was expected to be enrolled based on the study protocol. The study originally required 450 patients in Group 1 to achieve 90% power, but only 262 patients were ultimately included in this arm. This was decreased to 280 in the amended protocol to achieve 90% power with no further information. The primary outcome was SVR at 12 weeks post treatment. Over half of the subjects had been previously treated with a NS5A inhibitor (LDV, DCV, or OMB) plus NS5B inhibitor (SOF), while the remainder had the addition of a NS3 inhibitor. In the primary efficacy analysis, the SVR12 was compared to a performance goal of 85%. The basis for this performance goal was the overall trend toward increasing SVR rates; however, this is lower than trials have been demonstrating with currently recommended regimens. Approximately 46% (n=121) in the SOF/VEL/VOX group and 51% (n=34) in the placebo group had compensated cirrhosis. Eighty three percent of subjects had RAVs at baseline, the majority with an NS5A RAV. Overall, the SVR rate was 96% (95% CI 93 to 98), which was found to be superior to the pre-specified 85% performance goal, as expected ($p<0.001$). Although not statistically different, the SVR rate was slightly lower at 93% (113/121) in those with cirrhosis compared to 99% (140/142) in those without.[2] Of the 253 patients with a SVR12, 249 returned for a SVR24 and all patients had a SVR. Only 6 patients had a relapse, and only one had a virologic breakthrough, despite the high number of subjects with baseline RAV (83%). Baseline resistance did not seem to have an impact on SVR rates.

POLARIS-4 was an open-label trial with similar inclusion and exclusion criteria except that this trial did include patients previously treated with a regimen that did not contain a NS5A inhibitor.[2] Those whose only DAA exposure was an NS3/4A protease inhibitor were excluded. Patients were assigned to receive either SOF/VEL/VOX or SOF/VEL for 12 weeks; however, the study was not powered for a comparison between SOF/VEL/VOX and SOF/VEL. The majority of subjects in POLARIS-4 also were GT 1 (144/333). There were no patients with GT 5 or 6 enrolled. The majority of patients (85%) had previously received therapy with SOF. The overall SVR12 rate was 98% (95% CI 95 to 99) with SOF/VEL/VOX which was superior to the performance goal of 85%. The SVR12 with SOF/VEL was 90% which was not statistically superior to the performance goal ($p=0.09$). The SVR12 rate according to HCV genotype is included in Table 4. Although the regimens were not directly compared, there was a numerical benefit in SVR12 with SOF/VEL/VOX compared to SOF/VEL in those with GT 1a (98% vs. 89%) and GT 3 (96% vs. 85%). As there was no noticeable benefit in other genotypes and SOF/VEL is a reasonable treatment option, SOF/VEL/VOX is not FDA approved for these other genotypes. Nonetheless, SOF/VEL/VOX appears effective in achieving SVR 12 in GTs 1-4 in those who have failed a DAA-regimen not containing a NS5A inhibitor. The current AASLD guidelines recommend treatment with LDV/SOF in these populations based on 2 small trials.[38,39] Only 1 subject in the SOF/VEL/VOX group had a virologic relapse and 14 in the SOF/VEL group experienced virologic relapse after treatment. Of these patients, 8 had GT3 and 5 had GT1a.

Table 4: SVR12 rates with SOF/VEL/VOX in DAA-treatment experienced patients

	POLARIS-1	POLARIS-4	
		SOF/VEL/VOX	***SOF/VEL***
Overall	96% (253/263)	98% (178/182)	90% (136/151)
Compensated Cirrhosis	99% (140/141)	98% (82/84)	86% (59/69)
Without Cirrhosis	94% (113/121)	98% (96/98)	94% (77/82)
GT 1a	96% (97/101)	**98% (53/54)**	**89% (39/44)**

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GT 1b	100% (45/45)	96% (23/24)	95% (21/22)
GT 2	100% (5/5)	100% (31/31)	97% (32/33)
GT 3	95% (74/78)	**96% (52/54)**	**85% (44/52)**
GT 4	91% (20/22)	100% (19/19)	NA
GT 5	100% (1/1)	NA	NA
GT 6	100% (6/6)	NA	NA

Trial Limitations:
Both trials were funded by Gilead. Extensive exclusion criteria in both trials (renal insufficiency [CrCl <50 mL/min], psychiatric disease, significant alcohol or drug abuse in the previous 12 months, significant cardiac disease, HIV, HBV, and chronic liver disease of a non-HCV etiology) limits generalizability to the general population with multiple medical comorbidities. Due to drug-drug interactions, statins, proton-pump inhibitors, amiodarone, and strong CYP3A4 inhibitors were not allowed in the study. Additionally, there were small numbers of patients with GT3 and cirrhosis as well as other rare genotypes. There were limited patients who had been previously treated with VEL or ELB.

According to the study protocol, health related quality of life was measured using the SF-36, Chronic Liver Disease Questionnaire, Fatigue Index, and Work Productivity and Activity Impairment Questionnaire. However, results for these outcomes were not reported in the study.

The relevance of using a performance goal comparator in both trials is unclear. A goal of 85% was chosen; however, this is lower than what is expected with regimens approved today. POLARIS-4 was open-label in its entirety, and POLARIS-1 was open-label to treatment assignments for all genotypes except GT 1. This increases the risk of selection, performance and detection bias. Lastly, FDA approval for SOF/VEL/VOX for patients who are treatment experienced with a non-NS5A DAA regimen included only GT 1a and GT 3 based on subgroup analyses from the study. However, the study wasn't designed to detect differences between genotype subtypes.

Clinical Safety:
Overall, approximately 75% of subjects experienced an adverse event. Most common adverse events included headache, fatigue, diarrhea and nausea (Table 5). However, these were mild in nature, and there were very few (<5) discontinuations due to adverse events overall. Similarly, there were very few serious adverse events. There did not appear to be more elevations in liver enzymes in the SOF/VEL/VOX group compared to placebo.

Table 5: Common Adverse Events from Clinical Trials

	POLARIS-1		**POLARIS-4**	
	SOF/VEL/VOX	Placebo	SOF/VEL/VOX	SOF/VEL
Headache	21%	14%	23%	23%
Fatigue	17%	15%	19%	23%
Diarrhea	13%	9%	14%	3%

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Nausea	13%	7%	10%	3%

There are potential drug-drug interactions that need to be accounted for with SOF/VEL/VOX since they are substrates of P-glycoprotein and CYPP450 enzymes. Treatment with SOF/VEL/VOX is not recommended for those with moderate or severe hepatic impairment (Child-Pugh B or C) due to a presumed class effect of the protease inhibitors and the increased risk of serious liver injury in those with underlying advanced liver disease.

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	Sofosbuvir	Velpatasvir	Voxilaprevir
Mechanism of Action	NS5B RNA inhibitor	NS5A protein inhibitor	V NS3/4a protease inhibitor
Oral Bioavailability	NA	NA	NA
Distribution and Protein Binding	61% to 65%	>99%	>99%
Elimination	Urine (80%); feces (14%)	94% in feces	94% in feces
Half-Life	0.4 hours	17 hours	33 hours
Metabolism	Hepatic (non-CYP mediated)	Hepatic (CYP2B6, CYP2C8, CYP3A4)	Hepatic (CYP3A4)

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events
6) Quality of Life

Primary Study Endpoint:

1) Sustained Virologic Response at 12 weeks post treatment (SVR12)

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.Bourliere et al. (Polaris-1)[2] phase 3 trial	1. SOF/VEL/VOX	Demographics: GT1-6, DAA-experienced chronic	ITT: 1. 264 2. 152	SVR12: 1. 253/263; 96% (95% CI 93 to 98)	N/A	Discontinuations due to adverse events: 1. 1 (<1%)	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; interactive web response system used for randomization and treatment

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RCT, DB, PC, MC	2. Placebo (GT1 only) (Deferred treatment) X 12 weeks	HCV with an NS5A inhibitor Key Inclusion Criteria: >18 y/o, previous tx duration ≥4 weeks, GT1: previous NS5A inhibitor or 2 DAAs from different classes, other GT: previous DAA regimen Key Exclusion Criteria: noncompliance to previous regimens, decompensated cirrhosis, unstable psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin >1.5 ULN, plts <50,000, HgA1C >8.5%, CrCl <50mL/min, Hg <10, albumin <3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or drug abuse within the previous 12 months, medications (amiodarone, PPIs, statins, or anticonvulsants)	FAS: 1. 263 2. 152 Attrition: 1. 3 2. 3	P<0.001 for superiority compared to 85% performance goal SVR24: 1. 249/263; 95% (CI not reported)		2. 3 (<1%)		concealment. Only GT1 patients were randomized to placebo. Performance Bias: unclear; adequate blinding of participants and investigators, double-dummy design used. Only those with GT1 were blinded. Detection Bias: unclear; unclear if outcome assessors were blinded. Attrition Bias: low; FAS (all randomized pts who took ≥ 1 dose of drug). Missing data for HCV RNA imputed from last study dose. SVR24 data imputed as SVR12 if missing. Very low attrition overall. Reporting Bias: unclear; health related quality of life was listed as an exploratory outcome but was not reported in results. Also SVR results of deferred treatment group unknown. **Applicability**: Patient: Majority (300/415) were GT1. GT2: 5, GT3: 78, GT4:22, GT5:1. 46% had cirrhosis, 80% white. 85% of subjects failed previous treatment due to relapse. 133/263 had failed previous treatment with LDV. Intervention: No concerns. The addition of a protease inhibitor limits treatment to those without cirrhosis or Child-Pugh class A only. Comparator: Compared to a performance goal of 85%. This is lower than expected SVR12 with study drug. Outcomes: SVR12 remains an invalidated surrogate outcome. No evidence on long-term clinical outcomes. Setting: Multicenter: US, Canada, New Zealand, Australia. France, Germany, U.K. Sponsored by Gilead. Gilead was involved in data collection, statistical analysis, and writing of the manuscript.

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2. Bourliere et al. (Polaris-4)[2] Open-label, RCT, MC	1. SOF/VEL/VOX 2. SOF/VEL x 12 weeks	Demographics: GT1, 2, or 3,DAA-experienced chronic HCV without an NS5A inhibitor Key Inclusion Criteria: >18 y/o, previous tx duration ≥4 weeks, GT1: previous NS5A inhibitor or 2 DAAs from different classes, other GT: previous DAA regimen Key Exclusion Criteria: noncompliance to previous regimens, decompensated cirrhosis, unstable psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin > 1.5 ULN, plts < 50,000, HgA1C > 8.5%, CrCl < 50mL/min, Hg < 10, albumin < 3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or drug abuse within previous 12 months, medications	ITT: 1. 182 2. 151 FAS: 1. 182 2. 151 Attrition: 1. 0 2.2	SVR12: 1. 178/182; 98% (95% CI 95 to 99)* *P< 0.001 for superiority compared to 85% performance goal 2. 136/151; 90% (95% CI 84 to 94)** **p=0.09 compared to 85% performance goal	N/A	Discontinuations due to adverse events: 1. 0 2. 1 (<1%)	NS	**Risk of Bias (low/high/unclear)**: Selection Bias: high; open-label. Randomization via an interactive web response system. Performance Bias: high; open-label Detection Bias: high; open-label Attrition Bias: low; FAS (all randomized pts who took ≥ 1 dose of drug). Missing data for HCV RNA imputed from last study dose. SVR24 data imputed as SVR12 if missing. Very low attrition overall. Reporting Bias: unclear; health related quality of life was listed as an exploratory outcome but was not reported in results. **Applicability**: Patient: Majority (144/333) were GT1. GT2: 64, GT3: 106, GT4:19. 85% received previous therapy with SOF. 88% were white, 46% with cirrhosis. Intervention: No concerns. The addition of a protease inhibitor limits treatment to those without cirrhosis or Child-Pugh class A only. Comparator: Compared to a performance goal of 85%. This is lower than expected SVR12 with study drug. Outcomes: SVR12 remains an invalidated surrogate outcome. No evidence on long term clinical outcomes. Setting: Multicenter: U.S., Canada, New Zealand, Australia, France, Germany, U.K Sponsored by Gilead. Gilead was involved in data collection, statistical analysis, and writing of the manuscript.

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		(amiodarone, PPIs, statins, or anticonvulsants)						

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; ; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EBR = elbasvir; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype;; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; Tx = treatment; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.

Glecaprevir/Pibrentasvir (G/P)

See **Appendix 6** 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:

The FDA approved G/P based on evidence from nine clinical trials (n=2369) in both treatment naïve and treatment experienced patients without cirrhosis and with compensated cirrhosis.[40] The majority of these remain unpublished and are only available as poster abstracts. The FDA review documents are also not available yet.

Treatment-Experienced

Data to support G/P in DAA-treatment experienced comes from one phase 2 trial with two parts (MAGELLAN-1 part 1 and 2) (Table 8). Part 1 is an open-label, phase 2 dose-ranging study comparing 3 arms of G/P in HCV GT 1 patients without cirrhosis and with prior DAA treatment experience.[41] The lower dose arm was halted early, and all remaining patients were randomized to either G/P or G/P + RBV for 12 weeks (n=50) at the dose that was FDA approved (300 mg/120 mg). This study has many serious limitations and flaws including high risk of selection, performance, and detection bias due to the open-label design, no information on how patients were randomized, unbalanced baseline characteristics, and lack of a comparator group. A dose-response was not clear since the SVR12 rate was higher in the low dose group (100%; 6/6) compared to the high dose group (86%; 19/22), but the small population limits ability to make any conclusions. Additionally, the most common prior DAA-containing regimen was boceprevir plus PEG/RBV (n=10) and telaprevir plus PEG/RBV (n=8), both of which are no longer used in clinical practice. A total of 8 patients received LDV/SOF, and 8 received SOF/SMV. Sixty four percent (33/50) of patients had a

baseline fibrosis stage of F0-F1. Overall, SVR was achieved in 92% (46/50; 95% CI 81-97) of patients. The SVR in the higher dose group without RBV was 86% (19/22; 95% CI 67-95) and was 95% (21/22; 95% CI 78-99) in the high dose group with RBV. The sample size was not large enough to determine the impact of adding RBV to G/P.

MAGELLAN-1, part 2 was a multicenter, randomized, open label trial comparing G/P for 12 (n=44) or 16 weeks (n=47) in patients with GT 1 or 4 and prior DAA treatment failure with either a NS5A and/or NS3 protease inhibitor, including those with compensated cirrhosis.[42] Almost all of the patients were GT 1 (74% with GT 1a and 21% with GT 1b). The overall SVR12 was 89% (39/44) in those receiving G/P for 12 weeks and 91% (43/47) in those receiving therapy for 16 weeks. There were 4 patients in the 16-week group with virologic failure and zero with relapse compared to 1 patient with virologic failure and 4 with relapse in the 12-week group. When broken down based on prior DAA therapy, SVR rates were lower in those patients who had been on both a NS3 protease inhibitor and NS5A inhibitor (Table 8). This study is only available in poster abstract form and cannot be fully assessed for quality. Results broken down by cirrhosis or non-cirrhosis were not available, and numbers are extremely small. The study was not designed to make definitive conclusions based on prior DAA regimen.

There is insufficient evidence with G/P for DAA-treatment experienced patients with cirrhosis, hepatitis B virus (HBV), HIV coinfection, genotypes other than GT 1, or discontinuation of a previous treatment regimen due to non-adherence.

Table 8: SVR rates in clinical trials including treatment-experienced GT 1 patients treated with G/P:

	MAGELLAN-1 part 2		MAGELLAN-1 part 1	
	G/P x 12 weeks	**G/P x 16 weeks**	**G/P x 12 weeks**	**G/P + RBV x 12 weeks**
Overall	89% (39/44)	91% (43/47)	86% (19/22)	95% (21/22)
Compensated Cirrhosis	N/A	N/A	Excluded	Excluded
Without Cirrhosis	N/A	N/A	N/A	N/A
Prior NS3 PI	100% (14/14/)	100% (13/13)	N/A	N/A
Prior NS5A inhibitor	88% (14/16)	94% (17/18)	N/A	N/A
Prior NS3 PI + NS5A	79% (11/14)	81% (13/16)	N/A	N/A

Treatment-Naïve:

Efficacy of G/P in treatment naïve GT1-6 patients without cirrhosis was evaluated in two phase 2 open-label, multicenter, dose-ranging trials evaluating G/P for 8 and 12 weeks that excluded patients with HBV, HIV and cirrhosis (n=449).[43] These studies helped determine the optimal dose based on higher efficacy of the higher-dose in GT 3 patients. The 8-week treatment course resulted in 97-98% SVR12 in those with GT 1, 2, or 3.

Additionally, G/P was studied in six phase 3 trials (Tables 9 and 10). However, only one of these has been published and can be assessed for quality[44] (see evidence table). All of the phase 3 trials included treatment-naïve patients, or those who did not respond to treatment with PEG/RBV or SOF + RBV +/- PEG. Treatment with a DAA other than SOF was not included. Four of the clinical trials excluded those with cirrhosis (Table 9). The majority of patients included in these trials had fibrosis stage F0-F1 (~80%) and thus limits applicability to the Oregon Medicaid population. All trials except ENDURANCE 1 excluded HIV co-

infection, and all trials excluded HBV and those with CrCl less than 50 mL/min. The majority of patients were white and had more mild disease. All of thee trials remain unpublished and cannot be assessed for quality. They were all open-label other than ENDURANCE-2 in GT 2 HCV, which had a placebo comparator. ENDURANCE-3 was the only trial to include an active control group (SOF + DCV). Information on SVR24 is not available at this time. An 8 week regimen was included in GT 1 and GT 3. Trials including GT 2 and GT 4, 5, or 6 only included a 12 week arm of G/P.

ENDURANCE-1 demonstrated similar SVR12 rates with 8 weeks of therapy in GT 1 compared to 12 weeks (99.1% vs. 99.7%). This study included 33 patients with HIV co-infection, and all 33 achieved SVR12 regardless of duration. ENDURANCE-2 was a double blind, placebo controlled trial resulting in superiority of 12 weeks of G/P compared to a historical control SVR 12 of 95%. The SVR12 rate was 99.5%. Information on how the study was blinded or randomized is not available at this time. SVR12 rates for the deferred treatment placebo group are also not available. It is unclear why an 8 week course was not evaluated in the phase 3 trial. ENDURANCE-3 was the only trial including an active control, SOF + DCV for 12 weeks. The study also included an 8 week arm of G/P; however, this was a non randomized arm added after the completion of the study. Both the 8- and 12-week G/P regimens met non-inferiority criteria to SOF + DCV with SVR12 rates of 95-97%.

Table 9. Phase 3 unpublished trials in treatment naïve non-cirrhotic GT 1-6 patients

	Clinical Trials			
	ENDURANCE-1	**ENDURANCE-2**	**ENDURANCE-3**	**ENDURANCE-4**
Study Design	Open-label, MC	DB, PC, RCT	Open-label, partially randomized*, active-control	MC, open-label, single arm
Comparison	G/P 8 weeks (n=351) vs. G/P for 12 weeks (n=352)	G/P x 12 weeks (n=202) vs. placebo (deferred treatment) (n=100) vs. historical rate 95%	G/P 12 weeks (n=233) vs. SOF + DCV 12 weeks (n=115) versus G/P 8 weeks (n=157)	G/P x 12 weeks (n=121)
Genotypes included	GT 1	GT 2	GT 3	GT 4, 5, or 6
Cirrhosis Inclusion	Non-cirrhosis only	Non-cirrhosis only	Non-cirrhosis only	Non-cirrhosis only
Duration	8 vs. 12 weeks	12 weeks	8 weeks	8 weeks
Fibrosis Stage	85% F0-F1	80% F0-F2	83% F0-F1	86% F0-F1
Publication Status	Unpublished; poster only	Unpublished; poster only	Unpublished; poster only	Unpublished; poster only
SVR 12	99.1% (332/335) with 8 weeks vs. 99.7% (331/332) with 12 weeks	99.5% (195/196)	G/P 12 weeks: 95% (222/233) DCV + SOF: 97% (111/115) G/P 8 weeks 95% (149/157)	GT 4: 98.7%% (75/76) GT 5: 100% (26/26) GT 6: 100% (19/19)
*non-randomized 3rd arm with G/P for 8 weeks was added				

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

Two additional phase 3 trials included compensated cirrhosis only (Table 10), one of which has been published (see Evidence Table). These were both open-label, single arm, multicenter trials. The EXPEDITION-1 trial was an open-label, single-arm, phase 3 trial with many limitations.[44] It evaluated 12 weeks of G/P in patients (n=146) with GT 1, 2, 4, 5 or 6 with compensated cirrhosis (Child-Pugh A only). Patients with GT 3 HCV, decompensated cirrhosis, Child-Pugh B or C, HIV, HBV, or other sources of liver disease were excluded. Due to the study design (open-label and non-randomized), there is a high risk of bias in this trial. Nonetheless, the magnitude of effect was significant, and 99% (145/146) of patients achieved an SVR12 (95% CI 98-100).[44] The study did not report SVR24 rates. SVR was achieved regardless of baseline RAVs. This trial excluded those with GT 3 which is a more difficult patient population to treat and results may appear more favorable without this population. The only data in this population comes from a phase 2 open-label study comparing 12 weeks of G/P (n=28) to 12 weeks with RBV (n=27) in DAA-treatment naïve patients with GT 3 and compensated cirrhosis.[45] Those who had previous treatment with PEG/RBV in the group without RBV were extended to 16 weeks of G/P (n=4). The SVR12 rate was 96% (27/28; 95% CI 82 to 99) in GT3 patients who received G/P without RBV. Three out of the 4 treatment-experienced patients who received 16 weeks achieved SVR12. SVR12 was achieved by 100% (27/27; 95% CI 88 to 10) of patients in the G/P + RBV arm. Since this group wasn't included in the phase 3 follow up trials, the optimal treatment duration and the benefit of RBV for GT 3 patients with compensated cirrhosis remains unclear.

Almost all of the G/P trials excluded those with renal impairment (CrCl <50mL/min). However, G/P is currently approved for those with kidney disease based on the EXPEDITION-4 trial in patients (n=104) with stage 4 or 5 chronic kidney disease (CKD).[46] Twenty patients (19%) also had compensated cirrhosis and 82% were hemodialysis dependent. The overall SVR12 rate was 98% (102/104). This trial remains unpublished and cannot be assessed for quality. However, it was an open-label, single arm study with no comparator.

Table 10. Phase 3 G/P trials in treatment naïve CHC with compensated cirrhosis

	DAA-Treatment Experienced	
	EXPEDITION-1	**EXPEDITION-4**
Study Design	Open-label, single-arm, MC	Open-label, single-arm, MC
Comparator	None	None
Genotypes included	GT 1, 2, 4, 5, 6 (n=146)	GT 1-6 (n=104)
Cirrhosis Inclusion	Compensated Cirrhosis (Child-Pugh A) only	Non-Cirrhosis or compensated cirrhosis and stage 4/5 CKD
Duration	12 weeks	12 weeks
Fibrosis Stage/patient population	Compensated Cirrhosis	19% (20) with compensated cirrhosis; 82% hemodialysis dependent
Publication Status	Published	Unpublished; poster abstract
SVR 12	99% (145/146); 95% CI 98-100	98% (102/104)

Clinical Safety:

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

The most common adverse events in clinical trials were fatigue (11%), headache (13%), and nausea (8%).[40] There were low discontinuations due to adverse events (0.1%) or serious adverse events in clinical trials.

There were two controlled trials of G/P (ENDURANCE-2 and ENDURANCE-3). ENDURANCE-2 had a placebo group and adverse reactions that occurred in >5% of patients and more than placebo included headache (9% vs. 6%), nausea (6% vs. 2%) and diarrhea (5% vs. 2%).[40] ENDURANCE-3 included an active comparator group with DCV + SOF and adverse reactions reported in ≥5% of treatment-naïve adults without cirrhosis are included in Table 11.

Table 11: Adverse reactions occurring in ≥5% in treatment-naïve adults without cirrhosis in ENDURANCE-3:

	G/P x 8 weeks (n=157)	G/P x 12 weeks (n=233)	DCV + SOF x 12 weeks (n=115)
Headache	16%	17%	15%
Fatigue	11%	14%	12%
Nausea	9%	12%	12%
Diarrhea	7%	3%	2%

There are potential drug-drug interactions that need to be accounted for with G/P since they are substrates of P-glycoprotein inhibitors of CYPP450 enzymes. Treatment with G/P is not recommended for those with moderate or severe hepatic impairment (Child-Pugh B or C) due to a presumed class effect of the protease inhibitors and the increased risk of serious liver injury in those with underlying advanced liver disease.

Table 12. Pharmacology and Pharmacokinetic Properties.

Parameter	Glecaprevir	Pibrentasvir
Mechanism of Action	HCV NS3/4A protease inhibitor	NS5A inhibitor
Oral Bioavailability	N/A	N/A
Distribution and Protein Binding	97.5% protein bound	>99.9% protein bound
Elimination	Feces (92.1%), urine (0.7%)	Feces (96.6%)
Half-Life	6 hours	13 hours
Metabolism	Secondary to CYP3A	None

Abbreviations: HCV: hepatitis C virus, N/A: not available

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Hepatocellular Carcinoma
2) Mortality

Primary Study Endpoint:

2) Sustained Virologic Response at 12 weeks post-treatment (SVR12)

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3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events
6) Quality of Life

Table 13. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
2. .Forns et al. EXPEDITION-1[44] Single-arm, open-label, MC, phase 3	1. G/P X 12 weeks	Demographics: Treatment naïve, GT 1, 2, 3, 4 or 6 with compensated cirrhosis (Child-Pugh A) Key Inclusion Criteria: >18 y/o, treatment naïve, compensated cirrhosis. Key Exclusion Criteria: decompensated cirrhosis, Child-Pugh B or C unstable psychiatric disease, significant cardiac disease, malignancy, abnormal AST/ALT, bilirubin > 3 ULN, plts < 60,000, HgA1C > 8.5%, CrCl < 50mL/min, Hg < 12 albumin < 3, chronic liver disease of non-HCV origin, HBV, HIV, alcohol or	ITT: 1. 146 Attrition: 1. 0	SVR12: 1. 145/146; 99% (95% CI 98-100)	N/A	Discontinuations due to adverse events: 1. 0	N/A	**Risk of Bias (low/high/unclear)**: Selection Bias: high; open-label, single-arm, non-randomized Performance Bias: high; open-label Detection Bias: high; open-label Attrition Bias: unclear; low attrition overall Reporting Bias: unclear; full protocol not available **Applicability**: Patient: Majority (60%) were GT1, 82% white, 75% treatment-naïve. Extensive exclusion criteria limits generalizability. GT 3, a more difficult population to treat, excluded. Intervention: N/A Comparator: No active comparator Outcomes: SVR12 remains an invalidated surrogate outcome. Setting: Multicenter: Belgium, Canada, Germany, South Africa, Spain, U.S. Sponsored by Abbvie. Abbvie was involved in data collection, statistical analysis, and writing of the manuscript.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

		drug abuse within previous 6 months						

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; ; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype;; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; Tx = treatment; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	N
ORAL	TABLET	TECHNIVIE	OMBITASVIR/PARITAPREV/RITONAV	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 2: OVID Search Results

# ▲	Searches	Results	Type	Actions	Annotations
1	Hepatitis C, Chronic/ or Antiviral Agents/ or Hepatitis C/	88131	Advanced	Display Results | More	
2	direct acting antivirals.mp.	717	Advanced	Display Results | More	
3	sofosbuvir.mp. or Sofosbuvir/	820	Advanced	Display Results | More	
4	daclatasvir.mp.	326	Advanced	Display Results | More	
5	ledipasvir.mp.	262	Advanced	Display Results | More	
6	ombitasvir.mp.	133	Advanced	Display Results | More	
7	dasabuvir.mp.	118	Advanced	Display Results | More	
8	paritaprevir.mp.	119	Advanced	Display Results | More	
9	elbasvir.mp.	43	Advanced	Display Results | More	
10	grazoprevir.mp.	41	Advanced	Display Results | More	
11	voxilaprevir.mp.	1	Advanced	Display Results | More	
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	1610	Advanced	Display Results | More	
13	1 and 12	1546	Advanced	Display Results | More	
14	limit 13 to (english language and humans and yr="2016 -Current" and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	68	Advanced	Display Results | More	

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 3: Summary of Randomized Controlled Trials

Randomized Controlled Trials:
After initial review, 23 trials were manually reviewed from the literature search. The majority of trials were excluded due to wrong study design, wrong comparator, poor quality, or unapproved medication. The remaining 6 trials are briefly described in the table below.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Results (Primary Outcome; SVR12)
Gane, 2016[45] (2 phase II, open-label, single-arm trials)	ABT-493 (glecaprevir) + ABT-530 (pibrentasvir) +/- RBV, 12 or 16 weeks	GT3 and GT1, with compensated cirrhosis (n=82)	SVR12: *GT1; 12 weeks:* 26/27 (96%; 95% CI 82-99) SVR12: *GT3; 12 weeks:* 27/28 (96%; 95% CI 82-99) *GT3; + RBV* 27/27 (100%; 95% CI 88-100)
Kwo, 2017[43] (2 phase II, open-label trials)	Glecaprevir/pibrentasvir dose ranging study with or without RBV	GT1-6 without cirrhosis	SVR12: *GT1:* 200 mg/40 mg: 38/39 (97%; 95% CI 87-100) 200 mg/120 mg: 40/40 (100%; 95% CI 91-100) *GT2:* 200 mg/120 mg: 24/24 (10%; 95% CI 86-100) 300 mg/120 mg: 24/25 (96%; 95% CI 80-99) *GT3:* 200 mg/40 mg: 25/30 (83%; 95% CI 66-93) 200 mg/120 mg 28/30 (93%; 95% CI 79-98) 200 mg/120 mg + RBV: 29/30 (94%; 95% CI 79-98) 300 mg/120 mg: 28/30 (93%; 95% CI 79-98)
Gane, 2016[47] (phase II, open-label trial)	SOF/VEL/GS-9857 4, 6, and 8 weeks	GT 1 or 3 with or without compensated cirrhosis (n=161)	SVR12 GT1: *Treatment-naïve; 6 weeks:* 14/15 (93%; 95% CI 68-99) *Treatment-naïve, with cirrhosis; 6 weeks* 13/15 (87%; 95% CI 60 to 98) SVR12: GT3: *Treatment-naïve, with cirrhosis; 6 wk* 15/18 (83%; 95% CI 59-96) *PEG/RBV-experienced, with cirrhosis; 8 wk*

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

			PEG/RBV-experienced; 8 wk 17/17 (100%; 95% CI 81 to 100) *DAA-experienced, 6 wk* 20/30 (67%; 95% CI 47 to 83) *PI-experienced; 8 wk* 25/28 (89%;95% CI 72-98)	19/19 (100%; 95% CI 82-100) *DAA-experienced; 8 wk* 4/4 (100%; 40-100)
Bourliere, 2017[2] (2 phase III RCTs)	SOF/VEL/VXP	GT1-6 previously treated with a DAA-containing regimen	<u>Previous NS5A inhibitor</u> *SVR12:* SOF/VEL/VXP: 253/263 (96%)	<u>Previous treated with DAA, not including NS5A inhibitor</u> SOF/VEL/VXP: 178/182 (98%) SOF/VEL: 136/151 (90%)
Leroy, 2016[48] RCT, phase III, open-label	DCV/SOF + RBV for 12 or 16 weeks	GT 3 with advanced fibrosis or compensated cirrhosis	<u>SVR12:</u> 12 wk: 21/24 (87.5%; 95% CI 67.6-97.3) 16 wk: 24/26 (92.3%; 95% CI 74.9-99.1)	
Kwo, 2017[49] Phase III, open-label, RCT	EBR/GZR x 12 weeks vs. EBR/GZR + RBV x 12 weeks vs. EBR/GZR x 16 weeks vs. EBR/GZR + RBV x 16 week	GT 1, 4, or 6 with or without cirrhosis, previously treated with PEG/RBV (n=420)	<u>SVR12:</u> 12 weeks: EBR/GZR: 92.4% EBR/GZR + RBV: 94.2%	<u>SVR12:</u> 16 weeks: EBR/GZR: 92.4% EBR/GZR + RBV: 98.1%

Appendix 4: Abstracts of Randomized Controlled Trials:

1. Gane, Poordad, Wang, et al. High Efficacy of ABT-493 and ABT-530 Treatment in Patients With HCV Genotype 1 or 3 Infection and Compensated Cirrhosis. *Gastroenterology*. 2016 Oct;151(4):651-659.e1. doi: 10.1053/j.gastro.2016.07.020. Epub 2016 Jul 25.

BACKGROUND & AIMS:
The combination of ABT-493 (NS3/4A protease inhibitor) plus ABT-530 (NS5A inhibitor) has shown high rates of sustained virologic response at post-treatment week 12 (SVR12) in noncirrhotic patients infected with hepatitis C virus (HCV) genotypes (GTs) 1-6. We describe 2 open-label phase 2 studies investigating the efficacy and safety of ABT-493 plus ABT-530 with or without ribavirin (RBV) in GT1- or GT3-infected patients with compensated cirrhosis.

METHODS:
Patients with GT1 infection received 200 mg ABT-493 plus 120 mg ABT-530 for 12 weeks. Patients with GT3 infection were randomized 1:1 to receive 300 mg ABT-493 plus 120 mg ABT-530 with or without once-daily 800 mg RBV for 12 weeks; treatment-experienced patients who were not treated with RBV received 16 weeks of therapy. Efficacy was measured by SVR12, defined as an HCV-RNA level less than 25 IU/mL. Adverse events and laboratory parameters were evaluated throughout the study.

RESULTS:
Twenty-seven patients with GT1 infection and 55 patients with GT3 infection were enrolled. The majority were treatment-naive (84%) and male (65%). In patients with GT1 infection, SVR12 was achieved by 96% (26 of 27; 95% confidence interval [CI], 82-99) of patients, with 1 relapse. Among GT3-infected patients, SVR12 was achieved in 96% (27 of 28; 95% CI, 82-99) of patients in the RBV-free arm (1 relapse), and in 100% (27 of 27; 95% CI, 88-100) in the RBV-containing arm. The most common adverse events were headache, fatigue, and nausea. Laboratory abnormalities were rare; no patient discontinued treatment.

CONCLUSIONS:
In cirrhotic HCV GT1- or GT3-infected patients, ABT-493 plus ABT-530 with or without RBV achieved SVR12 rates of 96%-100% and was well tolerated. ClinicalTrials.gov identifiers NCT02243280 and NCT02243293.

2. Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol.* 2017 Aug;67(2):263-271. doi: 10.1016/j.jhep.2017.03.039. Epub 2017 Apr 13.

BACKGROUND & AIMS:
Hepatitis C virus (HCV) therapy that is highly efficacious, pangenotypic, with a high barrier to resistance and short treatment duration is desirable. The efficacy and safety of 8- and 12-week treatments with glecaprevir (ABT-493; NS3/4A protease inhibitor) and pibrentasvir (ABT-530; NS5A inhibitor) were evaluated in non-cirrhotic patients with chronic HCV genotype 1-6 infection.

METHODS:
SURVEYOR-I and SURVEYOR-II were phase II, open-label, multicenter, dose-ranging trials including patients with chronic HCV genotype 1-6 infection who were either previously untreated or treated with pegylated interferon plus ribavirin. Patients received once-daily glecaprevir plus pibrentasvir at varying doses with or without ribavirin for 8 or 12 weeks. The primary efficacy endpoint was the percentage of patients with a sustained virologic response at post-treatment week 12 (SVR12).
RESULTS:
Of the 449 patients who received varying doses of glecaprevir plus pibrentasvir, 25%, 29%, 39%, and 8% had HCV genotype 1, 2, 3, and 4-6 infection, respectively. Twelve-week treatment achieved SVR12 in 97-100%, 96-100%, 83-94%, and 100% in genotypes 1, 2, 3, and 4-6, respectively. Eight-week treatment with 300mg glecaprevir plus 120mg pibrentasvir in genotype 1-, 2-, or 3-infected patients yielded 97-98% SVR12 with no virologic failures. Three (0.7%) patients discontinued treatment due to adverse events; most events were mild (grade 1) in severity. No post-nadir alanine aminotransferase elevations were observed.

CONCLUSIONS:
Glecaprevir plus pibrentasvir was well tolerated and achieved high sustained virologic response rates in HCV genotypes 1-6-infected patients without cirrhosis following 8- or 12-week treatment durations.

LAY SUMMARY:
The combination of direct-acting antivirals glecaprevir and pibrentasvir comprise a once-daily, all-oral, pangenotypic treatment for HCV genotype 1-6 infection. This article describes results from two phase II trials investigating a range of doses at treatment durations of 8 or 12 weeks in 449 patients without cirrhosis. Efficacy of the optimal dose, as determined by rates of sustained virologic response at post-treatment week 12, ranged from 92%-100%; treatment was well tolerated and significant laboratory abnormalities were rare.

3. Gane EJ, Schwabe C, Hyland RH. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-Naïve or Previously Treated Patients With Hepatitis C Virus Genotype 1 or 3 Infections. Gastroenterology. 2016 Sep;151(3):448-456.e1. doi: 10.1053/j.gastro.2016.05.021. Epub 2016 May 27.

BACKGROUND & AIMS:
We performed a phase 2 trial of the efficacy and safety of 4, 6, and 8 weeks of sofosbuvir, given in combination with the NS5A inhibitor velpatasvir and the NS3/4A protease inhibitor GS-9857, in patients with hepatitis C virus (HCV) infection.

METHODS:
We enrolled 161 treatment-naïve or previously treated patients infected with HCV genotypes 1 or 3 with or without compensated cirrhosis at 2 centers in New Zealand, from September 2014 through March 2015. All patients received sofosbuvir (400 mg) and velpatasvir (100 mg) plus GS-9857 (100 mg) once daily. The primary efficacy end point was sustained virologic response at 12 weeks after therapy (SVR12). The duration of therapy was determined by baseline patient characteristics: 4 or 6 weeks for treatment-naïve patients without cirrhosis, 6 weeks for treatment-naïve patients with cirrhosis, and 6 or 8 weeks for treatment-experienced patients with or without cirrhosis.

RESULTS:
Four weeks of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in 4 of 15 (27%) treatment-naïve patients with HCV genotype 1 without cirrhosis. Six weeks of this combination produced a SVR12 in 14 of 15 (93%) treatment-naïve patients with HCV genotype 1 without cirrhosis, in 13 of 15 (87%) treatment-naïve genotype 1 patients with cirrhosis, in 15 of 18 (83%) treatment-naïve patients with HCV genotype 3 with cirrhosis, and in 20 of 30 (67%) patients with HCV genotype 1 who had failed an all-oral regimen of 2 or more direct-acting antiviral agents. Eight weeks of the drug combination produced an SVR12 in 17 of 17 (100%) patients with HCV genotype 1, in 19 of 19 (100%) patients with HCV genotype 3 and cirrhosis who had failed pegylated interferon plus ribavirin, in 25 of 28 (89%) patients with HCV genotype 1 who had failed protease inhibitor-based triple therapy, and in 4 of 4 (100%) patients with HCV genotype 3 who had failed an all-oral regimen of ≥2 direct-acting antiviral agents. The most common reported adverse events were headache, nausea, and fatigue.

CONCLUSIONS:
Eight weeks of treatment with the combination of sofosbuvir, velpatasvir, and GS-9857 produced an SVR12 in most treatment-naïve or previously treated patients with HCV genotype 1 or 3 infections, including those with compensated cirrhosis. ClinicalTrials.gov, Number: NCT02202980.

4. Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med*. 2017 Jun 1;376(22):2134-2146. doi: 10.1056/NEJMoa1613512.

BACKGROUND:
Patients who are chronically infected with hepatitis C virus (HCV) and who do not have a sustained virologic response after treatment with regimens containing direct-acting antiviral agents (DAAs) have limited retreatment options.

METHODS:
We conducted two phase 3 trials involving patients who had been previously treated with a DAA-containing regimen. In POLARIS-1, patients with HCV genotype 1 infection who had previously received a regimen containing an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive either the nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the protease inhibitor voxilaprevir (150 patients) or matching placebo (150 patients) once daily for 12 weeks. Patients who were infected with HCV of other genotypes (114 patients) were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group. In POLARIS-4, patients with HCV genotype 1, 2, or 3 infection who had previously received a DAA regimen but not an NS5A inhibitor were randomly assigned in a 1:1 ratio to receive sofosbuvir-velpatasvir-voxilaprevir (163 patients) or sofosbuvir-velpatasvir (151 patients) for 12 weeks. An additional 19 patients with HCV genotype 4 infection were enrolled in the sofosbuvir-velpatasvir-voxilaprevir group.

RESULTS:
In the three active-treatment groups, 46% of the patients had compensated cirrhosis. In POLARIS-1, the rate of sustained virologic response was 96% with sofosbuvir-velpatasvir-voxilaprevir, as compared with 0% with placebo. In POLARIS-4, the rate of response was 98% with sofosbuvir-velpatasvir-voxilaprevir and 90% with sofosbuvir-velpatasvir. The most common adverse events were headache, fatigue, diarrhea, and nausea. In the active-treatment groups in both trials, the percentage of patients who discontinued treatment owing to adverse events was 1% or lower.

CONCLUSIONS:
Sofosbuvir-velpatasvir-voxilaprevir taken for 12 weeks provided high rates of sustained virologic response among patients across HCV genotypes in whom treatment with a DAA regimen had previously failed. (Funded by Gilead Sciences; POLARIS-1 and POLARIS-4 ClinicalTrials.gov numbers, NCT02607735 and NCT02639247.).

5. Leroy V, Anugs P, Bronowicki, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology*. 2016 May;63(5):1430-41.

Patients with hepatitis C virus (HCV) genotype 3 infection, especially those with advanced liver disease, are a challenging population in urgent need of optimally effective therapies. The combination of daclatasvir (DCV; pangenotypic nonstructural protein 5A inhibitor) and sofosbuvir (SOF; nucleotide nonstructural protein 5B inhibitor) for 12 weeks previously showed high efficacy (96%) in noncirrhotic genotype 3 infection. The phase III ALLY-3+ study (N = 50) evaluated DCV-SOF with ribavirin (RBV) in treatment-naïve (n = 13) or treatment-experienced (n = 37) genotype 3-infected patients with advanced fibrosis (n = 14) or compensated cirrhosis (n = 36). Patients were randomized 1:1 to receive open-label DCV-SOF (60 + 400 mg daily) with weight-based RBV for 12 or 16 weeks. The primary endpoint was sustained virological response at post-treatment week 12 (SVR12). SVR12 (intention-to-treat) was 90% overall (45 of 50): 88% (21 of 24) in the 12-week (91% observed) and 92% (24 of 26) in the 16-week group. All patients with advanced fibrosis achieved SVR12. SVR12 in patients with cirrhosis was 86% overall (31 of 36): 83% (15 of 18) in the 12-week (88% observed) and 89% (16 of 18) in the 16-week group; for treatment-experienced patients with cirrhosis, these values were 87% (26 of 30), 88% (14 of 16; 93% observed), and 86% (12 of 14), respectively. One patient (12-week group) did not enter post-treatment follow-up (death unrelated to treatment). There were 4 relapses (2 per group) and no virological breakthroughs. The most common adverse events (AEs) were insomnia, fatigue, and headache. There were no discontinuations for AEs and no treatment-related serious AEs.

CONCLUSION:
The all-oral regimen of DCV-SOF-RBV was well tolerated and resulted in high and similar SVR12 after 12 or 16 weeks of treatment among genotype 3-infected patients with advanced liver disease, irrespective of past HCV treatment experience.

6. Kwo P, Gane EJ, Peng CY, Pearlman B. Effectiveness of Elbasvir and Grazoprevir Combination, With or Without Ribavirin, for Treatment-Experienced Patients With Chronic Hepatitis C Infection. *Gastroenterology*. 2017 Jan;152(1):164-175.e4. doi: 10.1053/j.gastro.2016.09.045. Epub 2016 Oct 5.

BACKGROUND & AIMS:
Patients infected with hepatitis C virus (HCV) genotype 1, 4, or 6, with or without cirrhosis, previously treated with peg-interferon and ribavirin, are a challenge to treat. We performed a phase 3 randomized controlled open-label trial to assess the effects of 12 or 16 weeks of treatment with once-daily elbasvir (an HCV NS5A inhibitor, 50 mg) and grazoprevir (an HCV NS3/4A protease inhibitor, 100 mg), in a fixed-dose combination tablet, with or without twice-daily ribavirin, in this patient population.

METHODS:
We analyzed data from 420 patients (35% with cirrhosis, 64% with a null or partial response to peg-interferon and ribavirin) who were randomly assigned (1:1:1:1) to groups given elbasvir and grazoprevir once daily, with or without twice-daily ribavirin, for 12 or 16 weeks, at 65 study centers in 15 countries in

Europe, Asia, and Central and North America. Randomization was stratified by cirrhosis status and type of peg-interferon and ribavirin treatment failure. HCV RNA was measured using COBAS TaqMan v2.0. The primary end point was HCV RNA <15 IU/mL, 12 weeks after completion of treatment (SVR12). We aimed to determine whether the proportion of patients achieving an SVR12 in any group was greater than the reference rate (58%).

RESULTS:
With 12 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 94.2% of patients given elbasvir and grazoprevir with ribavirin. With 16 weeks of treatment, an SVR12 was achieved by 92.4% of patients given elbasvir and grazoprevir and 98. 1% of patients given elbasvir and grazoprevir with ribavirin. Among patients treated for 12 weeks without ribavirin, virologic failure occurred in 6.8%, 0%, and 12.5% of patients with HCV genotype 1a, 1b, or 4 infection, respectively. Among patients given elbasvir and grazoprevir for 12 weeks, virologic failure occurred in 0% of patients infected with HCV genotypes 1 and 4 who relapsed after completing peg-interferon and ribavirin, and 7.5% infected with HCV genotypes 1 and 4, respectively, with a null or partial response to peg-interferon and ribavirin. Among patients treated for 16 weeks who received ribavirin, there were no incidences of virologic failure. Common adverse events were fatigue (23.1%), headache (19.8%), and nausea (11.0%).

CONCLUSIONS:
The combination tablet of elbasvir and grazoprevir, with or without ribavirin, was highly efficacious in inducing an SVR12 in patients with HCV genotype 1, 4, or 6 infection failed by previous treatment with peg-interferon and ribavirin, including patients with cirrhosis and/or a prior null response. The treatment was generally well tolerated. ClinicalTrials.gov Number: NCT02105701.

Appendix 5: Highlights of Prescribing Information for Vosevi®

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

VOSEVI™ (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

----------INDICATIONS AND USAGE----------

VOSEVI is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, an HCV NS3/4A protease inhibitor, and is indicated for the treatment of adult patients with chronic HCV infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have (1, 2.2, 14):

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
- genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
  - Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

----------DOSAGE AND ADMINISTRATION----------

- Testing prior to the initiation of therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: One tablet (400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir) taken orally once daily with food. (2.2)
- See recommended treatment regimen and duration in table below (2.2):

Genotype	Patients Previously Treated with an HCV Regimen Containing:	VOSEVI Duration
1, 2, 3, 4, 5, or 6	An NS5A inhibitor[a]	12 weeks
1a or 3	Sofosbuvir without an NS5A inhibitor[b]	12 weeks

a. In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
b. In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.3)
- VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg voxilaprevir (3)

----------CONTRAINDICATIONS----------

Coadministration with rifampin. (4)

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

- Risk of Hepatitis B virus reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone with VOSEVI, a sofosbuvir-containing regimen, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with VOSEVI is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.2, 7.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with VOSEVI for 12 weeks were headache, fatigue, diarrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- P-gp inducers and/or moderate to potent CYP inducers (e.g., St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir. Use of VOSEVI with P-gp inducers and/or moderate to potent CYP inducers is not recommended (5.3, 7)
- Consult the full prescribing information prior to use for potential drug interactions (4, 5.2, 5.3, 7)

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

Revised: 07/2017

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 6: Highlights of Prescribing Information for Mavyret®

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

MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.
Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

INDICATIONS AND USAGE

MAVYRET is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. (1)

DOSAGE AND ADMINISTRATION

- Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken orally once daily with food. (2.2)
- See recommended treatment duration in tables below. (2.2)

Treatment-Naïve Patients

HCV Genotype	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	8 weeks	12 weeks

Treatment-Experienced Patients

		Treatment Duration	
HCV Genotype	Patients Previously Treated With a Regimen Containing:	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	16 weeks

1. In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.
2. In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin
3. PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

- HCV/HIV-1 co-infection and patients with any degree of renal impairment: Follow the dosage recommendations in the tables above. (2.2)
- Hepatic Impairment: MAVYRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B); and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg glecaprevir and 40 mg pibrentasvir. (3)

CONTRAINDICATIONS

- Patients with severe hepatic impairment (Child-Pugh C). (4, 8.7, 12.3)
- Coadministration with atazanavir and rifampin. (4)

WARNINGS AND PRECAUTIONS

Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)

ADVERSE REACTIONS

In subjects receiving MAVYRET, the most commonly reported adverse reactions (greater than 10%) are headache and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Carbamazepine, efavirenz, and St. John's wort may decrease concentrations of glecaprevir and pibrentasvir. Coadministration of carbamazepine, efavirenz containing regimens, and St. John's wort with MAVYRET is not recommended. (5.2)
Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 7, 12.3)

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

Revised: 8/2017

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Appendix 7: Proposed Prior Authorization Criteria

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-162 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
4. Has all of the following pre-treatment testing been documented: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; and f. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status.	**Yes:** Record results of each test and go to #5	**No**: Pass to RPh. Request updated testing.

Approval Criteria		
~~5. Has the patient failed treatment with any of the following HCV NS5A inhibitors:~~ ~~a) Daclatasvir plus sofosbuvir;~~ ~~b) Ledipasvir/sofosbuvir;~~ ~~c) Paritaprevir/ritonavir/ombitasvir plus dasabuvir;~~ ~~d) Elbasvir/grazoprevir; or~~ ~~e) Sofosbuvir/velpatasvir)?~~ ~~Note: Patients who failed treatment with sofosbuvir +/- ribavirin or PEGylated interferon can be retreated (see table below).~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness.~~ ~~Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen.~~ ~~Refer to medical director for review.~~	~~**No:** Go to #6~~
~~6.~~5. Which regimen is requested?	Document and go to #~~7~~6	
~~7.~~6. Does the patient have HIV coinfection ~~AND: A biopsy, imaging test (transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE], or serum test if the above are not available (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF]) to indicate fibrosis (METAVIR F2) AND the patient~~ and is under treatment by a specialist with experience in HIV? Note: persons with HIV/HCV coinfection are at risk for rapidly progressing fibrosis	**Yes:** Go to #~~12~~11 ~~Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy~~ ~~For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.~~	**No:** Go to #~~8~~7

Approval Criteria		
~~8.~~7. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate portal fibrosis with septa (METAVIR F2) advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); **OR** Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)**?**	**Yes:** Go to #~~11~~10 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF], Fibrosure) can be used to confirm METAVIR ~~F3 or F4~~F2 or greater but cannot be used for denial.. For results falling in a range (e.g. F2 to F3), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values http://www.oregon.gov/oha/herc/CoverageGuidances/Liver-Fibrosis-CG.pdf) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.	**No:** Go to #~~9~~8

Approval Criteria		
~~9.~~8. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a) Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda or lichen planus d) Lymphomas (B-cell non-Hodgkin lymphoma) e) Type 2 Diabetes with insulin resistance	**Yes:** Go to #~~11~~10	**No:** Go to #~~10~~9
~~10.~~9. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #~~11~~10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~11.~~10. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR F3: Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist?	**Yes:** Go to #~~12~~11	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.
~~12.~~11. In the previous 6 months: • Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR • Has the patient been diagnosed with a substance use disorder; OR • Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #~~13~~12	**No:** Go to #~~14~~13
~~13.~~12. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #~~14~~13	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
~~14.~~13. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #~~15~~14	**No:** Pass to RPh. Deny; medical appropriateness.
~~15.~~14. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #~~16~~15	**No:** Go to #~~17~~16
~~16.~~15. Has the patient had a baseline NS5a resistance test show a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #~~17~~16
16. Is the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #17	**No:** Go to #18
17. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #18

Approval Criteria		
18. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or lost to follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #19
~~17.~~19. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-162~~4~~ weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

[Pending P&T Committee Recommendations]

P&T Review: *9/16 (MH); 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 2/12/16; 4/15; 1/15*

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Drug Class Update: Attention Deficit Hyperactivity Disorder

Date of Review: September 2017

Date of Last Review: March 2016
End Date of Literature Search: 06/30/2017

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

Purpose for Class Update:
The purpose of this update is to evaluate new comparative evidence for efficacy and safety of treatements for attention deficit hyperactivity disorder (ADHD) published since the previous class update in March 2016. Evidence for 3 new Food and Drug Administratin (FDA)-approved stimulant formulations is also reviewed.

Research Questions:
1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness or efficacy outcomes?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (tolerability, serious adverse events, abuse/misuse/diversion) outcomes?
3. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness, efficacy or harms outcomes in subgroups of patients based on demographics, socioeconomic status, other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

Conclusions:
- This review includes new evidence from 3 systematic reviews,[1-3] 2 guidelines,[4,5] 2 randomized control trials (RCTs),[6,7] and 2 FDA safety updates.[8] Evidence for new, FDA-approved formulations of lisdexamfetamine chewable tablets, mixed amphetamine salts, and methylphenidate extended release orally disintegrating tablets is also included in this review.
- Overall, there is insufficient new evidence which evaluates comparative effectiveness of medications or formulations for treatment of ADHD in children or adults. A Cochrane review examining differences between agents found similar symptom improvement with dexamphetamine, lisdexamfetamine, and mixed amphetamine salts (standardized mean difference [SMD] of -0.44 to -0.72) indicating medium effect size compared to placebo.[2] Evidence was limited by use of indirect comparisons, high heterogeneity between trials, and unclear risk of bias for many trials included in the systematic review. In addition, few trials examined long-term use of stimulants (median duration 28 days).[2]
- Guidelines generally recommended non-pharmacological interventions as first-line treatment for children with ADHD, followed by pharmacological treatment in children with moderate symptoms who fail to respond to psychosocial or behavioral interventions.[4] Stimulants are recommended as initial

pharmacological treatment followed by non-stimulant medications such as atomoxetine, clonidine and guanfacine as second-line therapy if stimulants are not tolerated or ineffective.

- There is limited evidence in children with concurrent autism, Tourette's syndrome, or learning disabilities which suggest stimulants may help to improve symptoms of ADHD. There was low quality evidence that compared to methylphenidate, behavioral interventions were more effective at improving ADHD symptoms including motor activity, disruptive behavior and academic engagement in children with learning disabilities.[5] There is insufficient data which compares differences in efficacy or safety between drugs or formulations in these subpopulations.
- There is no new evidence which evaluates safety or efficacy of combination treatment with multiple stimulant medications for ADHD.

Recommendations:

- There is no new evidence which would change previous conclusions. Evaluate comparative costs in the executive session.

Previous Conclusions: March 2016

- There is insufficient evidence that directly compares general effectiveness outcomes of different drugs for ADHD in children or adults.
- In children, there is low to moderate quality evidence of no difference in improvement of ADHD symptoms between immediate-release (IR) and extended-release (ER) stimulants; between ER stimulants (including controlled delivery (CD), sustained-release (SR), and transdermal formulations); or between IR stimulants. Exceptions of studies that do show differences between stimulants are of low quality and further studies are needed to determine if true differences in efficacy between these drugs exist.
- In children, there is moderate quality evidence non-stimulant atomoxetine may be inferior to stimulants on most efficacy outcomes, such as response rates. Comparisons between stimulants and non-stimulants other than atomoxetine are either lacking or do not demonstrate differences in efficacy.
- In children, there is insufficient evidence that compares efficacy between non-stimulant ADHD drugs with the exception of guanfacine ER and atomoxetine, for which there is low quality evidence guanfacine ER may be superior to atomoxetine at reducing ADHD-RS scores at 6 weeks (difference -5.1; scale 0-54).
- In adolescents and adults, there is insufficient evidence to adequately compare differences in efficacy of stimulants and non-stimulant drugs for ADHD.
- The most common adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; there is only low quality evidence to suggest any differences in harms between the agents.
- Insufficient evidence from survey data suggest lifetime non-medical use of methylphenidate IR and dextroamphetamine was more frequent compared to mixed amphetamine salts; the highest rate of diversion was with amphetamine/dextroamphetamine.

Previous Recommendations:

- No new evidence in the DERP report suggests changes should be made to the PDL based on clinical differences between agents.
- Designate QuilliChew ER™ and Adzenys XR-ODT™ as non-preferred based on limited evidence for safety and efficacy.
- Update the current safety edit.

Background:

ADHD is a neurobehavioral disorder which affects approximately 2-9% of children and adolescents characterized by hyperactivity, impulsivity, and inattention. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosis is based on presence of at least 6 symptoms for greater than 6 months present in 2 different settings which interfere with function and are inappropriate for the patients developmental level (or at least 5 symptoms in patients greater than 16 years of age).[9] Comorbid conditions which can be associated with a diagnosis of ADHD include mood disorders, tic

disorders, developmental and learning disorders and anxiety disorders.[9] Recommendations from the American Academy of Pediatrics guidelines are based on age and disease severity. In children age 4-5 years, behavioral therapy is recommended as first-line treatment. Methylphenidate is recommended as a second-line therapy or in cases of moderate-to-severe functional impairment. In children older than 6 years of age, behavioral therapy and/or pharmacotherapy may be used. Evidence is strongest evidence for stimulant medications, although non-stimulant medications including atomoxetine, clonidine and guanfacine are recommended as second-line therapy if stimulants are not tolerated or ineffective.[9,10]

Goals of care include management of symptoms, functional improvement, and improved quality of life. Symptom and functional improvement can be evaluated using a variety of assessment scales and metrics. Assessment scales commonly used in randomized controlled trials (RCTs) include the ADHD rating scale, the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), Permanent Product Measure of Performance (PERMP), and Conners Parent Rating Scale (CPRS). The ADHD rating scale assesses symptoms of inattentiveness, hyperactivety, and impulsivity based on DSM criteria for diagnosis of ADHD. The range for this scale based on DSM-IV criteria is 0 to 54 with more higher scores indicating more severe symptoms.[11] The CPRS scale evaluates a variety of ADHD symptoms, each assessed on a 0 to 3 scale corresponding to symptoms which are not present (0), just a little present (1), pretty much present (2), and very much present (3).[11] The SKAMP rating scale is a teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting. Scores assess 13 items including attention, quality of work, deportment and compliance. Each item is assessed on a 0 to 6 point scale with total score ranging from 0 to 78 and higher scores associated with more severe impairment.[12,13] The PERMP is another classroom assessment which evaluates attention using a skill-adjusted math test. The total PERMP score is a sum of the number of math problems attempted and the number answered correctly.[14] Because PERMP score is specific to the ability of the patient, the minimum clinically significant difference in PERMP score has not been determined.

In the Oregon Health Plan Fee-for-Service population, use of ADHD medications is restricted based on FDA approved age and dose. Use of duplicate therapy is permitted for the regimens listed in **Appendix 4,** and off-label use of these medications may be approved if the regimen is recommended by or in consultation with a specialist. Currently, patients receiving preferred or voluntary products in this class account for approximately 45% and 40% of claims, respectively. Of the non-preferred agents extended-release methylphenidate and extended-release dextroamphetamine-amphetamine are most commonly used. For patients requesting a non-preferred product, 64% of patients had a subsequent prior authorization approved. Only 9% of patients who initially request a non-preferred agent are switched to an alternate agent in 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, 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.

New Systematic Reviews:

A Cochrane systematic review published in 2016 examined the efficacy of amphetamines for children and adolescents age 3 to 17 with ADHD.[2] The review included 19 parallel group or cross-over trials comparing amphetamines to placebo. Full data was not included from 4 of these studies as 2 studies were ongoing and 2 were non-English studies which were awaiting review at the time of publication to determine if they were randomized or included patients with a formal diagnosis of ADHD.[2] Of these trials, 20 were conducted in the United States.[2] Dosing regimen varied between trials with 12 studies which used a fixed dosing regimen, 5 studies which titrated dose based on response, and 7 studies which used weight based dosing.[2] The mean dose used in these studies was 34 mg/day for dextroamphetamine, 50 mg/day for lisdexamfetamine, and 20 mg/day for mixed amphetamine salts.[2] The median duration was 28 days, and only one study examined a duration longer than 63 days. Overall, most trials included in the meta-analysis failed to report adequate methodology and had unclear risk of bias. Only 3 trials described methods of randomization, 4 described methods of allocation concealment, 10 described blinding methods for patients and providers and 2 stated outcome assessors were blinded. Thirteen trials were rated as having low risk for attrition bias and only 4 trials had low risk of reporting bias.[2] Safety outcomes included the proportion of patients who withdrew due to adverse events, proportion of patients who completed the trial, and proportion of patients who experienced common adverse effects of stimulants. Due to a lack of direct comparative trials for ADHD drugs, subgroup analyses were conducted to estimate the treatment effects and relative safety based on the type of stimulant and formulation. Because trial outcomes were recorded with different scales and metrics, results were reported using standard mean difference (SMD) with lower numbers indicating a lower frequency of events and higher numbers associated with more events. The total ADHD symptom score based on parent ratings was similar between dexamphetamine (SMD -0.60, 95% CI -1.36 to 0.16), lisdexamfetamine (SMD -0.72, 95% CI -1.59 to 0.14), and mixed amphetamine salts (SMD -0.44, 95% CI -0.63 to -0.24).[2] Similar results were observed for other measures of efficacy and safety with no difference between stimulants. Only one subgroup analysis (the proportion of patients who experienced a decrease in appetite) demonstrated statistically significantly different results for formulations of dexamphetamine (RR 1.41, 95% CI 0.95 to 2.11), lisdexamfetamine (RR 9.83, 95% CI 5.08 to 19.02), and mixed amphetamine salts (RR 6.42, 95% CI 1.56 to 26.52) compared to placebo.[2] Analysis was limited by high heterogeneity between trials (I^2=86%).[2] Similarly, subgroup analysis between long- and short-acting formulations found no difference in academic performance, proportion of responders, and ADHD symptom score based on parent ratings. Analysis of patient retention was significantly different between long-acting (RR 1.11, 95% CI 1.00 to 1.24) and short-acting formulations (RR 0.98, 95% CI 0.95 to 1.01; p=0.03 for subgroup differences, I^2=0.78%).[2] The proportion of patients experiencing a decreased appetite was also higher for extended release formulations (RR 7.67, 95% CI 3.33 to 17.65) compared to short-acting formulations (RR 1.58, 95% CI 0.69 to 3.62; p=0.008 for subgroup differences, I^2=0.86%).[2] The absolute differences between formulations was not reported. Subgroup analyses for other safety outcomes demonstrated no differences between groups. Results from these analyses should be interpreted with caution due to use of indirect comparisons, high heterogeneity between trials, and unclear risk of bias for many trials.[2]

In 2017, AHRQ published a report of medications for children with autism spectrum disorder.[3] The review evaluated comparative studies of patients age 2 to 12 years of age with at least 10 participants. A total of 5 RCTs (n=265) assessing methylphenidate (n=2), atomoxetine (n=2) or guanfacine (n=1) were included in the review.[3] Overall, included trials had low to moderate risk of bias. Authors concluded that compared to placebo, methylphenidate and atomoxetine improved hyperactivity and other challenging behaviors in patients with autism spectrum disorder though strength of evidence was low.[3] Data was limited by small study size, short treatment duration, significant placebo effect, and inconsistency in results reported by parents and teachers. The most common adverse effects associated with treatment were irritability, gastrointestinal symptoms, drowsiness, and decreased appetite.[3] There was insufficient data to examine differences between agents or to evaluate outcomes for guanfacine.

A systematic review funded by the National Institute for Health Research in the United Kingdom evaluated 70 RCTs or controlled before-and-after studies which examined effectiveness of pharmacotherapy for tics in children and adolescents with Tourette's syndrome.[1] The review included 7 placebo-controlled studies examining efficacy of clonidine (as oral or patch formulations), 2 studies of guanfacine, and one study of atomoxetine.[1] Results were reported as standardized

mean differences (SMD) which allows for comparison of trials which use different scales or metrics to evaluate symptom severity. Authors conclude there was moderate-quality evidence suggesting oral clonidine had a medium to large effect on tic severity (SMD -0.71, 95% CI -1.10 to -0.31) and impairment (SMD -0.54, 95% CI -0.93 to -0.16) compared to placebo after 12 to 16 weeks of treatment.[1] However, results from one large study comparing clonidine patch to placebo over 4 weeks provided moderate quality evidence of no difference in tic improvement compared to placebo.[1] There was moderate quality evidence that guanfacine demonstrated a large impact on tic severity (SMD -0.73, 95% CI -1.26 to -0.20) compared to placebo with 4 to 8 weeks of treatment.[1] One trial (n=145) provided moderate quality evidence that atomoxetine given for 18 weeks was associated with small to moderate symptom improvement (SMD -0.54 to -0.63) but had higher rates of decreased appetite and nausea.[1] The efficacy and safety of stimulants in children with comorbid ADHD and tic disorders was also examined for methylphenidate (3 trials), combination methylphenidate and clonidine (1 trial), and dexmethylphenidate (1 trial).[1] The primary goal of these studies was to identify if use of stimulants worsened tic disorders. There was very low quality evidence suggesting stimulants did not significantly impact tic severity or impairment (SMD -0.30, 95% CI -0.76 to 0.15; p=0.83) compared to placebo.[1] Direct comparisons included 3 RCTs comparing clonidine to levetiracetam, risperidone, and haloperidol. No differences were noted in clinical efficacy of clonidine compared to these agents.[1] Evidence was of low or very low quality and limited by small population size, high risk of bias and imprecision.[1] Overall, due to the limited number of trials and low quality of evidence, authors conclude that further research is needed to assess differences in efficacy and safety of treatment options for treatment of tic disorders and Tourette's syndrome.[1]

In 2016, CADTH conducted a systematic review to examine the clinical effectiveness of combination treatment (ie a long-acting stimulant or non-stimulant medication combined with a short-acting stimulant) for adults with ADHD.[15] Systematic reviews, meta-analyses, non-randomized studies, and RCTs were considered for the review. No studies were identified which compared combination treatment to placebo or monotherapy with a long-acting or short-acting stimulant in adults with ADHD.

New Guidelines:

A 2016 CADTH rapid response review examined recommendations from evidence based guidelines for the pharmacological treatment of ADHD in children, adolescents or adults.[4] Three guidelines from the British Association for Psychopharmacology, American Academy of Pediatrics, and Academy of Medicine/Singapore/Ministry of Health met inclusion criteria and were assessed for quality using the AGREE II tool.[4] All 3 guidelines addressed treatment in children and adolescents, and comparisons included both pharmacologic and non-pharmacologic interventions. Pharmacological treatments were broadly defined as stimulant and non-stimulant treatment options. All 3 guidelines recommended non-pharmacological interventions as first-line treatment for children with ADHD, followed by pharmacological treatment in children with moderate symptoms who fail to respond to psychosocial or behavioral interventions.[4] Overall, guidelines recommend stimulant medications as first-line therapy for children and adolescents with ADHD (strong recommendation).[4] Only one guideline addressed treatment of ADHD in adults, recommending stimulants as first-line treatment in adults with ADHD.[4] Guidelines recommend atomoxetine as an initial treatment in patient with a risk of abuse or misuse (strong recommendation) and patients for whom stimulants are contraindicated, ineffective, or not tolerated.[4] Two guidelines also had recommendations for extended-release stimulant formulations instead of immediate-release formulations in patients with a history of abuse of misuse (based on weak evidence).[4] All guidelines also noted that there was insufficient evidence for simultaneous use of stimulant and non-stimulant medication in patients with ADHD.[4] Guidelines included in this review were limited as one guideline (Academy of Medicine/Singapore/Ministry of Health) did not provide adequate description of the development process, sources of evidence, or conflicts of interest for participating members involved in the guideline development.[4] Members involved in development for the other guidelines declared consultation fees, honoraria for speaking, research grants, or conference support from pharmaceutical companies.[4]

In 2016, NICE updated guidelines for prevention, assessment and management of mental health problems in people with learning disabilities.[5] Pharmacologic therapy is commonly used in patients with learning disabilities and concomitant psychiatric diagnosis and/or challenging behavior (defined as behavior with intensity, frequency, or duration which threatens the safety of the patient or threatens other people, or restricts access to community facilities).[5] Very few RCTs examined efficacy of ADHD medications in this population and evidence was limited by small sample sizes, imprecision, and high risk of bias. Moderate quality evidence from a single RCT demonstrated that methylphenidate improved ADHD symptoms and hyperactivity score after 16 weeks of treatment.[5] Adverse effects from treatment included poor appetite, weight loss and difficulty sleeping. There was low quality evidence that compared to methylphenidate, behavioral interventions were more effective at improving ADHD symptoms including motor activity, disruptive behavior and academic engagement.[5] There was insufficient evidence to draw conclusions for other drugs or for other outcomes. The guideline committee concluded that behavior modification was likely more effective than pharmacotherapy and that the available evidence in patients with learning disabilities supported recommendations regarding treatment of ADHD.[5] No specific recommendations were made for this subpopulation of patients.[5]

New Formulations or Indications:
In January 2017, lisdexamfetamine (Vyvanse®) chewable tablets were FDA approved for treatment moderate to severe binge eating disorder (BED) in adults and ADHD in adult and pediatric patients.[16] Approval was based on bioequivalence studies compared to lisdexamfetamine capsules.

In June 2017, a new formulation of methylphenidate extended release orally disintegrating tablet (Cotempla XR-ODT®) was FDA approved for treatment of ADHD in pediatric patients 6 to 17 years of age.[12] Cotempla XR-ODT is available as 8.6, 17.3 and 25.9 mg orally disintegrating tablets and was approved on the basis of a single double-blind, placebo-controlled RCT.[12] The trial included an open-label dose optimization period before randomization in which all patients were initially started on 17.3 mg of methylphenidate-XR-ODT and titrated to an optimal dose (maximum 51.8 mg).[12] After the dose-optimization period (5 weeks total), patients were randomized to the individually optimized dose of Cotempla or placebo for a 1 week period.[12] The primary endpoint for this study was the average of the SKAMP-Combined rating scale over the course of the testing day (from 1 to 13 hours post-dose).[12] The SKAMP rating scale is a teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting. Scores assess 13-items and range from 0 to 78 with higher scores indicating more severe impairment.[12] Baseline scores at randomization were 21.1 and 20.4 points for methylphenidate and placebo groups, respectively.[12] Compared to placebo, patients randomized to methylphenidate had an average SKAMP-combined score of 14.3 points which was statistically significant compared to placebo (25.3 points; mean difference [MD] -11.0; 95% CI-13.9 to -8.2).[12] Largest differences in score were apparent at 3 hours post-dose and were no longer statistically significant compared to placebo by 13 hours post-dose.[12]

A new formulation of mixed amphetamine salts (Mydayis®) was FDA approved in June 2017 for ADHD in patients greater than 13 years of age.[14] In clinical trials, patients younger than 13 years of age had higher plasma concentrations and experienced more adverse effects than older adolescents when given the same dose.[14] Mydayis extended release capsules include amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate and are available as 12.5 mg, 25 mg, 37.5mg and 50 mg capsules.[14] This new formulation was approved on the basis of 2 short-term, multicenter, placebo-controlled, double-blind, RCTs in adult (n=275) and pediatric patients age 13 to 17 years (n=157).[14] The primary endpoint for these trials was change in the ADHD-rating scale from baseline to 4 weeks. Adult patients meeting DSM-5 criteria for ADHD were randomized in a 1:1:1 ratio to 12.5 mg daily, initial 12.5 mg daily with forced-titration to 37.5 mg daily, or placebo.[14] Mean baseline score for adult patients was 40 points indicating relatively severe symptoms (total possible range of 0 to 54 points). In patients randomized to mixed amphetamine salts, the mean change in the ADHD rating scale from baseline was -18.5 and -23.8 points compared to placebo (-10.4 points).[14] The mean difference compared to placebo was -8.1 points (95% CI -11.7 to -4.4) in patients given 12.5 mg and -13.4 points (95% CI -17.1 to -9.7) in patients titrated to 37.5 mg daily.[14] Pediatric patients who met DSM-4 TR criteria for ADHD were randomized to placebo or 12.5 mg of mixed amphetamine salts with titration to an optimal dose (maximum 25 mg daily).[14] The mean baseline score for the ADHD-rating scale-IV was 36-

37 points.[14] Patients randomized to mixed amphetamine salts had a mean improvement of 20.3 points compared to a mean 11.6 point improvement with placebo (MD compared to placebo of -8.7 points [95% CI -12.6 to -4.8]).[14] Results were statistically significant compared to placebo, though p-values were not reported. Supporting evidence also included 3 single-dose, double-blind, placebo-controlled, crossover RCTs in adult (n=2) and pediatric (n=1) patients.[14] The primary endpoint for these studies was the Permanent Product Measure of Performance (PERMP) which evaluates attention using a skill-adjusted math test. The total PERMP score is a sum of the number of math problems attempted and the number answered correctly. Assessments were evaluated at 2, 4, 8, 14 and 16 hours post-dose.[14] In adult patients, PERMP scores were statistically significant compared to placebo at 4 to 16 hours in patients given 25 mg and at 2 to 16 hours in patients given 50 mg (MD compared to placebo of 19.3 points [95% CI 10.9 to 27.6] and 18.4 [95% CI 11.3 to 25.5] for 25 and 50 mg, respectively).[14] In pediatric patients, patients randomized to amphetamine salts had a mean change from baseline of 272.7 points compared to 231.4 points in patients randomized to placebo (MD 41.3 points, 95% CI 32.2 to 50.3).[14]

New FDA Safety Alerts:
In 2017, product labeling for stimulants including lisdexamfetamine, amphetamine, methamphetamine, dextroamphetamine, and mixed amphetamine salts was updated to specify that these product are contraindicated in patients taking concomitant monoamine oxidase inhibitors (MAOI) or within 14 days of stopping a MAOI due to an increased risk of hypertensive crisis.[8] Warnings included risk for serotonin syndrome when taken in combination with other serotonergic medications. Labeling for mixed amphetamine salts, amphetamine, and dextroamphetamine were also updated to include contraindications in patients with previous hypersensitivity reactions to other amphetamine products.[8]

In February 2017, product labeling for methylphenidate hydrochloride products, QuilliChew ER and Quillivant XR, was revised to emphasize serious cardiovascular reactions including stroke and myocardial infarction in children and adolescents with structural cardiac abnormalities or in adults taking CNS stimulants at doses recommended for ADHD.[8]

Randomized Controlled Trials:
A total of 105 citations were manually reviewed from the initial literature search. After further review, 103 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Outcome	Results
Snircova E, et al. 2016.[6] AC, RCT N=78 Duration: 8 weeks	1. Atomoxetine - For <70kg: 0.5 mg/kg/day titrated to 0.8-1.2 mg/kg/day - For ≤70 kg: 40 mg titrated to 80 mg daily 2. Methylphenidate ER 5 mg titrated to 40 mg daily if needed	Patients 5-16 years of age with ADHD	ADHD rating scale IV at 8 weeks (range 0-54 with larger numbers indicating more severe disease) Conners Parent Rating Scale for anxiety at 8 weeks	ADHD rating scale-IV (mean, SD) 1. 20.44 (11.86) 2. 22.73 (9.80) p=0.389 Conners Parent Rating Scale for anxiety 1. 3.22 (3.49) 2. 5.54 (4.26) p=0.015

Nagy P, et al. 2016.[7] DB, AC, PG, RCT N=267 Duration: 9 weeks	1. Lisdexamphetamine 30 mg/day titrated to 70 mg as needed 2. Atomoxetine - For ≤70 kg: 40 mg/day titrated to 100 mg as needed - For <70kg: 1.2 mg/kg/day titrated to 1.4 mg/kg/day if needed	Patients 6-17 years of AGE with ADHD and inadequate response to methylphenidate	Mean change in Weiss Functional Impairment Rating Scale-Parent Report (range 0-3) at 9 weeks	1. -0.37 (95% CI -0.44 to -0.30) 2. -0.30 (95% CI -0.36 to -0.23) p-value NR

Abbreviations: AC = active-controlled; DB = double-blind, NR = not reported; PG = parallel group; RCT = randomized clinical trial; SD = standard deviation.

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Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL
CAPSULE	STRATTERA	ATOMOXETINE HCL	Y
CAPSULE	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	Y
CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	DEXMETHYLPHENIDATE HCL	Y
CPBP 50-50	FOCALIN XR	DEXMETHYLPHENIDATE HCL	Y
PATCH TD24	DAYTRANA	METHYLPHENIDATE	Y
TABLET	ADDERALL	DEXTROAMPHETAMINE/AMPHETAMINE	Y
TABLET	DEXTROAMPHETAMINE-AMPHETAMINE	DEXTROAMPHETAMINE/AMPHETAMINE	Y
TABLET	FOCALIN	DEXMETHYLPHENIDATE HCL	Y
TABLET	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	Y
TABLET	RITALIN	METHYLPHENIDATE HCL	Y
TAB ER 12H	CLONIDINE HCL ER	CLONIDINE HCL	Carve-out
TAB ER 12H	KAPVAY	CLONIDINE HCL	Carve-out
TAB ER 24H	GUANFACINE HCL ER	GUANFACINE HCL	Carve-out
TAB ER 24H	INTUNIV	GUANFACINE HCL	Carve-out
CAP ER 24H	ADDERALL XR	DEXTROAMPHETAMINE/AMPHETAMINE	N
CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	DEXTROAMPHETAMINE/AMPHETAMINE	N
CAPSULE ER	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	DEXTROAMPHETAMINE SULFATE	N
CPBP 30-70	METHYLPHENIDATE HCL CD	METHYLPHENIDATE HCL	N
CPBP 30-70	METHYLPHENIDATE HCL ER	METHYLPHENIDATE HCL	N
CPBP 50-50	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
CPBP 50-50	METHYLPHENIDATE LA	METHYLPHENIDATE HCL	N
CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	N
CSBP 40-60	APTENSIO XR	METHYLPHENIDATE HCL	N
SOLUTION	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
SOLUTION	METHYLIN	METHYLPHENIDATE HCL	N
SOLUTION	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
SOLUTION	PROCENTRA	DEXTROAMPHETAMINE SULFATE	N
SU ER RC24	QUILLIVANT XR	METHYLPHENIDATE HCL	N
SUS BP 24H	DYANAVEL XR	AMPHETAMINE	N
TAB CBP24H	QUILLICHEW ER	METHYLPHENIDATE HCL	N
TAB CHEW	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
TAB CHEW	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	N
TAB ER 24	CONCERTA	METHYLPHENIDATE HCL	N
TAB ER 24	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
TAB RAP BP	ADZENYS XR-ODT	AMPHETAMINE	N

TABLET	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
TABLET	DEXMETHYLPHENIDATE HCL	DEXMETHYLPHENIDATE HCL	N
TABLET	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
TABLET	EVEKEO	AMPHETAMINE SULFATE	N
TABLET	METHAMPHETAMINE HCL	METHAMPHETAMINE HCL	N
TABLET	ZENZEDI	DEXTROAMPHETAMINE SULFATE	N
TABLET ER	METADATE ER	METHYLPHENIDATE HCL	N
TABLET ER	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N

Nagy P, Hage A, Coghill DR, et al. Functional outcomes from a head-to-head, randomized, double-blind trial of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder and an inadequate response to methylphenidate. *Eur Child Adolesc Psychiatry.* 2016;25(2):141-149.

Attention-deficit/hyperactivity disorder (ADHD) is associated with functional impairments in multiple domains of patients' lives. A secondary objective of this randomized, active-controlled, head-to-head, double-blind, dose-optimized clinical trial was to compare the effects of lisdexamfetamine dimesylate (LDX) and atomoxetine (ATX) on functional impairment in children and adolescents with ADHD. Patients aged 6-17 years with an ADHD Rating Scale IV total score >= 28 and an inadequate response to methylphenidate treatment (judged by investigators) were randomized (1:1) to once-daily LDX or ATX for 9 weeks. Parents/guardians completed the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) at baseline and at week 9 or early termination. p values were nominal and not corrected for multiple comparisons. Of 267 randomized patients, 200 completed the study (LDX 99, ATX 101). At baseline, mean WFIRS-P total score in the LDX group was 0.95 [standard deviation (SD) 0.474; 95% confidence interval (CI) 0.87, 1.03] and in the ATX group was 0.91 (0.513; 0.82, 1.00). Scores in all WFIRS-P domains improved from baseline to endpoint in both groups, with least-squares mean changes in total score of -0.35 (95% CI -0.42, -0.29) for LDX and -0.27 (-0.33, -0.20) for ATX. The difference between LDX and ATX was statistically significant ($p < 0.05$) for the Learning and School (effect size of LDX vs ATX, 0.43) and Social Activities (0.34) domains and for total score (0.27). Both treatments reduced functional impairment in children and adolescents with ADHD; LDX was statistically significantly more effective than ATX in two of six domains and in total score.

Snircova E, Marcincakova-Husarova V, Hrtanek I, Kulhan T, Ondrejka I, Nosalova G. Anxiety reduction on atomoxetine and methylphenidate medication in children with ADHD. *Pediatr Int.* 2016;58(6):476-481.

BACKGROUND: Atomoxetine and methylphenidate are widely used to treat attention-deficit-hyperactivity disorder (ADHD) with similar effectiveness after 8 weeks of treatment, when atomoxetine has reached its a full effect. Both drugs have also been shown to have an effect on comorbid anxiety. To the best of our knowledge, no study has compared their effect on the dynamics of anxiety symptom reduction. The aim of this study was to compare the medication effect on core and comorbid anxiety symptom dynamics in children with ADHD.
METHODS: Sixty-nine patients participated in the study: 36 patients were taking atomoxetine and 33 patients, methylphenidate. Therapeutic effect on core symptoms of ADHD was measured on the ADHD-rating scale IV, and symptoms of anxiety were measured using the Conners Parent Rating Scale (CPRS). Symptoms were measured prior to and every 2 weeks during 8 weeks of treatment.
RESULTS: There was a significant decrease in CPRS anxiety subscale score in both medication groups. Anxiety subscale score was significantly lower in the atomoxetine group in the fourth week, and lasted through to 8 weeks of medication.
CONCLUSION: Both atomoxetine and methylphenidate reduced the symptoms of ADHD and anxiety. Atomoxetine was more effective in anxiety symptom reduction from the fourth week of treatment.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 4 2017**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update**

1	exp Atomoxetine Hydrochloride/	1402
2	exp methylphenidate/ or dexmethylphenidate hydrochloride/	7918
3	Amphetamines/	6843
4	exp Methylphenidate/ or exp Amphetamines/ or exp Dextroamphetamine/ or exp Lisdexamfetamine Dimesylate/	46290
5	exp Clonidine/	13809
6	Guanfacine/	745
7	exp Methamphetamine/	10178
8	1 or 2 or 3 or 4 or 5 or 6 or 7	16210
9	limit 8 to (english language and humans)	28312
10	limit 9 to yr="2016 -Current"	1341
11	limit 10 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	352
12	exp Attention Deficit Disorder with Hyperactivity/	31902
13	adhd.mp.	26773
14	exp "Attention Deficit and Disruptive Behavior Disorders"/	36480
15	12 or 13 or 14	42845
16	11 and 15	105

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

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

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS			NON-STIMULANTS		
Indication	**Methylphenidate and derivatives**	**Amphetamine and derivatives**	**Lisdexamphetamine**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years	Age ≥3 years	**Age ≥6 years**	Age ≥6 years	Children age 6-17 years only	Children age 6-17 years only
Narcolepsy	Age ≥6 years	Age ≥6 years	**Not approved**	Not approved	Not approved	Not approved
Moderate to Severe Binge Eating Disorder	**Not approved**	**Not approved**	**Age ≥18 years**	**Not approved**	**Not approved**	**Not approved**

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg

CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	Combination therapy not recommended
Age 6-17 years*	1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA 1 CNS Stimulant Formulation (LA or IR) + Clonidine LA
Age ≥18 years**	Combination therapy not recommended

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)
* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the treated diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4

Approval Criteria		
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA indication defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *9/17 (SS); 5/16; 3/16 (AG); 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

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Literature Scan: Parenteral Antipsychotics

Date of Review: September 2017

Date of Last Review: September 2016
Literature Search: July 22, 2017

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

Conclusions:
- Since the last literature scan one new systematic review has been published to compare the safety and tolerability of oral antipsychotics to long acting injectable versions of the same drug.[1] There were no significant differences between long acting injectable agents and oral antipsychotics on the incidence of serious adverse events or treatment discontinuation due to adverse events.[1]

Recommendations:
- No further review or research needed at this time.
- Evaluate comparative costs in executive session.

Previous Conclusions:
- One new high quality systematic review was published since the parenteral antipsychotic agents were last reviewed in May 2016. Otherwise, no new clinical practice guidelines, formulations, indications, or safety alerts were identified.
- One systematic review with meta-analysis specifically evaluated long-acting injectable risperidone. Evidence shows the drug may have similar efficacy and harms as oral second-generation antipsychotics and other long-acting parenteral antipsychotics.
- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

Previous Recommendations:
- No further review or research needed at this time.
- After comparison of drug costs in the executive session, add Abilify Maintenna (aripiprazole) extended-release injectable suspension and Aristada (aripiprazole lauroxil) extended-release injectable suspension to the Oregon Health Plan fee-for-service Preferred Drug List contingent upon executed supplemental rebates.

Background:

Schizophrenia is the most common psychotic disease, with a global prevalence of less than 1%.[2] However, because it is disabling condition that adversely impacts productivity, it is ranked by the World Health Organization as one of the top 10 illnesses that contributes to global burden of disease.[2] In a 2010 study, the mean annual health care costs of an American patient with schizophrenia were estimated at approximately $15,000 per year.[3] Schizophrenia is slightly more common in men compared to women. Symptom onset generally occurs between late adolescence and the third decade of life. Schizophrenia is characterized by positive symptoms (delusions and hallucinations), negative symptoms (impaired motivation and social withdrawal) and cognitive impairment.[4] The positive symptoms tend to relapse and remit. The negative and cognitive symptoms tend to be chronic and can have a long term impact on social function. The most effective treatment for schizophrenia is a multipronged approach including medication, psychological treatment and social support.

First line medication treatments for schizophrenia are either first generation antipsychotics (FGA) or second generation antipsychotic (SGA) agents. The FGA parenteral antipsychotics include chlorpromazine, fluphenazine, and haloperidol while SGA parenteral antipsychotics include aripiprazole, olanzapine, paliperidone, risperidone and ziprasidone. Long-acting injection (LAI) depot preparations of antipsychotics are widely used, especially for treating patients who show non-adherence or partial adherence to oral therapy. The proposed benefits of LAI's are their relapse-preventing properties, patient convenience, and improved compliance.[5] Drug adherence is essential in improving clinical and social outcomes in schizophrenia. The dosing and administration of the long acting parenteral antipsychotic agents is presented in **Table 1**. Chlorpromazine and ziprasidone are not available as long acting parenteral agents and are used to manage acute symptoms in schizophrenic patients.

In 2012 an Agency for Healthcare Research and Quality (AHRQ) systematic review evaluated the comparative benefits and harms of FGAs to SGAs in treating schizophrenia and found there were few differences in total symptom score improvement between the 2 classes of drugs.[6] The FGAs are dopamine antagonists while the SGAs are partial dopamine antagonists but also block serotonin and norepinephrine.[7] It is the differences in pharmacologic activity that are appear to results in different adverse effect profiles between the 2 generations of antipsychotics. The FGAs appear to cause more extrapyramidal symptoms while the SGAs seem to cause more weight gain and metabolic changes (hyperglycemia and lipid abnormalities).[7]

In Oregon, drugs for mental health conditions, including antipsychotics, are exempt from the traditional Preferred Drug List (PDL) and prior authorization (PA) requirements. However, specific clinical PA criteria may be placed to restrict medically inappropriate use or to address specific safety risks. In the second quarter of 2017 (April 1, 2017 through July 1, 2017) there were total of 2070 claims for the long acting parenteral antipsychotics. The most utilization was seen with Invega Sustenna (37%) followed by Risperdal Consta (20%), Abilify Maintena (18%), and Haloperidol Decanoate (15%). Minimal utilization of Fluphenazine Decanoate, Invega Trinza or Aristada was noted. Similar trends were observed in the first quarter of 2017. Most LAI's are administered once a month except for Risperdal Consta which must be administered twice a month. Aristada may be administered every 4, 6 or 8 weeks depending on the dose and Invega Trinza is given every 3 months.

Table 1. Dosing and Administration of Long Acting Parenteral Antipsychotics[8]

	Aripiprazole extended release	Aripiprazole lauroxil	Fluphenazine decanoate	Haloperidol decanoate	Olanzapine pamoate	Paliperidone palmitate (4-week)	Paliperidone palmitate (12-week)	Risperidone microspheres
Brand name	Abilify Maintena	Aristada	Prolixin	Haldol Decanoate	Zyprexa Relprevv	Invega Sustenna	Invega Trinza	Risperdal Consta
Injection interval	4 weeks	4 weeks (662 mg) 6 weeks (882 mg) 8 weeks (1064 mg)	2 to 4 weeks	4 weeks	2 to 4 weeks	4 weeks	12 weeks	2 weeks
Available dosage strengths	300 mg 400 mg	441 mg 662 mg 882 mg 1064 mg	25 mg/mL (variable dose)	50 mg/mL 100 mg/mL (variable dose)	210 mg 300 mg 405 mg	39 mg 78 mg 117 mg 156 mg 234 mg	273 mg 410 mg 546 mg 819 mg	12.5 mg 25 mg 37.5 mg 50 mg
Dose range (adult)¶	200 to 400 mg	441 to 1064 mg	12.5 to 100 mg	20 to 450 mg	150 to 405 mg	39 to 234 mg	273 to 819 mg	12.5 to 50 mg
Maximum recommended dose	400 mg every 4 weeks	882 mg every 4 weeks	100 mg every 2 weeks	450 mg every 4 weeks	300 mg every 2 weeks	234 mg every 4 weeks	819 mg every 12 weeks	50 mg every 2 weeks
Injection site	Deltoid or gluteal	Deltoid (441 mg only)	Gluteal	Gluteal	Gluteal	Deltoid only (load)	Deltoid or gluteal	Deltoid or gluteal

		Gluteal (441, 662, 882, or 1064 mg)				Deltoid or gluteal (maintenance)		
Injection technique	Standard	Standard	Z-Track	Z-Track	Standard	Standard	Standard	Standard

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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:
A meta-analysis and systematic review evaluated randomized controlled trials (RCTs) to assess the safety and tolerability of LAIs versus oral antipsychotics (OAPs).[1] Given that LAIs are administered in large single doses that cannot be rapidly discontinued there was concern that LAIs are underutilized due to the risk of possible adverse effects.[9] Only RCTs that randomized patients to the same antipsychotic, either as an LAI or OAP, were included in the analysis. The primary outcome was treatment discontinuation due to adverse events in trials that were conducted for at least 8 weeks (mean duration=52 weeks). Secondary outcomes included serious adverse events, death, greater than one adverse event and individual adverse event rates.[1]
Sixteen RCTs evaluating treatment of schizophrenia with antipsychotic therapy (n=4902) were included in the analysis. The studies were of low to moderate quality due to unclear randomization and blinding of outcome assessors which increased the risk of selection and detection biases. However, the systematic review was evaluated as having good methodological quality using the AMSTAR tool.[10]

Treatment discontinuation due to adverse events was not significantly different between LAIs and OAPs (RCTs = 14, n = 3570, relative risk (RR) 1.163, 95% confidence interval (CI) 0.88–1.52, p = 0.275).[1] The incidence of serious adverse events was not significantly different between LAIs and OAPs (RR 0.907, 95% CI 0.66–1.24, p = 0.542).[1] Altogether, 3 deaths occurred in the LAI groups (n = 2311) and 6 deaths occurred in the OAP group (n = 1816), without significant group difference (RR 0.613, 95% CI 0.17–2.12, p = 0.441).[1] The incidence of patients with at least one adverse event was not significantly different between LAIs and

OAPs (RR 1.026, 95% CI 0.98–1.07, p = 0.231).[1] With respect to specific adverse effects, LAIs were associated with significantly more akinesia (RR 20.54, 95% CI 1.24–337.94, p = 0.034, NNH = 3), low-density lipoprotein cholesterol increases (standardized mean difference (SMD) 0.096, 95% CI 0.006–0.18, p = 0.037) and anxiety (RR 1.495, 95% CI 1.13–1.97, p = 0.005, NNH = 40) compared to OAPs.[1] Conversely, LAIs were associated with significantly lower prolactin change (SMD − 0.152, 95% CI − 0.26 to − 0.043, p = 0.006) then OAPs. This meta-analysis concluded there were no significant differences between LAIs and OAPs on the incidence of serious adverse events or treatment discontinuation due to adverse events.

New Guidelines: No new guidelines have been published since the last literature scan.

New FDA Drug Approvals: No new drugs have been FDA approved since the last literature scan.

New Formulations/Indications:
The Food and Drug Administration (FDA) approved Abilify Maintena® for maintenance monotherapy treatment of bipolar I disorder in adults as of July 2017. The approval is based on RCT findings that indicated extended release injections of aripiprazole delayed time to recurrence of mood episode in adults with manic episodes.[11] To assess efficacy and safety of aripiprazole once-monthly (AOM) 400 mg injection, researchers conducted a 52-week, phase 3, double-blind, randomized withdrawal trial among adults with bipolar I disorder who experienced a manic or mixed episode that required hospitalization. The primary endpoint was time from randomization to recurrence of any mood episode. Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study.[11] The researchers imputed the data from patients who discontinued therapy using 3 different sensitivity analyses including a worst case analysis which assumed discontinued patients were to have recurrences one day after discontinuation.
AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo over one year (hazard ratio 0.45; 95% CI 0.30 to 0.68; P<0.0001).[11] Significantly fewer patients (P<0 .0001) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%) over 52 weeks, with the effects observed predominantly on manic episodes (P<0.0001).[11] Treatment-emergent adverse events which were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety (total incidence >5%).[11] During the stabilization phase (transition from oral tablets to long acting injectable agent), treatment-emergent adverse events included akathisia (17.4%), weight increase (11.1%), insomnia (9.6%), anxiety (7.1%), restlessness (5.6%), fatigue (5.2%), and nasopharyngitis (5.2%).[11]

A new dosing regimen for Aristada® (aripiprazole laurixil) was FDA approved for every 2 months as of June 2017.[12] Prior to the latest approval, aripiprazole laurixil was only approved to be administered intramuscularly in doses ranging from 441, 662, or 882 mg every month or 882 mg every 6 weeks. A 1064 mg/3.9 ml strength kit designed to be administered every 2 months is now being marketed by the manufacturer. Tolerability to oral aripiprazole should be established before initiating treatment with long acting injectable doses of aripiprazole.

New FDA Safety Alerts:

The labeling for Invega Sustenna® (paliperidone palmitate) was updated to include long term data on hyperprolactinemia associated with paliperidone palmitate therapy in June 2017.[13] Data was obtained from one 33 week double blind placebo controlled trial in patients with schizophrenia. Four females (4.2%) in the paliperidone palmitate group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menstruation irregular N=1), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1).[13] One male (0.9%) in the paliperidone palmitate group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.[13]

In another trial conducted in patients with schizoaffective disorder over 15 months, 11 females (13.9%) with elevated prolactin levels in the paliperidone palmitate group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3). Only 5 females (5.8%) in the placebo group had 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1).[13] Six males (7.1%) in the paliperidone palmitate group experienced 6 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) in the placebo group experienced adverse reaction of increased blood prolactin.[13]

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Appendix 1: Current Status on Preferred Drug List

Brand	Generic	Route	Formulation	PDL	Carve out
CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	INJECTION	AMPUL	Y	Y
FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	INJECTION	VIAL	Y	Y
FLUPHENAZINE HCL	FLUPHENAZINE HCL	INJECTION	VIAL	Y	Y
HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	INTRAMUSC	VIAL	Y	Y
HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	INTRAMUSC	AMPUL	Y	Y
HALDOL	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y	Y
HALOPERIDOL	HALOPERIDOL LACTATE	INJECTION	AMPUL	Y	Y
HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	INJECTION	VIAL	Y	Y
RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	INTRAMUSC	SYRINGE	Y	Y
ABILIFY MAINTENA	ARIPIPRAZOLE	INTRAMUSC	SUSER VIAL	Y	Y
ABILIFY MAINTENA	ARIPIPRAZOLE	INTRAMUSC	SUSER SYR	Y	Y
ARISTADA	ARIPIPRAZOLE LAUROXIL	INTRAMUSC	SUSER SYR	Y	Y
OLANZAPINE	OLANZAPINE	INTRAMUSC	VIAL	V	Y
ZYPREXA	OLANZAPINE	INTRAMUSC	VIAL	V	Y
GEODON	ZIPRASIDONE MESYLATE	INTRAMUSC	VIAL	V	Y
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	INTRAMUSC	SYRINGE	V	Y
INVEGA TRINZA	PALIPERIDONE PALMITATE	INTRAMUSC	SYRINGE	V	Y
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	INTRAMUSC	VIAL	V	Y

Appendix 2: New Clinical Trials

A total of 18 citations were manually reviewed from the literature search. After further review, 17 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. The full abstract is included in **Appendix 3**.

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Calabrese JR et al[11] DB, PC, MC, RCT 52 weeks	AOM 400mg IM Vs. Placebo IM once monthly	Men and women aged 18-65 years with a diagnosis of BP-1 with ≥ 1 manic or mixed episode requiring hospitalization and treatment N = 266 enrolled, 102 (38.3%) completed the study	Time to recurrence of any mood episode in patients with BP-1	Time to recurrence over 1 year - AOM 400 vs PBO HR = 0.45; 95% CI 0.30 to 0.68 p < 0.0001 Proportion of patients with mood episode recurrence AOM 400 mg 35/132 (26.5%) PBO 68/133 (51.1%) P<0.0001 (CI not reported)

Abbreviations: AOM = aripiprazole once monthly; BP-1 = bipolar disorder type I; CI = confidence interval; DB =double blind; HR = hazard ratio; MC = multi-center; PBO = placebo; PC = placebo controlled; RCT = randomized controlled trial

Appendix 3: Abstracts of Clinical Trials

1. Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, Perry P, Hertel P, Such P, Salzman PM, McQuade RD, Nyilas M, Carson WH. J Clin Psychiatry. 2017 Mar; 78(3):324-331. doi: 10.4088/JCP.16m11201.

OBJECTIVE:
To evaluate efficacy, safety, and tolerability of long-acting injectable antipsychotic aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment for bipolar I disorder (BP-I).

METHODS:
In a double-blind, placebo-controlled, 52-week randomized withdrawal study conducted from August 2012 to April 2016, patients with a DSM-IV-TR diagnosis of BP-I currently experiencing a manic episode were stabilized sequentially on oral aripiprazole and AOM 400 and then randomized to AOM 400 or placebo. The primary end point was time from randomization to recurrence of any mood episode. Other end points included proportion of patients with recurrence of any mood episode and recurrence by mood episode type.

RESULTS:
Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study. AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio: 0.45; 95% CI, 0.30 to 0.68; P < .0001). Significantly fewer patients (P < .0001) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%), with the effects observed predominantly on manic episodes (P < .0001). Patients were not depressed at study entry, and between-group differences in depressive episodes were not significant (P < .864). The treatment-emergent adverse events (incidence > 5%) that were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety.

CONCLUSIONS:
AOM 400 delayed the time to and reduced the rate of recurrence of mood episodes and was generally safe and well tolerated. These findings support the use of AOM 400 for maintenance treatment of BP-I.

TRIAL REGISTRATION:
ClinicalTrials.gov identifier: NCT01567527.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 3 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July

1	exp Chlorpromazine/	1571
2	exp Haloperidol/	5624
3	exp Fluphenazine/	294
4	exp Aripiprazole/	1909
5	exp Paliperidone Palmitate/	600
6	exp Risperidone/	5385
7	olanzapine.mp.	8001
8	1 or 2 or 3 or 4 or 5 or 6 or 7	19463
9	parenteral.mp.	31727
10	Injections, Intramuscular/	12393
11	Injections/	19278
12	9 or 10 or 11	62671
13	8 and 12	605
14	limit 13 to (english language and humans and yr="2016 -Current" and (clinical study or 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 meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	18

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *9/17(DM); 9/16; 5/05*
Implementation: *10/13/16; 11/18/04*

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Literature Scan: Growth Hormone

Date of Review: September 2017

Date of Last Review: September 2016
Literature Search: July 19, 2017

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

Conclusions:
- No new evidence regarding the safety or efficacy of growth hormone (GH) has been published since the last literature scan.
- One guideline was updated by the Pediatric Endocrine Society to assist in guidance of GH treatment for 3 specific indications including idiopathic short stature, growth hormone deficiency (GHD), and primary IGF-1 deficiency in children and adolescents.[1]

Recommendations:
- No further review or research needed at this time.
- Review comparative costs in executive session.

Previous Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., Growth Hormone) products and formulations.
- There is no new evidence that further describes efficacy outcomes associated with use of GH.
- The updated Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health (CADTH) found low to moderate quality evidence that suggest improvement in body composition for patients with Prader-Willi Syndrome (PWS) that received growth hormone treatment. Furthermore, growth hormone therapy should be continued for as long as the demonstrated benefits outweigh the risks.
- There is insufficient evidence to show a clinically significant benefit in HIV patients with respect to wasting.
- Evidence is insufficient to identify a clinically meaningful benefit in adults.
- There is low quality evidence that use of GH in childhood may increase all-cause mortality as an adult but has no significant effect on malignancy-related mortality or cardiovascular-related mortality.
- There is low quality evidence that use of GH in childhood may increase incidence of cancer as an adult and increase secondary malignancies in cancer survivors.

Previous Recommendations:

- After evaluation of comparative drug costs in the executive session, add Genotropin (somatropin) to the OHP fee-for-service Preferred Drug List (PDL) and remove Saizen (somatropin) from the PDL.
- It is recommended that at least one growth hormone product be included with pediatric indications. There is insufficient evidence to determine a recommendation for coverage for adult patients.
- Update clinical PA criteria to reflect HERC Guideline Note 74.

Background:

Growth hormone products are Food and Drug Administration (FDA) approved to treat syndromes associated with growth hormone deficiency (GHD). GHD is the result of impaired production of growth hormone (GH) and may be congenital or acquired. Children most at risk for GHD include those with short stature or a family history of short stature, short stature homeobox-containing gene (SHOX), chronic kidney disease (CKD), Turner's syndrome, Noonan's Syndrome, or Prader-Willi Syndrome. The diagnosis of GH deficiency in childhood is a multistep process involving clinical history, physical examination with detailed growth pattern assessment, biochemical testing, and pituitary imaging.[2] Most GH products are approved for use in pediatrics. Treatment with GH is indicated for children who need GH therapy and who have open epiphyses. Only 3 indications are approved for use in adults: cachexia associated with AIDS (Serostim®), short bowel syndrome (Zorbtive®) and GH deficiency. FDA approved indications for GH vary by brand name product and are presented in **Table 1**.

Table 1. Pediatric and Adults FDA Approved Indications for Growth Hormone[3,4]

	Accretropin®	Genotropin®	Humatrope®	Norditropin®	Nutropin AQ®	Omnitrope®	Saizen®	Serostim®	Zomacton®	Zorbtive®
Pediatric Indications										
GHD	X	X	X	X	X	X	X		X	
Prader-Willi Syndrome		X				X				
Noonan Syndrome				X						
Turner Syndrome	X	X	X	X	X	X				
Idiopathic Short Stature		X	X		X	X				
SHOX deficiency			X							
CKD with Growth Failure				X	X					

Small for gestational age		X	X	X		X				
Adult Indications										
GHD		X	X	X	X	X	X			
HIV Associated Cachexia								X		
Short Bowel Syndrome										X

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = Human immunodeficiency virus; SHOX = Short stature homeobox-containing gene

The NICE guidelines published in 2010 recommend that GH be initiated and monitored by a pediatrician and that the choice of brand name product should be made on an individual basis after consideration of likelihood of adherence to treatment and cost.[5] The treatment of GH should be discontinued if growth velocity increases less than 50% from baseline in the first year of treatment, final height is approached and growth velocity is less than 2 cm total growth in 1 year, adherence issues arise, or if final height is attained.[5] Clinical guidelines do not prefer one growth hormone product over another. The safety of recombinant human GH is currently the subject of much debate and research, and long-term controlled studies are needed to clarify the consequences of childhood growth hormone administration on cancer risk and the long-term safety of its treatment.[2]

Adult GHD (AGHD) is most often due to hypopituitarism secondary to head trauma, tumor of the hypothalamus or pituitary gland, or the consequences of cancer treatment such as surgery or radiation. Growth hormone deficiency is characterized by decreased lean body mass and bone mineral density, increased visceral adiposity, abnormal lipid profile, decreased muscle strength and decreased exercise endurance.[6] The diagnosis of GH deficiency is confirmed if other pituitary hormones such as thyroid stimulating hormone (TSH), corticotropin (ACTH), and gonadotropins are also diminished. A subnormal serum insulin-like growth factor-1 (IGF-1) concentration or subnormal serum GH response to a stimulation test also assists in confirming AGHD. The insulin tolerance test (ITT) and GHRH-arginine test are two tests recommended by the Endocrine Society to establish diagnosis of AGHD.[7] However, GH stimulation testing is invasive, time consuming, and can have increased risks in patients with seizure disorders or cardiovascular disease.[8]

Per the Health Evidence Review Commission (HERC) guideline note 74, treatment with growth hormone is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, SHOX, CKD (stages 3, 4, 5 or 6) and those with renal transplant.[9] Treatment with growth hormone should continue only until adult height as determined by bone age is achieved.[9] Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.[9]

In the second quarter of 2017 a total of 53 claims were received for growth hormone in the fee for service Oregon Medicaid population. Twenty-five (47%) claims were for preferred agents: Norditropin, Omnitrope, and Genotropin. Twenty-eight (53%) percent of claims were for non-preferred agents including Saizen, Humatrope, and Nutropin.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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 Food and Drug Administration (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 systematic reviews have been published since the last review.

New Guidelines:
Pediatric Endocrine Society
The 2016 publication by the Pediatric Endocrine Society (PES) updated 2003 guidance for the use of growth hormone in children and adolescents.[1] The guidelines were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[10] Due to the numerous indications for growth hormone, the report focused on 3 indications including idiopathic short stature (ISS), GHD, and primary IGF-1 deficiency (PIGFD). GHD is defined by PES as the patients who have growth failure due to inadequate secretion of endogenous GH.[1] Idiopathic short stature is defined by a height standard deviation score of less than or equal to 2.25.[1] Severe PIGFD is defined as both height and serum IGF-I concentration below 3 standard deviations despite normal or elevated GH levels or patients with GH gene deletion who developed neutralizing antibodies to GH after a trial of GH therapy.[1] One of the major challenges for the task force was a lack of long term outcomes to evaluate GH therapy because most of the published studies are short term (less than 3 years).[1] No recommendations are made for particular growth hormone products, and only strong recommendations that are based on moderate to high quality evidence are presented below:

- The use of GH is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, high quality evidence)[1]
- Reliance on GH provocative test results is not recommended as the sole diagnostic criterion of GHD. (Strong recommendation, high quality evidence)[1]
- Use of weight-based or body surface area (BSA)-based GH dosing is recommended in children with GHD. (Strong recommendation, moderate quality evidence)[1]
- Guidelines recommend monitoring of GH recipients for potential development of intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation, high quality evidence)[1]
- Use of IGF-I therapy is recommended to increase height in patients with severe PIGFD. (Strong recommendation, high quality evidence)[1]

New FDA Drug Approvals: No new drug approvals were identified since the last review.

New Formulations/Indications: No new formulations or indications were identified since the last review.

New FDA Safety Alerts:
The FDA issued an import alert April 18, 2017 due an increased volume of unapproved GH products being imported into the United States (U.S.). In their alert the FDA noted that human growth hormone (HGH) has important benefits, but also serious, known risks. Possible long-term side effects which have been associated with use of HGH include an increased risk of cancer, nerve pain, and elevated cholesterol and glucose levels. For this reason, HGH is carefully regulated in the U.S. The cost of approved HGH products is high, averaging several hundred dollars per dose. Because of this high cost, HGH drugs have been counterfeited and unapproved HGH products are offered for sale to U.S. consumers. For example, the FDA reports HGH products have been imported as a lyophilized powder for use as an active pharmaceutical ingredient for pharmacy compounding. Some pharmacies promote compounded HGH for anti-aging purposes. It is sold as a "fountain of youth" in longevity clinics and to build body mass, decrease weight loss, increase libido, and gain stamina. None of these indications are in the labeling of the FDA approved products. The FDA is aware of unapproved HGH products being imported into the U.S. and recently noted a large increase of HGH imported for pharmacy compounding. If the drug is bought from foreign sources or over the Internet, safeguards built into the U.S. drug distribution system may be bypassed, placing consumers who use HGH at higher risk.[11]

Product labeling revisions:
Hypersensitivity
Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with post-marketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.[12-14]

Acute Critical Illness Treatment
Acute critical illness treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure.[12] Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3–8 mg/day) compared to those receiving placebo.[12] The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.[12]

Hypoadrenalism
Patients receiving somatropin therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of somatropin treatment.[12-14]

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Appendix 1: Current Status on Preferred Drug List

Brand	Generic	Route	Formulation	PDL
GENOTROPIN	SOMATROPIN	SUB-Q	CARTRIDGE	Y
GENOTROPIN	SOMATROPIN	SUB-Q	SYRINGE	Y
OMNITROPE	SOMATROPIN	SUB-Q	CARTRIDGE	Y
NORDITROPIN FLEXPRO	SOMATROPIN	SUB-Q	PEN INJCTR	Y
HUMATROPE	SOMATROPIN	INJECTION	VIAL	N
HUMATROPE	SOMATROPIN	INJECTION	CARTRIDGE	N
SEROSTIM	SOMATROPIN	SUB-Q	VIAL	N
SAIZEN	SOMATROPIN	SUB-Q	VIAL	N
SAIZEN	SOMATROPIN	SUB-Q	CARTRIDGE	N
ZOMACTON	SOMATROPIN	SUB-Q	VIAL	N
OMNITROPE	SOMATROPIN	SUB-Q	VIAL	N
ZORBTIVE	SOMATROPIN	SUB-Q	VIAL	N
NUTROPIN AQ NUSPIN	SOMATROPIN	SUB-Q	PEN INJCTR	N

Appendix 2: New Clinical Trials

A total of 24 citations were manually reviewed from the literature search. After further review, 23 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 1 trial is briefly described in the table below. Full abstracts are included in **Appendix 3.**

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results			
				Metric	Relative Change PBO	Relative Change GH vs. PBO	Mean Difference between PBO and GH
Kuppens et al[15] RCT, DB, PC, Crossover study	1. GH 0.67mg/m^2 SC once daily x 1 year Vs. 2. PBO SC once daily x 1 year	Young adults (mean age = 17.2 years) with Prader Willi syndrome treated with GH during childhood for at least 2 years who had attained adult height n=27	Body composition, including lean body mass and fat mass as measured by dual-energy x-ray absorptiometry	FM	+21.5%	-17.3%	-2.9 kg (p = 0.004)
				LBM	-2.0%	+3.5%	1.5 kg (p = 0.005)

Abbreviations: DB = double blind**;** FM = fat mass; GH= growth hormone**;** LBM = lean body mass**;** MC = multi-center; OL = open label; PC = placebo controlled; PBO = placebo; RCT = randomized controlled trial; SC = subcutaneous; SGA = small for gestational age

Appendix 3: Abstract of Clinical Trial

1. Beneficial Effects of GH in Young Adults with Prader-Willi Syndrome: A 2-Year Crossover Trial.
Kuppens RJ, Bakker NE, Siemensma EP, Tummers-de Lind van Wijngaarden RF, Donze SH, Festen DA, van Alfen-van der Velden JA, Stijnen T, Hokken-Koelega AC.
J Clin Endocrinol Metab. 2016 Nov; 101(11):4110-4116. Epub 2016 Aug 23

Abstract: Patients with Prader-Willi syndrome (PWS) are severely at risk to develop morbid obesity, diabetes mellitus type 2, and cardiovascular disease, leading to high mortality. They have an increased fat mass (FM) and decreased lean body mass (LBM). During childhood, GH treatment counteracts the natural course of increasing obesity. Discontinuation of GH treatment at attainment of adult height (AH) might deteriorate their improved clinical condition, whereas continuation might benefit them.
OBJECTIVE: To investigate the effects of GH versus placebo on body composition in young adults with PWS who were GH treated for many years during childhood and had attained AH.
DESIGN: Two-year, randomized, double-blind, placebo-controlled crossover study with stratification for gender and body mass index in 27 young adults with PWS.
SETTING: PWS Reference Center in The Netherlands.
INTERVENTION: Crossover intervention with GH (0.67 mg/m^2 · d) and placebo, both during 1 year.
MAIN OUTCOME MEASURES: Body composition, measured by dual-energy x-ray absorptiometry.
RESULTS: During placebo, FM increased (relative change +21.5%; P < .001). Compared with placebo, GH treatment resulted in lower FM (-2.9 kg; P = .004) and higher LBM (+1.5 kg; P = .005), representing relative changes of -17.3% FM and +3.5% LBM. Both limb and trunk FM percentage were lower during GH versus placebo (relative change +17.3% and +15.6%; P < .001 and P = .007, respectively). No GH-related adverse events occurred.
CONCLUSIONS: GH-treated young adults with PWS who have attained AH benefit from continuation of GH treatment. FM increases during placebo, whereas GH versus placebo results in lower FM and higher LBM. Thus, GH treatment maintains the improved body composition without safety concerns.
PMID: 27552545 DOI: 10.1210/jc.2016-2594

Appendix 4: Medline Search Strategy

[Example]
Ovid MEDLINE(R) without Revisions 1946 to July Week 2 2017; Ovid Medline In-Process and Other Non-Indexed Citations July 19, 2017

1	exp Growth Hormone/	22834
2	somatotropin.mp.	3416
3	somatropin.mp.	163
4	humatrope.mp.	16
5	nutropin.mp.	20
6	serostim.mp.	33
7	zomacton.mp.	2
8	saizen.mp.	23
9	norditropin.mp.	53
10	zorbtive.mp.	2
11	genotropin.mp.	81
12	omnitrope.mp.	36
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	24186
14	limit 13 to (full text and humans and yr="2016 -Current" and (clinical study or 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 practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	24

Growth Hormones

Goal(s):
- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with growth hormone (GH) is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stage 3 or higher) and those with renal transplant. Treatment with GH should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.

Length of Authorization:
- Up to 12 months

Requires PA:
- All GH products require prior authorization for OHP coverage. GH treatment for adults is not funded by the OHP.

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/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the patient an adult (>18 years of age)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Go to #3
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
5. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #6
6. Is the diagnosis one of the following? • Turner's syndrome (ICD10 Q969) • Noonan's syndrome (ICD10 E7871-7872, Q872-873, Q875, Q8781, Q8789, Q898) • Prader-Willi syndrome (PWS) (ICD10 Q871) • Pituitary dwarfism (ICD10 E230) • Short stature homeobox-containing gene (SHOX) (ICD10 R6252) • Chronic kidney disease (CKD, Stage ≥3) (ICD10 N183-N185) • Renal transplant (ICD10 Z940)	**Yes:** Document and go to #7	**No:** Pass to RPh. Deny; not funded by the OHP.
7. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #10
10. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: 09/17 (DM); 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06

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Drug Class Literature Scan: Newer Antiemetics

Date of Review: September 2017

Date of Last Review: January 2016
Literature Search: 03/27/17 – 04/17/17

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

Conclusions:

- A search of the evidence on antiemetics identified three systematic reviews and meta-anlayses,[1–3] four guidelines,[4–7] two new formulations and one new indication.[8–10] There was insufficient evidence on subgroup populations and analyses related specifically to Medicaid patients. The evidence contributing to this review supports current antiemetic policy or lacks the quality of evidence required to prompt change to current preferred drug list (PDL) recommendations.
- A Cochrane review was performed on antiemetic use for the prevention and treatment of chemotherapy induced nausea and vomiting in children.[2] There was insufficient evidence to pool results of comparisons. Evidence was limited and firm conclusions were not identified. In a comparison of combination treatment with 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA) and dexamethasone compared to 5-HT3 RAs alone, more patients experienced no vomiting with combination therapy. A second comparison found rates of emesis were reduced with granisetron compared to ondansetron for control of vomiting in the acute phase (pooled relative risk [RR] 2.26; 95% CI, 2.04 to 2.51; ARR not available) but nausea comparisons and delayed phase results suggest similar efficacy.[2]
- A small number of trials with few patients found ondansetron to be as effective as metoclopramide in prevention of nausea symptoms and vomiting episodes in pregnant women with nausea and vomiting or hyperemesis gravidarum (low quality evidence).[1,3]
- Guidelines recommend a neurokinin 1 receptor antagonist (NK1 RA), a 5-HT3 RA and dexamethasone for the prevention of acute and delayed nausea and vomiting in patients receiving chemotherapy.[4,6] The American Society of Clinical Oncology (ASCO) guideline update recommends the NK1 RA netupitant and palonosetron (NEPA) as an option for a three-drug regimen in patients receiving highly emetogenic chemotherapy (HEC).[4] The recommendation was based on two phase three trials but was not graded. NEPA was previously reviewed and presented to the P and T committee. Conclusions are presented below.
- Multinational Association of Supportive Care in Cancer/European Society of Medical Oncology (MASSC/ESMO) guidelines on anticipatory nausea and vomiting in adults and children receiving chemotherapy remain unchanged from the 2011 update due to no new evidence.[5] Optimizing management of acute and delayed phase nausea and vomiting is recommended as the most effective preventative strategy for avoiding anticipatory manifestations.
- Updated guidance from MASSC/ESMO on prevention of nausea and vomiting in patients receiving chemotherapy, radiation, multiple-day chemotherapy, or high-dose chemotherapy and patients with advanced cancer, or breakthrough nausea or vomiting were published in 2016 and support the current policy recommendations for antiemetics.[6,7]

Author: Kathy Sentena, PharmD

- A new extended-release granisetron (ERG) formulation (Sustol®) was approved by the FDA to be used in combination with other antiemetics for the prevention of acute and delayed chemotherapy induced nausea and vomiting for patients receiving moderately emetogenic chemotherapy (MEC) and anthracycline and cyclophosphamide combination chemotherapy.[8] Approval was based on one trial which demonstrated ERG to be non-inferior to palonosetron.
- An extended-release formulation of doxylamine 20 mg and pyridoxine 20 mg (Bonjesta®) was approved for nausea and vomiting in pregnant women.[9] No new evidence was available for analysis. Approval was based off data demonstrating bioequivalence between two combination tablets of doxylamine 10 mg and pyridoxine 10 mg to the fixed dose combination of doxylamine 20 mg and pyridoxine 20 mg.
- Review of 2016 fourth quarter utilization data for the antiemetic class shows PDL adherence to be 98% for the preferred agent ondansetron.

Recommendations:
- Literature evaluated in this review supports the current preferred drug list (PDL) status of therapies in the antiemetic class.
- No further review or research is needed at this time. Evaluate comparative drug costs in executive session.

Previous Conclusions:
- There is insufficient new comparative effectiveness or comparative harms evidence for any given antiemetic indication.
- One new guideline for the management of chemotherapy-induced nausea and vomiting (CINV) from the National Comprehensive Cancer Network (NCCN) has been published. Key recommendations from clinical practice guidelines include up to 3 days of an antiemetic for patients beyond length of the chemotherapy regimen or radiation.
- Low strength of evidence from one systematic review and meta-analysis demonstrated that neurokinin-1 (NK1) receptor antagonists (RA) may be effective in controlling post-operative nausea and vomiting (PONV). The majority of the evidence was for aprepitant 80 mg compared to placebo, which reduced post-operative nausea, 45.2% vs. 76.1% (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting, 3.8% vs. 21.1% (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) based on 3 randomized controlled trials (RCTs) (n=224).
- Low strength of evidence from one RCT found the fixed dose combination product NEPA (netupitant 300 mg/palonosetron 0.5 mg) (Akynzeo®) to be superior to palonosetron for complete response (i.e., no rescue treatment required and no emesis) during the delayed phase (25-120 hours) in patients who received moderate emetogenic chemotherapy (MEC), 76.9% vs. 69.5% (p=0.001), number needed to treat (NNT) of 14. Guideline revisions in 2011 changed the chemotherapy regimen used in this study from a MEC designation to high emetogenic chemotherapy (HEC), providing evidence to support NEPA use in HEC. NEPA provided superior response rates compared to palonosetron for key secondary endpoints; complete response in the acute phase (0-24 hours), complete response in the overall phase (0-120 hours), no significant nausea overall and no emesis overall. External validity of this study is limited by the study participants being primarily female (98%) with breast cancer (97%).
- There is low strength of evidence from two additional trials that support the use of NEPA for MEC and HEC regimens in the acute and delayed phases in a more diverse population with a variety of malignant diseases. NEPA + dexamethasone was found to provide a complete response in 81-91% of patients, compared to 84-92% of patient taking a control regimen of aprepitant + palonosetron + dexamethasone, receiving six cycles of chemotherapy in a safety study. Evidence for the efficacy of oral palonosetron, in the acute phase after HEC, was demonstrated in a comparative trial of oral palonosetron compared to intravenous (IV) palonosetron. Complete response rates in the acute phase were higher for oral palonosetron 0.50 mg compared to IV palonosetron 0.25 mg, 76.3% vs. 70.4%.
- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (Varubi™). Currently, only prescribing information could be found.

Previous Recommendations:

- No changes are recommended to the PDL.
- Approve antiemetic PA as amended:
    - Patients who receive chemotherapy or radiation are allowed 3 days of antiemetic therapy beyond length of treatment.
    - Require PA for doxylamine/pyridoxine to cover for pregnancy-induced n/v after a failed trial of pyridoxine.
    - Require PA for NEPA and rolapitant.

Fourth Quarter 2016 Utilization:

Fourth quarter (10/1/16 through 12/31/16) utilization data for the newer antiemetics for the Oregon Medicaid fee-for-service (FFS) population shows the preferred agent, ondansetron, resulted in the majority of utilization. Claims for non-preferred agents were for doxylamine/pyridoxine (Diclegis) and rolapitant (Varubi).

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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 (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane: Antiemetics for the Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Childhood

A systematic review and meta-analysis evaluated pharmacotherapies used for anticipatory, acute and delayed nausea and vomiting in children (less than 18 years) who are receiving or about to receive chemotherapy.[2] Pharmacotherapies included were: 5-HT3 RAs, benzodiazepines, cannabinoids, corticosteroids, cyclizine, dopamine blockers, and levomepromazine (not available in the US). NK1 RAs and non-pharmacological therapy were not included. Thirty-four RCTs were available for analysis, 27 investigating the treatment of acute nausea and vomiting (1719 patients). Outcomes assessed included complete control of nausea (no nausea and no rescue medication) in the acute phase (first 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours of treatment with chemotherapy) and complete control of vomiting in both the acute and delayed phase. No trials assessed anticipatory nausea or vomiting. There was limited data beyond the first 24 hours of chemotherapy. Nausea outcomes were inconsistently reported and were not assessed via a validated measurement.

Pooled analysis of trial data was not possible for many of the trials due to the quality and quantity of trials identified. The effects of dexamethasone added to 5-HT3 RAs (ondansetron and granisetron) were studied in 2 trials.[2] The combination dexamethasone/5HT3 RA group completely controlled vomiting in more patients

than 5-HT3 RAs alone (RR 2.03; 95% CI, 1.35 to 3.04) (ARR not provided). Granisetron 20 mcg/kg was compared to granisetron 40 mcg/kg for complete control of vomiting and found to have similar efficacy (pooled RR 0.93; 95% CI, 0.80 to 1.07). No differences were found between granisetron 10 mcg/kg and 40 mcg/kg in controlling acute vomiting. Data from three trials suggest that granisetron was more effective than ondansetron for acute vomiting (pooled RR 2.26; 95% CI, 2.04 to 2.51); however complete control of acute nausea (pooled RR 1.05; 95% CI, 0.94 to 1.17), delayed nausea (pooled RR 1.13; 95% CI, 0.93 to 1.38) and delayed vomiting (pooled RR 1.13; 95% CI, 0.98 to 1.29) were similar between the two treatments.[2] Evidence was insufficient to make firm conclusions. Data on cannabinoids was conflicting and results were not able to be pooled.

Cochrane: Interventions for Treating Hyperemesis Gravidarum

The efficacy and safety of treatments for hyperemesis gravidarum in patients who were pregnant up to 20 weeks' gestation were included.[1] Studies of nausea and vomiting in pregnancy were excluded. Of the newer antiemetics, only 2 trials evaluated ondansetron were included in the review. Very low evidence based on one trial of 83 women found similar efficacy between metoclopramide and ondansetron. Severity of nausea and vomiting was similar between metoclopramide and ondansetron based on a 10-point visual analog scale (MD 1.70; 95% CI, -0.15 to 3.55).[1] Metoclopramide was associated with a higher incidence of drowsiness and dry mouth. A trial evaluating duration of hospital admission found no difference between ondansetron and promethazine based on very low quality evidence.

McParlin et al – Treatment for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy

In a systematic review, evidence for treatment of nausea and vomiting and hyperemesis gravidarum were reviewed.[3] Authors declared no conflict of interest and the analysis was funded by the National Institute for Health Research Technology Assessment Program. Seventy-eight trials were identified, 67 were RCTs. The American Heart Association (AHA) evidence grade and recommendation methodology was used to grade each assessment. Strength of the recommendation ranged from level A (high quality) to level C (expert opinion) and quality of evidence from class I (strong) to class III (harm). A meta-analysis was not possible due to heterogeneity and incomplete findings. A multitude of interventions were studied; however, for this analysis only results for newer antiemetics will be presented.

Five RCTs evaluated pyridoxine/doxylamine in the treatment of nausea and vomiting in pregnancy or hyperemesis gravidarum and determined the combination to be effective in women with moderate to severe symptoms as a second-line therapy (Level A, class IIa). In three trials (n=280) comparing pyridoxine/doxylamine to placebo or ondansetron, symptom improvement was demonstrated in both groups with higher rate of improvement in the pyridoxine/doxylamine group with a mean change in Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score of 4.8 versus 3. 9 (p=0.006). The PUQE measures symptoms on a scale of 0 (no symptoms) to 15 (worst possible symptoms). A small trial (n=60) in pregnant women found pyridoxine/doxylamine demonstrated reduced risk of recurrence of symptoms when used preventatively. Symptoms occurred in 15.4% of patients treated with pyridoxine/doxylamine compared to 39.1% in the group that was treated after symptoms presented (p<0.04; ARR 23.7%; NNT 4).[3] Seven RCTs with low or unclear risk of bias evaluated 5-HT3 RAs compared to placebo or active treatment. Authors concluded that 5-HT3 RAs were effective for all severity levels of nausea and vomiting (Level A, class IIa).

New Guidelines:

ASCO – Antiemetic Focused Guideline Update

A 2015 ASCO clinical practice guideline on the use of antiemetics was published to evaluate the combination of netupitant and palonosetron (NEPA) for prevention of acute and delayed nausea and vomiting due to chemotherapy.[4] ASCO guideline process is to grade the literature and make recommendations based on the strength of the evidence; however, the grading of trials included in the analysis was not provided.

ASCO recommends that patients who receive HEC (including anthracycline and cyclophosphamide) should be offered a three-drug antiemetic regimen.[4] A combination regimen of a NK1 RA, 5-HT3 RA and dexamethasone are recommended. An additional option is the combination of oral NEPA plus dexamethasone (recommendation grade not provided). Previous recommendations found in the 2011 update were unchanged:

- The preferred 5-HT3 RA for patients receiving MEC is palonosetron in addition to a corticosteroid.
- Antiemetic therapy should be based on the chemotherapy agent that has the highest emetic risk if the patient is receiving multiple chemotherapy agents.
- Patients receiving HEC should receive dexamethasone and a 5-HT3 RA.
- 5-HT3 RA and corticosteroids should be used for pediatric patients receiving MEC or HEC.
- HEC radiotherapy should be treated with a 5-HT3 RA before each fraction and a 5-day course of dexamethasone. The same recommendations apply for MEC radiotherapy, but the 5-day course of dexamethasone is optional.
- Patients receiving combination radiation therapy and chemotherapy should receive an antiemetic based on the emetogenicity of chemotherapy unless there is more risk of emesis with radiation.

2016 MASCC and ESMO Guidelines for Nausea and Vomiting Prevention in Patients Receiving Chemotherapy and Radiotherapy and in Advanced Cancer Patients

Updated MASCC/ESMO recommendations from the 2010 guideline were published on the most effective management of nausea and vomiting in patients undergoing treatment for malignancy with advanced cancer.[6] The level of evidence and the grading of the recommendations according to ESMO were based on adaptations of the grading methodology used by the Infectious Diseases Society of America (IDSA). IDSA grades the strength of the recommendation as the following: A (good evidence), B (moderate evidence) and C (poor evidence). The quality of the evidence is also graded: I (high quality from more than one randomized trials), II (evidence from more than one body of evidence that is not randomized or from a cohort or case-controlled study) or II (expert opinion evidence). The MASCC evaluates the evidence based on the levels of Scientific Confidence. The ranges were the following: high, moderate, low, very low and no confidence. Each recommendation received an assessment according to both the ESMO and MASCC. MASCC and ESMO were solely responsible for the funding the guidelines. Thirteen authors had conflicts of interest and six had none.

Treatment recommendations for prophylaxis of acute and delayed nausea and vomiting are presented in **Table 1**.[6] **Table 2** outlines the antiemetic treatment options for patients receiving radiation therapy. **Table 3** provides recommendations for antiemetic prophylaxis for children receiving chemotherapy. Lastly, the guidelines recommend prophylaxis with metoclopramide for prevention of emesis in patients with advanced cancer (MASCC high level of consensus and moderate level of confidence, ESMO level of evidence: III, ESMO grade of recommendation: C). Other prophylaxis options are: haloperidol, levomepromazine (not available in the US) or olanzapine. In patients with malignant bowel obstruction, octreotide is recommended with a conventional antiemetic. If relief is suboptimal, then the use of an anticholinergic anti-secretory agent and/or corticosteroids is recommended in combination with the other agents or as an alternative. There was no evidence to support the use of antiemetics for opioid-induced nausea and vomiting.

Table 1. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
Non-AC highly emetic chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A

Non-AC highly emetic chemotherapy	Dexamethasone on days 2-4 in combination with the above	High/ moderate	I/B
Women with breast cancer receiving AC chemotherapy	3 drug regimen: single doses of 5-HT3 RA, dexamethasone and an NK1 RA given before chemotherapy	High/ high	I/A
Women with breast cancer receiving AC chemotherapy	Dexamethasone should be given on days 2-3 with the above except if fosaprepitant, netupitant or rolapitant were used on day 1	Moderate/ moderate	II/B
Olanzapine Use – prophylaxis of delayed nausea and in prevention of acute symptoms	Olanzapine may be appropriate, especially for nausea, with a 5-HT3 RA plus dexamethasone	Low/ low	II/B
Prevention of acute emesis in MEC	5-HT3 RA plus dexamethasone	Moderate/ moderate	II/B
Prevention of delayed emesis in patients receiving MEC with known potential for delayed emesis	Dexamethasone on days 2-3	Low/ moderate	III/C
Prevention of delayed emesis in patients receiving MEC	No routine prophylaxis	No confidence possible/ high	IV/D
Prevention of carboplatin-induced acute nausea and vomiting	NK1 RA, dexamethasone and 5-HT3 RA	Moderate/ moderate	II/B
Prevention of carboplatin-induced delayed nausea and vomiting	If fosaprepitant, netupitant or rolapitant were used on day 1 then no antiemetic prophylaxis is required. If aprepitant is given on day 1 then aprepitant should be given on days 2-3	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin acute nausea and vomiting prevention	5-HT3 RA plus dexamethasone plus aprepitant	Moderate/ moderate	II/B
Metastatic germ cell tumors receiving multiple-day cisplatin delayed nausea and vomiting prevention	Dexamethasone is recommended	Moderate/ moderate	II/B
Prevention of nausea and vomiting with low or minimal emetogenic chemotherapy	A single regimen of dexamethasone or 5-HT3 RA or a dopamine RA (e.g., metoclopramide) may be considered	No confidence possible/ moderate	II/B
Prevention of nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Prevention of delayed nausea and vomiting with minimal emetogenic chemotherapy	No antiemetic should be routinely administered before chemotherapy if no history of nausea or vomiting	No confidence possible/ high	IV/D
Treatment of breakthrough nausea and vomiting	Use of an antiemetic with a different mechanism of action than that of the antiemetic used for prophylaxis Olanzapine 10 mg orally for 3 days is recommended	Moderate/ moderate	II/B
Anticipatory nausea and vomiting	Benzodiazepines are recommended	Moderate/moderate	II/A
Anticipatory nausea and vomiting	Behavioral therapies including: progressive muscle relaxation training, systematic desensitization and hypnosis	Moderate/moderate	II/B

High-dose chemotherapy for stem cell transplant	Combination of 5-HT3 RA with dexamethasone and aprepitant (124 mg on day 1 and 80 mg on days 2-4)	High/high	I/A

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); AC-anthracycline-cyclophosphamide; MEC – moderately emetogenic chemotherapy; NK1 RA – neurokinin 1 receptor antagonist (aprepitant, fosaprepitant, netupitant, rolapitant)

Table 2. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Patients Receiving Radiotherapy.[6]

Emetic Risk Level	Area of Treatment	Antiemetic Guideline	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High	Total body irradiation	Prophylaxis with a 5-HT3 RA and dexamethasone	High/high Moderate/high - for addition of dexamethasone	II/B IIIC – for addition of dexamethasone
Moderate	Upper abdomen, craniospinal	Prophylaxis with a 5-HT3 RA and optional dexamethasone	High/high Moderate/high – for the addition of dexamethasone	II/A II/B - for the addition of dexamethasone
Low	Cranium	Prophylaxis or rescue with dexamethasone	Low/high	IV/D
Low	Head and neck, thorax region and pelvis	Prophylaxis or rescue with dexamethasone, a dopamine receptor antagonist or a 5-HT3 RA	Low/high	IV/D
Minimal	Extremities, breast	Rescue with dexamethasone, a dopamine receptor antagonist or 5-HT3	Low/high	IV/D
Concomitant chemotherapy	Any area	Follow recommendations for antiemetic prophylaxis for chemotherapy regimen unless the RT regimen has a higher emetic risk and then treatment recommendation should be followed according to the highest risk	Low/high	IV/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, palonosetron); RT – radiation therapy

Table 3. MASCC/ESMO Guideline Recommendations for Antiemetic Therapy in Children Receiving Chemotherapy.[6]

Indication	Recommendation	MASCC Level of Confidence/ Level of Consensus	ESMO Level of Evidence/ Grade of Recommendation
High emetic risk chemotherapy	5-HT3 RA plus dexamethasone plus aprepitant	High/high	II/B
High emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
High emetic risk chemotherapy and patient is unable to receive aprepitant	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy	5-HT3 RA plus dexamethasone	Moderate/high	II/B
Medium emetic risk chemotherapy and patient is unable to receive dexamethasone	5-HT3 RA plus aprepitant	Moderate/high	II/B
Low emetic risk chemotherapy	5-HT3 RA	Moderate/moderate	II/B
Minimal emetic risk chemotherapy	No antiemetic prophylaxis is recommended	Moderate/high	V/D

Abbreviations: 5-HT3 RA – 5-HT3-receptor antagonist (ondansetron, granisetron, tropisetron, palonosetron)

MASCC/ESMO Anticipatory Nausea and Vomiting in Adults and Children Receiving Chemotherapy

In 2016, the MASCC/ESMO updated their 2011 recommendations on the treatment of patients with anticipatory nausea and vomiting who are receiving chemotherapy.[5] Evidence was graded as described in the MASCC/ESMO guideline above. An updated literature search was performed with the following inclusion criteria: full text primary studies; published in English; evaluated an intervention for the treatment of nausea and vomiting; the outcome of complete control was measured; and included at least 10 participants. No new literature was found meeting the inclusion criteria. Previous recommendations of optimizing acute and delayed phase nausea and vomiting control for prevention of anticipatory nausea and vomiting were reiterated (MASCC moderate confidence and high consensus and ESMO level of evidence III and grade A). Behavioral therapies and benzodiazepines can also be considered for treatment.

MASCC/ESMO Recommendations for Prevention of Nausea and Vomiting Following Multi-Day Chemotherapy, High-dose Chemotherapy and Breakthrough Nausea and Vomiting

Multiple day chemotherapy regimens, high-dose chemotherapy and breakthrough nausea and vomiting are conditions that require specialized management for the prevention of nausea and vomiting.[7] In the recent MASCC/ESMO recommendations, updated evidence on antiemetic treatment options for patients with these conditions included two new RCTs. Guideline development utilized the IDSA and Scientific Confidence methodology described above. Changes from the previous recommendations included olanzapine for breakthrough pain and the use of aprepitant for multiple-day regimens and high-dose regimens. Recommendations for prevention of nausea and vomiting are as follows:

- In the acute phase receiving multiple-day cisplatin chemotherapy
    - 5-HT3 RA, dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- In the delayed phase receiving multiple-day cisplatin chemotherapy
    - Dexamethasone and aprepitant (moderate confidence/moderate consensus and ESMO level II/B)[7]
- Breakthrough

- Olanzapine 10 mg daily for three days (moderate confidence/moderate consensus and ESMO level II/B)[7]

- High-dose chemotherapy for stem cell transplant
  - 5-HT3 RA, dexamethasone and aprepitant (high confidence/high consensus and ESMO level I/A)[7]

New Formulations:

A new extended-release granisetron (ERG) injection (Sustol®) was approved in 2016 for the use in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting with initial and repeat courses of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide combination chemotherapy regimens.[8] ERG injection should be given as a 10 mg subcutaneous (SQ) dose at least 30 minutes before the start of emetogenic chemotherapy on Day 1. ERG injection should not be given more than once every 7 days and for not more than 6 months in patients receiving successive emetogenic chemotherapy cycles.

ERG 10 mg SQ was approved based on one clinical trial comparison to palonosetron 0.25 mg IV.[8] The trial was a multi-center, double-blind, parallel group study in patients with cancer undergoing treatment with MEC or anthracycline plus cyclophosphamide combination chemotherapy. A single dose of each agent, in combination with IV dexamethasone 8 mg or 20 mg, was given 30 minutes prior to chemotherapy on Day 1. The study population (n=733) was 63% Caucasian and 79% female with a mean age of 57 years. MEC was given to 55% of patients and 45% received combination therapy with anthracycline and cyclophosphamide. The primary endpoint was the percent of patients obtaining a complete response (defined as no emetic episodes and no rescue medication use) in the acute phase (within 24 hours) and the delayed phase (>24 to 120 hours) following chemotherapy. A complete response was demonstrated in 166 (83%) of patients receiving ERG and in 183 (89%) of patients receiving palonosetron in the acute phase receiving MEC.[8] In the delayed phase, ERG was associated with a complete response in 137 (69%) of patients and in 144 (70%) in palonosetron treated patients.[8] In patients receiving anthracycline and cyclophosphamide, there was a complete response rate in the acute phase in 120 (70%) of patients receiving ERG and 99 (64%) of patients receiving palonosetron. ERG was associated with 85 (50%) of patients treated with ERG obtaining a complete response compared to 74 (47%) in the palonosetron group during the delayed phase. ERG was shown to be non-inferior, but not superior, to palonosetron.

The most common adverse reactions are injection site reactions, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia and gastrointestinal reflux. Hypersensitivity reactions have occurred up to 7 days or longer after an ERG injection.

Additional RCTs are presented below and abstracts are available in **Appendix 3**.

Table 4. Description of Randomized Comparative Clinical Trials for Extended-Release Granisetron.

Study	Comparison	Population	Primary Outcome	Results
Raftopoulos, et al[11] RCT, DB, MC, Phase 3, non-inferiority	ERG 5 mg SQ or ERG 10 mg SQ vs. Palonosetron 0.25mg IV One dose 30-60 min. prior to chemotherapy Both treatments were given with IV dexamethasone HEC regimens were also given oral dexamethasone 8 mg twice daily on days 2-4	Adults with confirmed malignancy and scheduled to receive MEC or HEC during first cycle N=1,341	The percentage of patients obtaining a complete response in the acute and delayed phase (no emetic episodes and no use of rescue medication during acute and delayed phase)	<u>MEC Acute Phase</u> ERG 5 mg: 160 (74.8%) ERG 10 mg: 163 (76.9% Palonosetron: 156 (75.0%) ERG 5 mg vs. Palonosetron: P = 1.0 ERG 10 mg vs. Palonosetron: P = 0.73 <u>MEC Delayed Phase</u> ERG 5 mg: 110 (51.4%) ERG 10 mg: 124 (58.5%) Palonosetron: 119 (57.20%) ERG 5 mg vs. Palonosetron: P = 0.24 ERG 10 mg vs. Palonosetron: P = 0.84 <u>HEC Acute Phase</u> ERG 5 mg: 178 (77.7%) ERG 10 mg: 195 (81.3%) Palonosetron: 192 (80.7%) ERG 5 mg vs. Palonosetron: P = 0.49 ERG 10 mg vs. Palonosetron: P = 0.91 <u>HEC Delayed Phase</u> ERG 5 mg: 143 (62.4%) ERG 10 mg: 161 (67.1%) Palonosetron: 153 (64.3%) ERG 5 mg vs. Palonosetron: P = 0.70 ERG 10 mg vs. Palonosetron: P = 0.56 • CI not provided for results
Schnadig, et al[12] RCT, DB, DD, PG, MC, Phase 3	ERG 10 mg SQ vs. Ondansetron 0.15 mg/kg IV Both treatments were given with dexamethasone 12 mg IV and fosaprepitant 150 mg IV. Regimens were also given oral	Adults with confirmed malignancy scheduled to receive highly emetogenic chemotherapy receiving their first cycle	Delayed phase (24-120 hours) complete response (no emesis or rescue medication)	ERG 10 mg: 291 (64.7%) Ondansetron: 256 (56.6%) ARR 8.0% (95% CI, 1.7 to 14.4) P = 0.014

	dexamethasone 8 mg once daily on day 2 and twice daily on days 3-4.	N = 450		
Boccia, et al[13] RCT, MC, DB, PC, PG, Phase 3	<u>Cycle 1</u> ERG 5 mg SC or ERG 10 mg SC vs. Palonosetron 0.25 mg IV <u>Cycle 2-4</u> ERG 5 mg SC vs. ERG 10 mg SC Both treatments were given with IV dexamethasone	Adults with confirmed malignancy receiving MEC or HEC N = 1,395	Complete response (no emetic episodes, no rescue medication) of ERG 10 mg during acute (0-24 hours) and delayed (>24-120 hours) phases during chemotherapy cycles 2-4	<u>Complete Response HEC Acute Phase</u> ERG 10 mg cycle 1: 81.3% ERG 10 mg cycle 4: 87.8% Palonosetron cycle 1: 75% <u>Complete Response HEC Delayed Phase</u> ERG 10 mg cycle 1: 67.1% ERG 10 mg cycle 4: 83.1% Paonosetron cycle 1: 81% * Results for palonosetron cycle 4 were not provided.

Abbreviations: ARR = actual risk reduction; DB = double-blind; DD = double-dummy; ERG = extended-release granisetron; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; SQ = subcutaneous.

<u>Doxylamine/Pyridoxine (Bonjesta)</u>

A new extended-release, fixed dose formulation of the currently available doxylamine/pyridoxine was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[9] The combination product is 20 mg doxylamine and 20 mg pyridoxine to be given as one tablet at bedtime on Day 1. If symptoms are not adequately controlled on Day 2, then the dose can be increased to one tablet in the morning and one tablet at bedtime. The maximum dosage is 2 tablets a day.

The extended-release doxylamine/pyridoxine formulation was not studied in clinical trials. The approval was based on a clinical trial of doxylamine 10 mg/pyridoxine 10 mg (Diclegis) formulation that has been previously reviewed.[9] A pharmacokinetic crossover trial of 48 women found extended-release doxylamine 20 mg/pyridoxine 20mg to be bioequivalent to two combination tablets of 10 mg doxylamine and 10 mg pyridoxine. A second multi-dose, crossover trial found bioequivalence of one ER doxylamine 20 mg/pyridoxine 20 mg tablet given twice daily to one tablet of doxylamine 10 mg/pyridoxine 10 mg given three times daily.

<u>Aprepitant Use in Pediatrics</u>

In 2015, aprepitant (Emend) was approved for pediatric use (ages 12 to 17 years and for patients less than 12 years who weight at least 30 kg) for the prevention of chemotherapy-induced acute and delayed nausea and vomiting in combination with other antiemetic agents for patients receiving initial and repeat MEC or

HEC (including cisplatin) regimens.[10] The dose for pediatric patients is the same as for adults, 125 mg aprepitant on day 1 and 80 mg on days 2 and 3. The study used for the pediatric indication is presented below.

Table 5. Description of Randomized Comparative Clinical Trials for Aprepitant.

Study	Comparison	Population	Primary Outcome	Results
Kang, et al[14] RCT, MC, Phase 3, DB	Aprepitant* vs. Placebo† * Aprepitant 125 mg orally for 12-17 years; 3.0 mg/kg (maximum 125 mg) orally for ages 6 mo. to <12 years and ondansetron on day 1. On day 2 and 3, aprepitant 80 mg for ages 12-17 years and 2.0 mg/kg (max 80 mg) for ages 6 months to <12 years. Ondansetron was given on day 1 according to manufacturer recommendations. † Oral placebo and ondansetron were given on day 1. Placebo only was given on days 2 and 3. Ondansetron dosing was based on manufacturer's recommendation. *† Dexamethasone IV was allowed for both groups	Patients 6 months to 17 years with documented malignancy receiving MEC or HEC N = 307	The proportion of patients who obtained a complete response (no vomiting, retching or use of rescue medications) in the delayed phase (25-120 hours post chemotherapy)	<u>Delayed phase</u> Aprepitant: 77 (51%) Placebo: 39 (26%) ARR: 25%; P < 0.0001

Abbreviations: ARR = actual risk reduction; DB = double-blind; HEC = highly emetogenic chemotherapy; IV = intravenous; MC = multi-center; MEC = moderately emetogenic chemotherapy; PC = placebo controlled; RCT = randomized clinical trial.

New FDA Safety Alerts:
No safety alerts identified.

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Appendix 1: Current Preferred Drug List

Antiemetics, 5HT3 and Substance P Antagonists

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	SOLUTION	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	SOLUTION	ZOFRAN	ONDANSETRON HCL	Y
ORAL	TAB RAPDIS	ONDANSETRON ODT	ONDANSETRON	Y
ORAL	TAB RAPDIS	ZOFRAN ODT	ONDANSETRON	Y
ORAL	TABLET	ONDANSETRON HCL	ONDANSETRON HCL	Y
ORAL	TABLET	ZOFRAN	ONDANSETRON HCL	Y
INTRAVEN	VIAL	EMEND	FOSAPREPITANT DIMEGLUMINE	N
ORAL	CAP DS PK	EMEND	APREPITANT	N
ORAL	CAPSULE	AKYNZEO	NETUPITANT/PALONOSETRON HCL	N
ORAL	CAPSULE	EMEND	APREPITANT	N
ORAL	FILM	ZUPLENZ	ONDANSETRON	N
ORAL	TABLET	ANZEMET	DOLASETRON MESYLATE	N
ORAL	TABLET	GRANISETRON HCL	GRANISETRON HCL	N
ORAL	TABLET DR	DICLEGIS	DOXYLAMINE/PYRIDOXINE HCL	N
TRANSDERM	PATCH TDWK	SANCUSO	GRANISETRON	N
ORAL	TABLET	VARUBI	ROLAPITANT	N
ORAL	TABLET	BONJESTA	DOXYLAMINE/PYRIDOXINE	N
INTRAVEN	VIAL	ALOXI	PALONOSETRON	
SUBCUTA	VIAL	SUSTOL	GRANISETRON	N

Appendix 2: New Comparative Clinical Trials

A total of 151 citations were manually reviewed from the initial literature search. After further review, 149 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 two trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Navari, et al[15] RCT, DB, Phase 3	Olanzapine 10 mg* vs. Placebo* * Given on days 1-4 Both groups received dexamethasone, aprepitant or fosaprepitant and a 5-hydroxy-tryptamine type 3-recetptor antagonist	Adult patients with malignant disease naïve to chemotherapy receiving cisplatin or cyclophosphamide-doxarubicin N=380	Nausea prevention (defined as zero on a visual analog scale for nausea) during the overall assessment (0-120 hours), the early assessment period (0-24 hours) and the later assessment period (25-120 hours)	<u>No nausea 0-24 hours</u> Olanzapine: 135 (74%) Placebo: 82 (45%) ARR: 29%; P = 0.002 <u>No nausea 25-120 hours</u> Olanzapine: 75 (42%) Placebo: 45 (25%) ARR: 17%; P = 0.002 <u>No nausea 0-120 hours</u> Olanzapine: 66 (37%) Placebo: 39 (22%) ARR: 15%; P = 0.002
Kovács, et al [16] MC, DB, DD, RCT, Phase 3	IV Palonosetron 10 mcg/kg* or IV Palonosetron 20 mcg/kg* vs. IV Ondansetron 150 mcg/kg given as 3 doses 4 hours apart on day 1 * Given up to 4 cycles on day 1	Pediatric patients (0-17 years) scheduled to receive MEC or HEC for treatment of malignant disease N=502	Complete response (no vomiting, retching or rescue drug treatment) during the acute phase (0-24 hours post-chemotherapy) during the first cycle of chemotherapy	<u>Complete Response</u> Palonosetron 10 mcg/kg: 90 (54%) Palonosetron 20 mcg/kg: 98 (59%) Ondansetron: 95 (59%) <u>Palonosetron 20 mcg/kg vs. Ondansetron</u> WSD 0.36% (97.5% CI, -11.7 to 12.4) P = 0.0022 (non-inferiority achieved) <u>Palonosetron 10 mcg/kg vs. Ondansetron</u> WSD -4.41% (97.5% CI, -16.4 to 7.6) P = NS

Abbreviations: ARR = absolute risk reduction; DB = double-blind; DD=double-dummy; IV = intravenous; MC = multi-center; RCT = randomized clinical trial; WSD = weighted sum of the difference

Appendix 3: Abstracts of Comparative Clinical Trials

Randomized phase III trial of APF530 versus palonosetron in the prevention of chemotherapy-induced nausea and vomiting in a subset of patients with breast cancer receiving moderately or highly emetogenic chemotherapy
Boccia R, Cooper W, Boyle E

Background
APF530 provides controlled, sustained-release granisetron for preventing acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). In a phase III trial, APF530 was noninferior to palonosetron in preventing acute CINV following single-dose moderately (MEC) or highly emetogenic chemotherapy (HEC) and delayed CINV in MEC (MEC and HEC defined by Hesketh criteria). This exploratory subanalysis was conducted in the breast cancer subpopulation.
Methods
Patients were randomized to subcutaneous APF530 250 or 500 mg (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg during cycle 1. Palonosetron patients were randomized to APF530 for cycles 2 to 4. The primary efficacy end point was complete response (CR, no emesis or rescue medication) in cycle 1.
Results
Among breast cancer patients (*n* = 423 MEC, *n* = 185 HEC), > 70 % received anthracycline-containing regimens in each emetogenicity subgroup. There were no significant between-group differences in CRs in cycle 1 for acute (APF530 250 mg: MEC 71 %, HEC 77 %; 500 mg: MEC 73 %, HEC 73 %; palonosetron: MEC 68 %, HEC 66 %) and delayed (APF530 250 mg: MEC 46 %, HEC 58 %; 500 mg: MEC 48 %, HEC 63 %; palonosetron: MEC 52 %, HEC 52 %) CINV. There were no significant differences in within-cycle CRs between APF530 doses for acute and delayed CINV in MEC or HEC in cycles 2 to 4; CRs trended higher in later cycles, with no notable differences in adverse events between breast cancer and overall populations.
Conclusions
APF530 effectively prevented acute and delayed CINV over 4 chemotherapy cycles in breast cancer patients receiving MEC or HEC.

Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial
Raftopoulos H, Cooper W, O'Boyle, et al

Purpose
Subcutaneous APF530 provides controlled sustained release of granisetron to prevent acute (0–24 h) and delayed (24–120 h) chemotherapy-induced nausea and vomiting (CINV). This randomized, double-blind phase 3 trial compared APF530 and palonosetron in preventing acute and delayed CINV after moderately (MEC) or highly emetogenic chemotherapy (HEC).
Methods
Patients receiving single-day MEC or HEC received single-dose APF530 250 or 500 mg subcutaneously (SC) (granisetron 5 or 10 mg) or intravenous palonosetron 0.25 mg. Primary objectives were to establish APF530 noninferiority to palonosetron for preventing acute CINV following MEC or HEC and delayed CINV following MEC and to determine APF530 superiority to palonosetron for preventing delayed CINV following HEC. The primary efficacy end point was complete response (CR [using CI difference for APF530 − palonosetron]). A lower confidence bound greater than −15 % indicated noninferiority.

Results
In the modified intent-to-treat population (MEC = 634; HEC = 707), both APF530 doses were noninferior to palonosetron in preventing acute CINV after MEC (CRs 74.8 % [−9.8, 9.3] and 76.9 % [−7.5, 11.4], respectively, vs. 75.0 % palonosetron) and after HEC (CRs 77.7 % [−11.5, 5.5] and 81.3 % [-7.7, 8.7], respectively, vs. 80.7 % palonosetron). APF530 500 mg was noninferior to palonosetron in preventing delayed CINV after MEC (CR 58.5 % [−9.5, 12.1] vs. 57.2 % palonosetron) but not superior in preventing delayed CINV after HEC. Adverse events were generally mild and unrelated to treatment, the most common (excluding injection-site reactions) being constipation.
Conclusions
A single subcutaneous APF530 injection offers a convenient alternative to palonosetron for preventing acute and delayed CINV after MEC or HEC.

APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy
Schnadig I, Agajanian R, Dakhil C, et al

AIM
APF530, extended-release granisetron, provides sustained release for ≥5 days for acute- and delayed-phase chemotherapy-induced nausea and vomiting (CINV). We compared efficacy and safety of APF530 versus ondansetron for delayed CINV after highly emetogenic chemotherapy (HEC), following a guideline-recommended three-drug regimen.
METHODS
HEC patients received APF530 500 mg subcutaneously or ondansetron 0.15 mg/kg intravenously, with dexamethasone and fosaprepitant. Primary end point was delayed-phase complete response (no emesis or rescue medication).
RESULTS
A higher percentage of APF530 versus ondansetron patients had delayed-phase complete response (p = 0.014). APF530 was generally well tolerated; treatment-emergent adverse event incidence was similar across arms, mostly mild-to-moderate injection-site reactions.
CONCLUSION
APF530 versus the standard three-drug regimen provided superior control of delayed-phase CINV following HEC.

Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.
Kang HJ, Loftus S, Taylor A, DiCristina C, Green S, Zwaan CM.

BACKGROUND:
Oral aprepitant, a neurokinin-1 receptor antagonist, is recommended in combination with other anti-emetic agents for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy in adults, but its efficacy and safety in paediatric patients are unknown. We did this phase 3 trial to examine the safety and efficacy of such treatment in children.
METHODS:
In this final analysis of a phase 3, randomised, multicentre, double-blind study, patients aged 6 months to 17 years with a documented malignancy who were scheduled to receive either moderately or highly emetogenic chemotherapy were randomly assigned with an interactive voice response system to an age-based and weight-based blinded regimen of aprepitant (125 mg for ages 12-17 years; 3·0 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant (80 mg for ages 12-17 years; 2·0 mg/kg up to 80 mg for ages 6 months to <12 years) on days 2 and 3, or placebo plus ondansetron on

day 1 followed by placebo on days 2 and 3; addition of dexamethasone was allowed. Randomisation was stratified according to patient age, planned use of chemotherapy associated with very high risk of emetogenicity, and planned use of dexamethasone as an anti-emetic. Ondansetron was dosed per the product label for paediatric use or local standard of care. The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25-120 h (delayed phase) after initiation of emetogenic chemotherapy. Efficacy and safety analyses were done with all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01362530.

FINDINGS:

Between Sept 22, 2011, and Aug 16, 2013, 307 patients were randomly assigned at 49 sites in 24 countries to either the aprepitant group (155 patients) or to the control group (152 patients). Three patients in the aprepitant group and two in the control group did not receive study medication, and thus were excluded from analyses. 77 (51%) of 152 patients in the aprepitant group and 39 (26%) of 150 in the control group achieved a complete response in the delayed phase ($p<0{\cdot}0001$). The most common grade 3-4 adverse events were febrile neutropenia (23 [15%] of 152 in the aprepitant group vs 21 [14%] of 150 in the control group), anaemia (14 [9%] vs 26 [17%]), and decreased neutrophil count (11 [7%] vs 17 [11%]). The most common serious adverse event was febrile neutropenia (23 [15%] patients in the aprepitant group vs 22 [15%] in the control group).

INTERPRETATION:

Addition of aprepitant to ondansetron with or without dexamethasone is effective for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients being treated with moderately or highly emetogenic chemotherapy.

FUNDING:

Merck & Co., Inc.

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting.

Navari RM, Qin R, Ruddy KJ, et al

BACKGROUND:

We examined the efficacy of olanzapine for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy.

METHODS:

In a randomized, double-blind, phase 3 trial, we compared olanzapine with placebo, in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-hydroxytryptamine type 3-receptor antagonist, in patients with no previous chemotherapy who were receiving cisplatin (≥70 mg per square meter of body-surface area) or cyclophosphamide-doxorubicin. The doses of the three concomitant drugs administered before and after chemotherapy were similar in the two groups. The two groups received either 10 mg of olanzapine orally or matching placebo daily on days 1 through 4. Nausea prevention was the primary end point; a complete response (no emesis and no use of rescue medication) was a secondary end point.

RESULTS:

In the analysis, we included 380 patients who could be evaluated (192 assigned to olanzapine, and 188 to placebo). The proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine than with placebo in the first 24 hours after chemotherapy (74% vs. 45%, P=0.002), the period from 25 to 120 hours after chemotherapy (42% vs. 25%, P=0.002), and the overall 120-hour period (37% vs. 22%, P=0.002). The complete-response rate was also significantly increased with olanzapine during the three periods: 86% versus 65% (P<0.001), 67% versus 52% (P=0.007), and 64% versus 41% (P<0.001), respectively. Although there were no grade 5 toxic effects, some patients receiving olanzapine had increased sedation (severe in 5%) on day 2.

CONCLUSIONS:
Olanzapine, as compared with placebo, significantly improved nausea prevention, as well as the complete-response rate, among previously untreated patients who were receiving highly emetogenic chemotherapy. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT02116530.).

Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study.
Kovács G, Wachtel AE, Basharova EV, Spinelli T, Nicolas P, Kabickova E.
BACKGROUND:
Palonosetron has shown efficacy in the prevention of chemotherapy-induced nausea and vomiting in adults undergoing moderately or highly emetogenic chemotherapy. We assessed the efficacy and safety of palonosetron versus ondansetron in the prevention of chemotherapy-induced nausea and vomiting in paediatric patients.
METHODS:
In this multicentre, multinational, double-blind, double-dummy, phase 3 study, paediatric patients aged between 0 and younger than 17 years, who were naive or non-naive to chemotherapy, and scheduled to undergo moderately or highly emetogenic chemotherapy for the treatment of malignant disease were randomised centrally (1:1:1) to receive up to four cycles of 10 μg/kg or 20 μg/kg palonosetron on day 1, or three 150 μg/kg doses of ondansetron on day 1, scheduled 4 h apart, according to a static central permuted block randomisation scheme by an interactive web response system. Randomisation was stratified according to age and emetogenicity. Treatment allocation was masked to project team members involved in data collection and analysis, and members of the investigator's team. The primary endpoint was complete response (no vomiting, retching, or use of rescue drugs) during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle, as assessed in the population of randomly assigned patients who received moderately or highly emetogenic chemotherapy and an active study drug. The primary efficacy objective was to show the non-inferiority of palonosetron versus ondansetron during the acute phase (0-24 h post-chemotherapy) of the first on-study chemotherapy cycle through comparison of the difference in the proportions of patients who achieved a complete response with palonosetron (πT) minus ondansetron (πR) versus a preset non-inferiority margin (δ -15%). To be considered as non-inferior to ondansetron, for at least one of the doses of palonosetron, the lower limit of the 97·5% CI for the weighted sum of the differences in complete response rates had to be superior to -15%. Safety was assessed, according to treatment received. This study is registered with ClinicalTrials.gov, number NCT01442376, and has been completed.
FINDINGS:
Between Sept 12, 2011, and Oct 26, 2012, we randomly assigned 502 patients; 169 were assigned to receive 10 μg/kg palonosetron, 169 to receive 20 μg/kg palonosetron, and 164 to receive 3 × 150 μg/kg ondansetron, of whom 166, 165, and 162, respectively, were included in the efficacy analysis. In the acute phase, complete responses were recorded in 90 (54%) patients in the 10 μg/kg palonosetron group, 98 (59%) in the 20 μg/kg palonosetron group, and 95 (59%) in the ondansetron group. Non-inferiority versus ondansetron was shown for 20 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates 0·36% [97·5% CI -11·7 to 12·4]; p=0·0022). Non-inferiority versus ondansetron was not shown for 10 μg/kg palonosetron in the acute phase (weighted sum of the differences in complete response rates -4·41% [97·5% CI -16·4 to 7·6]). In the first on-study treatment cycle, treatment-emergent adverse events were reported in 134 (80%) of 167 patients who received 10 μg/kg palonosetron, 113 (69%) of 163 who received 20 μg/kg palonosetron, and 134 (82%) of 164 who received ondansetron. The most common drug-related treatment-emergent adverse events were nervous system disorders, mainly headache, which occurred in three (2%) patients who received 10 μg/kg palonosetron, one (<1%) patient who received 20 μg/kg palonosetron, and two (1%) patients who received ondansetron. The incidence of serious adverse events in the first on-study treatment cycle was lower in the 20 μg/kg palonosetron group (43 [26%]) than in the 10 μg/kg palonosetron group (52 [31%]) and the ondansetron group (55 [34%]).

INTERPRETATION:
Non-inferiority was shown for 20 µg/kg palonosetron during the acute phase of the first on-study chemotherapy cycle. 20 µg/kg palonosetron is now indicated by the European Medicines Agency and the US Food and Drug Administration for the prevention of chemotherapy-induced nausea and vomiting in paediatric patients aged 1 month to younger than 17 years.
FUNDING:
Helsinn Healthcare.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to March Week 5 2017
Search Strategy:

#	Searches	Results
1	rolapitant.mp.	24
2	(netupitant and palonosetron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	34
3	ondansetron.mp. or Ondansetron/	2880
4	fosaprepitant.mp.	58
5	aprepitant.mp.	634
6	dolasetron.mp.	251
7	granisetron.mp. or Granisetron/	1093
8	(doxylamine and pyridoxine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	83
9	palonosetron.mp.	375
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	4474
11	limit 10 to (english language and humans and yr="2015 -Current")	296
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	151

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs will be subject to PA criteria

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for doxylamine/pyridoxine (Diclegis®) or (Bonjesta) for pregnancy-related nausea or vomiting?	**Yes:** Go to #4	**No:** Go to #5

4. Has the patient failed a trial of pyridoxine? Message: • Preferred vitamin B products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Approve for up to 3 months	**No:** Pass to RPh; deny and recommend a trial of pyridoxine.
5. Is the request for dronabinol (Marinol®)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have anorexia associated with HIV/AIDS?	**Yes:** Approve for up to 6 months*	**No:** Go to #7
7. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	**Yes:** Approve for up to 6 months	**No:** Go to #8
8. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months*	**No:** Go to #9
9. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	**Yes:** Approve for up to 6 months*	**No:** Pass to RPh. Deny; medical appropriateness. Must trial at least 2 preferred antiemetics.
* If the request is for dronabinol (Marinol®) do not exceed 3 doses/day for 2.5 mg and 5 mg strengths and 2 doses/day for the 10 mg strength.		

P&T / DUR Review: *7/17 (KS); 1/17 (DM) 1/16; 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03*
Implementation: *TBD; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03*

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Drug Class Literature Scan: Pancreatic Enzymes

Date of Review: September 2017

Date of Last Review: March 2014
Literature Search: 03/01/14 – 05/12/17

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

Conclusions:
- This class scan identified 1 systematic review from the Cochrane Collaboration, 1 new randomized controlled trial, 1 guideline update, and 1 new FDA safety alert.
- There is insufficient comparative evidence between pancreatic enzyme preparations. There is insufficient evidence to support a difference in safety or efficacy of pancreatic enzyme preparations among cystic fibrosis patients or subgroups.

Recommendations:
- No further review or research needed.
- Evaluate comparative costs in executive session.

Previous Conclusions:
- Overall, there is a lack of large, high-quality trial data and no comparative studies are available. All trials are relatively small ranging from 17 to 54 subjects. Therefore, there is insufficient evidence to determine any differences in efficacy or safety between the agents. Efficacy endpoints are highly dependent on nutritional consults and accurate food diaries of study subjects.
- The included trials favored the studied pancreatic enzyme replacement products (PEPs) in the primary efficacy endpoints, improved coefficient of fat absorption (CFA), either change in CFA or overall CFA, from baseline to the end of the study compared to placebo. Mean CFAs for treatment groups ranged from 82.8-88.6%, which was statistically significantly larger than the mean CFA found in patients treated with placebo (47.4-49.6%).
- In clinical trials, patient diets were developed by nutritionists and tightly controlled, thus, trials did not account for inter-patient variability in diet, which can potentially affect efficacy of PEP products.
- Adverse effects for all available products are similar to placebo, with the most common side effects being various measures of abdominal discomfort. Other side effects include headache, weight loss, rash, flatulence and nasopharyngitis.
- The most important factor to consider in the treatment of EPI is administering the appropriate amount of lipase units to each individual patient based on diet.

Author: D. Engen

Previous Recommendations:

- Due to no apparent differences in efficacy or safety, continue to recommend inclusion of at least one agent in this class in accordance with FDA recommendations and administration concerns.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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:

Cochrane: Pancreatic Enzyme Replacement Therapy for People with Cystic Fibrosis

A 2016 Cochrane systematic review evaluated the efficacy and safety of various formulations of pancreatic enzyme replacement therapies (PERT) for cystic fibrosis patients.[1] Thirteen studies included children and adults of different age groups (n=512).[1] Eight of the trials involved children ages 1-17 years, four trials studied adults ages 21-24 years, and one study included ages 12 and older.[1] All studies were of 4 weeks duration. Seven studies compared enteric coated microspheres (ECM) with other enteric-coated preparations, four compared ECM versus another ECM, and two compared various doses of PERT.[1] Primary outcomes assessed were changes in weight, height, and body mass index (BMI).[1] Study quality was mixed as all 13 trials lacked details of randomization and allocation concealment methods, 6 of the 13 studies gave no details of blinding methods, and several studies had a high risk of attrition and reporting bias due to incomplete outcome data and selective reporting.[1] Due to heterogeneous trial data, small sample sizes, and unclear to high risk of bias in a majority of the trials, the evidence was insufficient to quantify treatment effect size of the different pancreatic enzyme formulations on the nutritional status of cystic fibrosis patients.[1]

New Guidelines:

Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation published a clinical practice guideline to address nutritional care of preschool children ages 2 to 5 years old with cystic fibrosis (CF).[2] The guideline committee consisted of 16 CF pediatric experts and parents; however, non-specialists or experts in methodology were not included on the guideline committee. Overall, there are very little data in children ages 2 to 5 years old and therefore the recommendations included in the guideline are based on expert opinion and are likely to change based on additional research. Consensus recommendations included in the guideline were based on extrapolation from other CF Foundation or general pediatrics guidelines due to the small pool of subjects and gaps in evidence. An 80% agreement threshold was decided a priori for recommendations. The consensus recommendations for children of preschool-aged children with CF and pancreatic insufficiency suggests PERT be

adjusted to a dose of no greater than 2500 lipase units per kilogram per meal with a maximum daily dose of 10,000 lipase units per kilogram. These recommendations are clearly consensus statements and are not systematically developed from a thorough evidence review and evaluation.

New Formulations:
No new formulations were identified.

New FDA Safety Alerts:
Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP)
The FDA updated questions and answers directed to healthcare professionals and the public about the safe use of approved PEPs.[3] The original text was posted on April 12, 2010 with the most recent version dated October 20, 2016.[3] Each question addressed a particular area of product concern. The post included information on the most current PEP products available and their FDA-approved uses, as well as important details regarding safe administration, availability, and key points for patients and prescribers.[3] Key points included:

1. Creon, Zenpep, Pancreaze, Viokace, and Pertzye are currently the only FDA-approved PEPs that are marketed in the United States.
2. PEPs are not interchangeable at the pharmacy. Patients currently taking an unapproved PEP will require a new prescription for Creon, Zenpep, Pancreaze, Viokace, or Pertzye.
3. When switching a patient to another PEP, consider starting with a similar amount of lipase enzyme, then adjust the dose based on the patient's response.
4. Recognize that the labeled contents of FDA-approved PEPs reflect the actual enzyme content of the product, whereas the labeled contents of unapproved PEPs underestimate the actual lipase content.
5. Recognize that it may take 1-2 weeks for a patient to adjust their dose of the new PEP. Individual patient response should be monitored when switching from an unapproved PEP to an approved one.

References:

1. Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD008227.pub3/abstract.
2. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. Pediatrics. 2016;137(4):e20151784. doi:10.1542/peds.2015-1784.
3. The Food and Drug Administration. CDER Postmarket Drug Safety Information for Patients and Providers - Updated Questions and Answers for Healthcare Professionals and the Public: Use an Approved Pancreatic Enzyme Product (PEP). https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm204745.htm. Accessed June 21, 2017.
4. Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15(5):675-680. doi:10.1016/j.jcf.2016.02.010.

Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL
CAPSULE DR	CREON	LIPASE/PROTEASE/AMYLASE	Y
CAPSULE DR	PANCREAZE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	PERTZYE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 12	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 18	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 20	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ULTRASE MT 6	LIPASE/PROTEASE/AMYLASE	N
TABLET	VIOKACE	LIPASE/PROTEASE/AMYLASE	N
CAPSULE DR	ZENPEP	LIPASE/PROTEASE/AMYLASE	N

Appendix 2: New Comparative Clinical Trials

A total of 9 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Taylor et al.[4] 2015 RCT, DB, Crossover, Noninferiority study, Multicenter	Group A: Zenpep® followed by Creon® Group B: Creon® followed by Zenpep®; 28 days per treatment arm Dosing: patients began assigned treatment at a dose as close as possible to their established PEP treatment (maximum of 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day, not to exceed a dose of 10,000 lipase units/kg of body weight per day)	One clinical feature of CF and 2 disease causing mutations in genotype or sweat chloride concentration >60 mmol/L	CFA over 72 hours calculated from dietary fat intake and stools collected during the last 3 days (72 consecutive hours) of each treatment period	No difference: Noninferiority established; LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; p = 0.297

Abbreviations: RCT = randomized clinical trial; DB = double blind; CF = cystic fibrosis; CFA = Coefficient of Fat Absorption; MD = mean difference; LS = least squares; SE = standard error

Appendix 3: Abstracts of Comparative Clinical Trials

Taylor CJ, Thieroff-Ekerdt R, Shiff S, Magnus L, Fleming R, Gommoll C. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. Journal of Cystic Fibrosis. 2016;15(5):675-680. doi:10.1016/j.jcf.2016.02.010.

Background:
Zenpep (APT-1008) is a pancreatic enzyme product for the treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF).

Methods:
Zenpep and Creon, both containing 25,000 lipase units, were compared in a randomized, double-blind, crossover, non-inferiority study for CF-associated EPI in patients aged ≥ 12 years. Patients on a standardized diet and stabilized treatment were randomized to two treatment sequences: Zenpep/Creon or Creon/Zenpep. The primary efficacy endpoint was the coefficient of fat absorption over 72 h (CFA-72 h).

Results:
96 patients (mean age 19.2 years, 60.4% males) were randomised with 83 completers of both sequences comprising the efficacy population. Zenpep demonstrated non-inferiority and equivalence to Creon in fat absorption (LS mean CFA-72 h: Zenpep, 84.1% [SE 1.1] vs. Creon, 85.3% [SE 1.1]; p = 0.297). Safety and tolerability were similar.

Conclusions:
Zenpep is comparable with Creon in efficacy and safety for the treatment of adolescents and adults with CF-associated EPI. (NCT01641393)

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 2 2017
1 Viokase.mp.4
2 Pertzye.mp. 2
3 Pancreaze.mp. 5
4 Zenpep.mp. 9
5 Creon.mp. 59
6 Ultresa.mp. 2
7 Pancrelipase/ or pancrealipase.mp. 207
8 lipase.mp. or Lipase/ 21068
9 protease.mp. 83937
10 amylase.mp. 11735
11 8 and 9 and 10 220
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 11 450
13 limit 12 to (humans and english and (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 practice guideline or randomized controlled trial or systematic reviews) and last 3 years) 9

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Drug Class Literature Scan: Antiplatelets

Date of Review: September 2017

Date of Last Review: July 2015
Literature Search: July 2015-June 2017

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

Conclusions:

- A Cochrane systematic review evaluated the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis on the outcome of graft patency.[3] The overall applicability of this systematic review to clinical practice is low and results cannot be used to make policy changes at this time. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) could not be calculated.
- There are significant new data from multiple trials, systematic reviews, and guidelines addressing the most appropriate duration of dual antiplatelet therapy (DAPT) with aspirin and other antiplatelet agent following acute coronary syndrome (ACS). Overall, the data suggests that DAPT beyond 12 months decreases ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk.
- Previous large randomized controlled trials (RCTs) have demonstrated a reduction in ischemic events with the more potent P2Y12 inhibitors (prasugrel and ticagrelor) compared to clopidogrel with an absolute risk reduction (ARR) of approximately 2%.[1,2] A recent network meta-analysis[7] and a large RCT[20] have conflicting results. The meta-analysis with many limitations found no difference in mortality, cardiovascular (CV) death, myocardial infarction (MI) or stent thrombosis with either prasugrel or ticagrelor compared to clopidogrel. Additionally, a large RCT in patients with symptomatic peripheral arterial disease found no difference in a composite CV outcome or major bleeding with ticagrelor versus clopidogrel (10.8% vs. 10.6%).
- A fixed-dose combination of aspirin and omeprazole (Yosprala®) was FDA approved in September 2016 for those patients at high risk of developing aspirin associated gastric ulcers. Approval studies demonstrated a significant reduction at 6 months in the incidence of gastric or duodenal ulcer formation compared to aspirin alone (ARR 3.8%-4.9%).[6] However, these studies remain unpublished and cannot be assessed for quality. Additionally, only patients with a history of gastric or duodenal ulcer were included in trials and comparison to aspirin alone in these high risk patients is not a clinically relevant comparison.

Recommendations:

- No changes to the PDL recommended at this time
- Review comparative costs in executive session

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Previous Conclusions:

- There is moderate quality evidence that prasugrel is associated with a lower rate of major adverse cardiovascular events (MACEs) compared to clopidogrel in patients with coronary artery disease (CAD) (OR 0.86; 95% CI 0.78 to 0.94), but also a high risk of major bleeding (OR 1.33; 95% CI 1.09 to 1.61). However, a recent meta-analysis demonstrated that the risk of MACEs far outweighed that of major bleeding (OR 7.48; 95% CI 3.75 to 14.94, p<0.0001) and of minor bleeding (OR 3.77; 95% CI 1.73 to 8.22; p=0.009).
- There is low quality evidence that short-term DAPT (less than 12 months) compared to-12 month therapy is associated with a similar rate of stent thrombosis and MI, with a reduced risk of major bleeding, while extended therapy (>12 months) compared with 12-month therapy is associated with reduction in stent thrombosis (NNT 100-250) and MI (NNT 50-125), but increased risk of major bleeding (NNH 111-325). Studies have also demonstrated an increase in all-cause mortality with extended DAPT beyond one year (2.0% vs. 1.5%; OR 1.36; 95% CI 1.00-1.85; NNH 200), driven by non-cardiovascular events. Further studies are needed to evaluate this risk and define the optimal duration of therapy. At this time, DAPT should be recommended for a year in most patients receiving a DES with high risk patients considering longer term use (up to 30 months) and patients at high risk of bleeding considering therapy for less than 6 months.
- There is moderate quality evidence that long term use (>1 year) of ticagrelor may reduce risk of myocardial infarction (MI) (NNT 118) and stroke (NNT 303), but increase risk of major bleeding (NNH 65) in patients with prior MI (more than 1 year previously) taking aspirin, based on the PEGASUS-TIMI 54 trial.
- New recommendations from the AHA for the primary prevention of stroke do not recommend antiplatelet regimens other than aspirin (and cilostazol for patients with PAD) be used for prevention of stroke due to a lack of evidence from relevant clinical trials. Primary prevention of stroke with aspirin is recommended for high risk individuals (10-year risk >10%), for persons with chronic kidney disease, and as a reasonable treatment option for patients with heart failure who do not have Atrial Fibrillation (AF) or a previous thromboembolic event.

Previous Recommendations:

- Continue to list aspirin and clopidogrel as preferred drugs due to high level evidence of benefit for multiple indications (Coronary Artery Disease [CAD], ACS, stroke and PAD).
- Make cilostazol a preferred drug on the PDL

Methods:

A DERP scan searched Ovid MEDLINE from December 2015 through January 2017 using terms for included drugs. An additional 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 from January 2017 through June 2017. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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:

Lower Limb Atherosclerosis

A Cochrane systematic review was done to determine the effects of antiplatelet agents for prevention of thrombosis in those with lower limb atherosclerosis undergoing bypass grafting.[3] A total of 16 studies (n=5683) were included in the analysis. The quality of evidence was low to moderate. Many of the treatment comparisons had few data to contribute, treatment dosages varied between studies, and the majority of studies did not describe their methods of randomization, allocation concealment or blinding of outcome assessors. The primary efficacy outcome was success of therapy, measured by graft patency. Six of the studies compared aspirin (ASA) or ASA plus dipyridamole (ASA/DIP) versus placebo or no treatment. There was improved graft patency in the ASA or ASA/DIP treatment group (OR 0.42; 95% CI 0.22 to 0.83; p=0.01). However, there was no improvement in those who received venous grafts. Additionally, studies included in the comparison were very old, and ASA doses ranged from 300mg to 325 mg given two to three times daily which is not consistent with doses used in clinical practice today. There was no difference in CV events (OR 1.27; 95% CI 0.43 to 3.80; 4 trials). The data was too scarce to combine and make definitive conclusions for all other comparisons of antiplatelet agents or other comparisons were not applicable to clinical practice standards. There was one large study (n=851) that evaluated clopidogrel and ASA versus ASA alone, and there was no difference of primary patency at 24 months (OR 0.95; 95% CI 0.69 to 1.31). There were fewer cases of total bleeding in the ASA alone group compared to ASA + clopidogrel (OR 2.65; 95% CI 1.69 to 4.15), but there was no difference in severe bleeding or fatal bleeding with few events in either group. There was no difference in all-cause mortality (OR 1.44; 95% CI 0.76 to 2.72). The overall applicability of this systematic review to practice is low and results cannot be used to make policy changes at this time. Further high-quality studies evaluating clinically meaningful outcomes are necessary. Absolute rates from trials were not included in the systematic review and the absolute risk reduction (ARR) and number needed to treat (NNT) were not able to be calculated.

Dual Antiplatelet Therapy

Three systematic reviews were published evaluating the duration of dual antiplatelet therapy (DAPT).[7–9] One review included studies with patients after acute myocardial infarction (MI), one included trials with patients after a drug-eluting stent (DES) implantation, and the third review included all secondary prevention populations. The results are consistent with previous data and guidelines suggesting that DAPT beyond 1 year decreased ischemic events but also increases the risk of bleeding and duration should be individualized taking into account risk of bleeding and ischemic risk. Since these trials only compared duration of treatment and did not compare individual antiplatelet agents, they will not impact the current preferred drug list (PDL) or prior authorization policy and will not be explored further.

Comparison of platelet adenosine diphosphate (ADP) $P2Y_{12}$ Inhibitors

A network meta-analysis to compare clinical outcomes of patients receiving clopidogrel, prasugrel, ticagrelor and cangrelor prior to or during percutaneous coronary intervention (PCI) was performed.[7] A literature search identified RCTs comparing at least 2 of the P2Y12 inhibitors in those who had a PCI. The Cochrane Collaboration tool for assessing risk of bias was used to evaluate included trials. The meta-analysis used indirect comparisons to compare each agent to clopidogrel. A total of 15 RCTs (n=54,025) were included in the meta-analysis.[7] Of the patients included in these trials, 29.4% of patients had a STEMI, 87.2% with ACS, and 92.4% underwent PCI. Compared to clopidogrel, there was no significant difference between either prasugrel or ticagrelor in all-cause mortality, CV death, MI, stent thrombosis, stroke, or major bleeding. There was an increased risk of minor bleeding with ticagrelor compared to clopidogrel (OR 1.59; 95% CI 1.10 to 5.03). Previous literature has suggested that prasugrel and ticagrelor achieve faster and greater inhibition of platelet binding compared to clopidogrel and individual RCTs have demonstrated a reduction in ischemic events after PCI for these agents compared to placebo.[7] Results of this analysis conflict with those findings. However, there are limitations of a network meta-analysis, a loss of statistical power for direct comparison, and follow-up times which varied greatly among the studies. This systematic review was not funded.

Aspirin in Peripheral Vascular Disease:

A systematic review registered in PROSPERO International prospective register of systematic reviews evaluated aspirin in patients with peripheral vascular disease.[10] A literature search limited to RCTs through January 2017 identified 11 studies that were included (n=6560). The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary efficacy outcome was all-cause mortality, and the primary safety outcome was major bleeding. The majority of trials had an unclear risk of bias due to lack of reporting of detailed methods. Two trials had a low risk of bias. Using the GRADE assessment tool, the level of evidence was considered low to moderate. Results from 9 trials found no difference in the incidence in all-cause mortality with aspirin versus control (7.7% vs. 8.5%; RR -0.93; 95% CI 0.8 to 1.1).[10] The incidence of MI and stroke were also similar between both groups. There was no difference incidence of major bleeding with aspirin compared to control (1.3% vs. 1.1%; RR 1.59; 95% CI 0.96 to 2.62).[10] These results conflict with recent guideline recommendations for aspirin in symptomatic peripheral vascular disease. The authors point out that the guideline recommendations were made based on 3 studies only with a high risk of bias in combination with older evidence using antiplatelet agents other than aspirin.[10]

New Guidelines:

Aspirin for Primary Prevention of Cardiovascular Disease

The U.S. Preventive Services Task Force (USPSTF) updated their recommendations to prevent cardiovascular disease (CVD) in June 2016.[11] The USPSTF is an independent, voluntary body and authors had no conflicts of interest. The USPSTF commissioned 3 systematic reviews and a decision-analysis model to develop its recommendation. The following recommendations were made:

Population	Recommendation	Evidence Grade
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	the USPTF recommends initiating low-dose aspirin for the primary prevention of CVD and colorectal cancer (CRC) in those who are not at increased risk of bleeding, have a life expectancy of at least 10 years and are willing to take low-dose aspirin for at least 10 years	B (high certainty that the net benefit is moderate)
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate aspirin should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C (recommend selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small)
Adults younger than 50 years	Evidence is insufficient	I
Adults aged 70 years or older	Evidence is insufficient	I

Management of Patients with Lower Extremity Peripheral Artery Disease (PAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published guidelines in 2016.[12]

The guidelines were sponsored by ACC/AHA and without commercial support. Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry. Approximately half of the other members disclosed some sort of relationship with industry within 12 months prior. There was one lay volunteer/patient representative on the guideline committee; however, the majority of other members were cardiovascular specialists and the committee was missing representation from primary care or other non-specialty practitioners. A contracted methodologist and external evidence review committee addressed systematic review questions and appraised the evidence.

The following recommendations for medical therapy with antiplatelets for the patient with PAD were provided. There were no strong recommendations for one agent over another, but aspirin is the favored medication for symptomatic PAD. Clopidogrel remains an alternative.

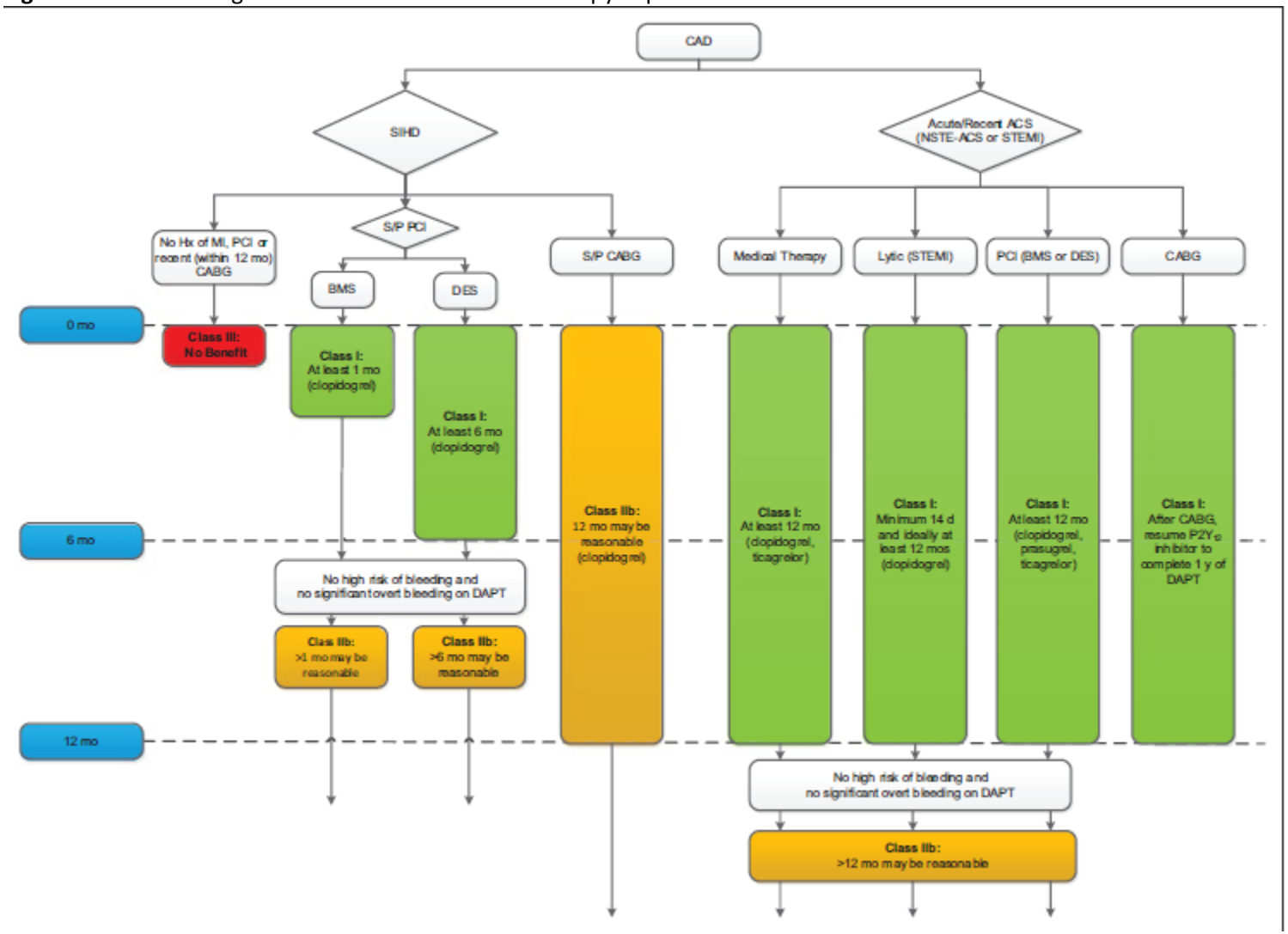
- Antiplatelet therapy with aspirin alone (75-325 mg) or clopidogrel alone is recommended to reduce myocardial infarction (MI), stroke and vascular death in patients with symptomatic PAD. Symptomatic PAD includes those with claudication and those with prior lower extremity revascularization.
    - Class of Recommendation I (Strong)
    - Level of Evidence A (high quality)
- In asymptomatic patients with PAD, antiplatelet therapy is reasonable to reduce the risk of MI, stroke or vascular death.
    - Class of Recommendation IIa (Moderate)
    - Level of Evidence C-EO (Expert Opinion)
- The effectiveness of dual antiplatelet therapy (DAPT) to reduce the risk of CV ischemic events in patients with symptomatic PAD is not well established.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)
- The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.
    - Class of Recommendation IIb (weak)
    - Level of Evidence B-R (randomized)

Duration of Dual Antiplatelet Therapy (DAPT) in Coronary Artery Disease (CAD)

The American College of Cardiology/American Heart Association (ACC/AHA) published a focused update on DAPT in CAD in 2016.[13] This update was necessary due to 11 studies of patients with stent implantation assessing shorter-duration or longer-duration of DAPT and one large RCT assessing DAPT versus aspirin monotherapy. This guideline focused on duration of DAPT and aspirin dosing and not if one particular $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) is preferred over another. Recommendations were made based on a systematic review conducted by an external evidence review committee.[14] Writing committee members were required to recuse themselves from voting on sections to which they had specific relationship with industry or other entities. The chair was required to have no relevant relationships with industry.

Overall, the new evidence supports the concept that duration of DAPT should be individualized based on risk of bleeding and ischemic risk. Longer duration compared with shorter duration of DAPT generally results in decreased ischemic risk at the expensive of an increased bleeding risk. Additionally, use of more potent $P2Y_{12}$ inhibitors in place of clopidogrel may result in decreased ischemic risk and increased bleeding risk. For patients with acute coronary syndrome (ACS), there is a strong recommendation that DAPT should be given for a minimum period of time (usually 6 to 12 months) and a weak recommendation for continuation of DAPT beyond that period of time. Additionally, shorter duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk. This is outlined in **Figure 1**.

Figure 1: Treatment algorithm for duration of DAPT therapy in patients with CAD[13]



In regards to choosing an antiplatelet, the guidelines state that "*it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel in patients with ACS treated with DAPT after coronary stent implantation and to use ticagrelor in those treated with medical therapy alone".* These are both moderate recommendations based on moderate quality evidence from 1 RCT.

New Formulations:

Yosprala® is a combination of aspirin and omeprazole approved September 2016 for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin associated gastric ulcers.[6] This is the only prescription fixed-dose combination of aspirin and a proton pump inhibitor and is available with both 81 and 325 mg of aspirin in combination of 40 mg of omeprazole. Approval was based on 2 unpublished, randomized, double-blind studies (n=524) over 6 months evaluating incidence of gastric ulcer formations with Yosprala compared to aspirin 325 mg alone in those at risk for developing gastric ulcers.[6] Patients had a cerebro- or cardiovascular diagnosis, were on aspirin for at least 3 months, and had a history of gastric or duodenal ulcer within the past 5 years. At month 6, the incidence of gastric or duodenal ulcer formation was lower in the Yosprala group compared to aspirin in study 1 and study 2 (3.8% vs. 8.7%; ARR 4.9%; NNT 21 and 8.5% vs. 2.7%; ARR 5.8%; NNT 18, respectively).[6] One study reported a higher rate of serious adverse events in the study group compared to aspirin alone (8.95% vs. 6.56%). Conversely, in the second study, rate of serious adverse events was higher in the aspirin group (9.06% vs. 6.06%). P-values were not reported. These studies remain unpublished and could not be assessed for quality. Results were collected from the prescribing information[6] and clinicaltrials.gov. Additionally, the comparison to aspirin alone in those with a history of an ulcer is not a clinically relevant comparison.

Long term CV and gastrointestinal (GI) safety were evaluated in a 12-month, open-label, phase 3 study in adults requiring aspirin for secondary prevention of cardiovascular or cerebrovascular events with history of a gastric or duodenal ulcer (n=380).[14] Only 290 subjects completed the 12 month study. The most common GI events were diarrhea, dyspepsia, and nausea which were reported in 4-5% of the overall population. The overall incidence of treatment emergent adverse events was 75%. Adverse events leading to study withdrawal occurred in 13.5% of subjects, with the most common reason being gastroesophageal reflux disease (1.1%).[14]

New FDA Safety Alerts:

A safety alert was released in November 2015 after an FDA review on long-term treatment with clopidogrel.[15] The FDA concluded that the long term use of clopidogrel does not increase or decrease overall risk of death in patients with heart disease and there does not appear to be an increase in the risk of cancer related deaths or cancer related adverse events.

New FDA Approved Medications:

Cangrelor (Kengreal™) is a $P2Y_{12}$ inhibitor approved on 6/22/2015 as an adjunct to PCI for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.[16] It is administered as an intravenous bolus prior to PCI followed by an infusion during the procedure. Because it is not used in outpatients, the evidence will not be evaluated further.

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CPMP 12HR	AGGRENOX	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	CPMP 12HR	ASPIRIN-DIPYRIDAMOLE ER	ASPIRIN/DIPYRIDAMOLE	Y
ORAL	TABLET	CILOSTAZOL	CILOSTAZOL	Y
ORAL	TABLET	CLOPIDOGREL	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	PLAVIX	CLOPIDOGREL BISULFATE	Y
ORAL	TABLET	DIPYRIDAMOLE	DIPYRIDAMOLE	Y
ORAL	TAB CHEW	ASPIRIN	ASPIRIN	Y
ORAL	TAB CHEW	CHILDREN'S ASPIRIN	ASPIRIN	Y
ORAL	TABLET	ASPIRIN	ASPIRIN	Y
ORAL	TABLET DR	ASPIR 81	ASPIRIN	Y
ORAL	TABLET DR	ASPIRIN EC	ASPIRIN	Y
ORAL	TABLET DR	ASPIR-LOW	ASPIRIN	Y
ORAL	TABLET DR	ECPIRIN	ASPIRIN	Y
ORAL	TABLET DR	LOW DOSE ASPIRIN EC	ASPIRIN	Y
ORAL	CAP ER 24H	DURLAZA	ASPIRIN	N
ORAL	TABLET	BRILINTA	TICAGRELOR	N
ORAL	TABLET	EFFIENT	PRASUGREL HCL	N
ORAL	TABLET	TICLOPIDINE HCL	TICLOPIDINE HCL	N
ORAL	TABLET	ZONTIVITY	VORAPAXAR SULFATE	N

Appendix 2: New Comparative Clinical Trials

A total of 13 citations were manually reviewed from the initial literature search and an additional 5 were reviewed from the DERP scan. After further review, 15 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (platelet reactivity, platelet aggregation rates, mean platelet volume). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
PHILO[17] RCT, DB	Clopidogrel vs. ticagrelor	ACS in patients in Asia treated with PCI on background aspirin	Time to occurrence of myocardial infarction, stroke or death from vascular causes	Composite CV outcome: Clo: 25 (6.3%) Tic: 36 (9.0%) HR 1.47; 95% CI 0.88 to 2.44 Major Bleeding: Clo: 26 (6.8%) Tic: 40 (10.3%) HR 1.54; 95% CI 0.94 to 2.53
He at al.[18] RCT, open-label	Clopidogrel + ASA vs. ASA	Minor stroke or TIA	Neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days after admission	Deterioration of stroke: Clo+ASA: 9 ASA: 19 *Statistics not provided
Johnston et al.[19] RCT, DB	Ticagrelor vs. ASA	Non-severe ischemic stroke or high-risk TIA	Time to occurrence of stroke, myocardial infarction, or death within 90 days	Composite of stroke, myocardial infarction, or death Tic: 442/6589 (6.7%) ASA: 497/6610 (7.5%) HR 0.89; 95% CI 0.78 to 1.01 Major Bleeding: Tic: 31(0.5%) ASA: 38 (0.6%) HR 0.83; 95% CI 0.52 to 1.34
Hiatt et al.[20] RCT, DB	Ticagrelor vs. Clopidogrel	Symptomatic peripheral arterial disease	Composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke	Composite CV outcome: Clo: 740 (10.6%) Tic: 751 (10.8%) HR 1.02; 05% CI 0.92 to 1.13 P=NS Major Bleeding: Clo: 109 (1.6%) Tic: 113 (1.6%) HR 1.10; 95% CI

Abbreviations: ASA = aspirin; DB = double blind; PCI = percutaneous coronary intervention; RCT = randomized clinical trial; TIA = transient ischemic attack

Author: M. Herink Date: September 2017

1. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. *Circ J*. 2015;79(11):2452-60. doi: 10.1253/circj.CJ-15-0112. Epub 2015 Sep 16.

BACKGROUND:
Few data on the relative efficacy and safety of new P2Y12inhibitors such as prasugrel and ticagrelor in Japanese, Taiwanese and South Korean patients with acute coronary syndromes (ACS) exist.

METHODS AND RESULTS:
The multicenter, double-blind, randomized PHILO trial compared the safety and efficacy of ticagrelor vs. clopidogrel in 801 patients with ACS (Japanese, n=721; Taiwanese, n=35; South Korean, n=44; unknown ethnicity, n=1). All were planned to undergo percutaneous coronary intervention and randomized within 24 h of symptom onset. Primary safety and efficacy endpoints were time to first occurrence of any major bleeding event and to any event from the composite of myocardial infarction, stroke or death from vascular causes, respectively.At 12 months, overall major bleeding occurred in 10.3% of ticagrelor-treated patients and in 6.8% of clopidogrel-treated patients (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94-2.53); the composite primary efficacy endpoint occurred in 9.0% and in 6.3% of ticagrelor- and clopidogrel-treated patients, respectively (HR, 1.47; 95% CI: 0.88-2.44). For both analyses, the difference between groups was not statistically significant.

CONCLUSIONS:
In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population.

2. He F, Xia C, Zhang JH, Li XQ, Zhou ZH, Li FP, Li W, Lv Y, Chen HS. Clopidogrel plus aspirin versus aspirin alone for preventing early neurological deterioration in patients with acute ischemic stroke. *J Clin Neurosci.* 2015 Jan;22(1):83-6. doi: 10.1016/j.jocn.2014.05.038. Epub 2014 Sep 10.

Abstract
Recent studies have suggested that combination antiplatelet therapy may be superior to monotherapy in the treatment of acute stroke. However, additional prospective studies are needed to confirm this finding. The present trial compared the efficacy and safety of clopidogrel plus aspirin versus aspirin alone in the treatment of non-cardioembolic ischemic stroke within 72 hours of onset. Six hundred and ninety patients aged $\geqslant$ 40 years with minor stroke or transient ischemic attack (TIA) were identified for enrollment. Experienced physicians determined baseline National Institutes of Health Stroke Scale scores at the time of admission. All patients were randomly allocated (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100mg/day). The main endpoints were neurological deterioration, recurrent stroke, and development of stroke in patients with TIA within 14 days of admission. After 43 patients were excluded, 321 patients in the dual therapy group and 326 patients in the monotherapy group completed the treatment. Baseline characteristics were similar between groups. During the 2 week period, stroke deterioration occurred in nine patients in the dual therapy group and 19 patients in the monotherapy group. Stroke occurred after TIA in one patient in the dual therapy group and three patients in the monotherapy group. Similar

numbers of adverse events occurred in both groups. This study showed that early dual antiplatelet treatment reduced early neurological deterioration in patients with acute ischemic stroke, compared with antiplatelet monotherapy. These results imply that dual antiplatelet therapy is superior to monotherapy in the early treatment of acute ischemic stroke.

3. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med.* 2016 Jul 7;375(1):35-43. doi: 10.1056/NEJMoa1603060. Epub 2016 May 10.

BACKGROUND:
Ticagrelor may be a more effective antiplatelet therapy than aspirin for the prevention of recurrent stroke and cardiovascular events in patients with acute cerebral ischemia.

METHODS:
We conducted an international double-blind, controlled trial in 674 centers in 33 countries, in which 13,199 patients with a nonsevere ischemic stroke or high-risk transient ischemic attack who had not received intravenous or intraarterial thrombolysis and were not considered to have had a cardioembolic stroke were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or aspirin (300 mg on day 1 followed by 100 mg daily for days 2 through 90). The primary end point was the time to the occurrence of stroke, myocardial infarction, or death within 90 days.

RESULTS:
During the 90 days of treatment, a primary end-point event occurred in 442 of the 6589 patients (6.7%) treated with ticagrelor, versus 497 of the 6610 patients (7.5%) treated with aspirin (hazard ratio, 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and in 441 patients (6.7%) treated with aspirin (hazard ratio, 0.87; 95% CI, 0.76 to 1.00). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3%, respectively, and fatal bleeding in 0.1% and 0.1%.

CONCLUSIONS:
In our trial involving patients with acute ischemic stroke or transient ischemic attack, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01994720.).

4. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med*. 2017 Jan 5;376(1):32-40. doi: 10.1056/NEJMoa1611688. Epub 2016 Nov 13.

BACKGROUND:
Peripheral artery disease is considered to be a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. Data from previous trials have suggested that patients receiving clopidogrel monotherapy had a lower risk of cardiovascular events than those receiving aspirin. We wanted to compare clopidogrel with ticagrelor, a potent antiplatelet agent, in patients with peripheral artery disease.

METHODS:
In this double-blind, event-driven trial, we randomly assigned 13,885 patients with symptomatic peripheral artery disease to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patients were eligible if they had an ankle-brachial index (ABI) of 0.80 or less or had undergone previous revascularization of the lower limbs. The primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety end point was major bleeding. The median follow-up was 30 months.

RESULTS:
The median age of the patients was 66 years, and 72% were men; 43% were enrolled on the basis of the ABI and 57% on the basis of previous revascularization. The mean baseline ABI in all patients was 0.71, 76.6% of the patients had claudication, and 4.6% had critical limb ischemia. The primary efficacy end point occurred in 751 of 6930 patients (10.8%) receiving ticagrelor and in 740 of 6955 (10.6%) receiving clopidogrel (hazard ratio, 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65). In each group, acute limb ischemia occurred in 1.7% of the patients (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85) and major bleeding in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49).

CONCLUSIONS:
In patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups. (Funded by AstraZeneca; EUCLID ClinicalTrials.gov number, NCT01732822 .).

Appendix 4: Medline Search Strategy

1	Platelet Aggregation Inhibitors/ or antiplatelets.mp.	27809
2	aspirin.mp. or Aspirin/	33795
3	Aspirin/	22000
4	Dipyridamole/ or Aspirin, Dipyridamole Drug Combination/	2499
5	clopidogrel.mp.	10526
6	ticagrelor.mp.	1229
7	prasugrel.mp. or Prasugrel Hydrochloride/	1540
8	Ticlopidine/ or ticlodipine.mp.	8530
9	vorapaxar.mp.	191
10	acute coronary syndrome.mp. or Acute Coronary Syndrome/	17978
11	Coronary Artery Bypass/ or Myocardial Revascularization/ or Angioplasty, Balloon, Coronary/ or coronary revascularization.mp.	62248
12	Stents/ or drug eluding stent.mp.	53562
13	Arterial Occlusive Diseases/ or Cerebral Infarction/ or Stroke/ or ischemic stroke.mp. or Ischemic Attack, Transient/	107484
14	peripheral vascular disease.mp. or Peripheral Vascular Diseases/	11432
15	1 or 2 or 4 or 5 or 6 or 7 or 8 or 9	54413
16	10 or 11 or 12 or 13 or 14	229804
17	15 and 16	15201
18	limit 17 to (english language and humans and yr="2017 -Current" and (clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or systematic reviews))	13

Antiplatelets

Goal:

- Approve antiplatelet drugs for funded diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives 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?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is this continuation of hospital treatment?	**Yes:** Approve for 30 days only and inform provider of preferred products.	**No:** Go to #5

Approval Criteria		
5. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

FDA Approved Indications (July 2017)

	2º Stroke	2º PAD	2º MI	ACS	
				No PCI	PCI
ASA/DP ER	x				
clopidogrel	x	x	x	x	x
prasugrel	CI				x
ticagrelor				x	x
vorapaxar	CI	x	x		

Abbreviations: 2º = secondary prevention; ACS=Acute Coronary Syndrome; ASA/DP ER = aspirin/dipyridamole; CI=contraindication; PCI=Percutaneous Intervention; X = FDA-approved indication.

P&T / DUR Review: *7/17; (MH) 7/15 (KK); 11/11*
Implementation: *10/15, 8/15; 7/31/14; 4/9/12*

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Drug Class Literature Scan: Topical Steroids

Date of Review: September 2017

Date of Last Review: March 2015
Literature Search: 3/1/2015– 6/9/2017

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

Conclusions:
- Since the last review additional evidence has become available with the publication of 2 systematic reviews and 1 CADTH Rapid Response Report. There are also 2 new topical steroid formulations.
- There is no new comparative evidence since the last review to support a difference in safety or efficacy among equipotent topical corticosteroids.
- There is insufficient evidence that the betamethasone valerate foam formulation provides any clinical benefit over other formulations currently available.

Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Previous Conclusions:
- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- At least one agent in each of the potency categories should be preferred.

Previous Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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 (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A 2016 Cochrane Collaboration systematic review evaluated topical treatments for scalp psoriasis.[1] Comparisons in safety and efficacy were made between very high, high, and medium-potency topical steroids, vitamin D3 analogues, corticosteroid plus vitamin D combination products, corticosteroid plus salicylic acid combination products, tar-based preparations, anthralin, salicylic acid monotherapy, and ciclopirox olamine, and calcineurin inhibitors. Fifty-nine randomized controlled trials in 11,561 participants were included. Data on age of participants were available in 38 of the studies (n=9051) with a mean age of 45.2 years. Follow-up lasted for a median duration of 2.4 weeks (range: 1-8 weeks). Primary outcomes included either lesion clearance or clinical response as measured by the 5-point Investigator's Global Assessment (IGA) scale, quality of life improvements, and adverse events leading to treatment withdrawal. The IGA scale ranges from 0 or 1 (clear) to 5 (severe disease). Investigators used the proportion of patients with at least a 2 point IGA point reduction from baseline to define clearance or clinical response to therapy in clinical trials.

Between topical steroid preparations, there was no difference found in lesion clearance or clinical response between the very high potency steroid clobetasol propionate and high potency steroid comparator betamethasone dipropionate.[1] Likewise, high potency steroids betamethasone and fluocinolone acetonide 0.025% were unable to demonstrate a significant difference in lesion clearance or response when compared to treatment with medium potency hydrocortisone 17-butyrate 0.1%.[1] Among high potency steroids, one study (n=203) of moderate quality demonstrated a higher proportion of participants achieved scalp lesion clearance with mometasone furoate than betamethasone valerate 0.1% (RR 1.84; 95% Confidence Interval (CI) 1.09 to 3.11; ARR = 14%; Number Needed to Treat (NNT) = 8), as measured by a 2-point IGA reduction. However, there was insufficient information on allocation concealment, participant and personnel blinding, and outcome assessment blinding which resulted in a unclear to high risk of bias.[1] Data from 4 studies (n=2180) demonstrated that topical steroids improved psoriatic lesion clearance in 29% of patients compared to 16% of patients on calcitriol (Relative Risk (RR) 1.82; 95% CI 1.52 to 2.18; Absolute Risk Reduction (ARR) = 13%; NNT = 8).[1] Three of the 4 studies had unclear blinding of the outcome assessment and all four studies had unclear allocation concealment which resulted in the quality of evidence downgraded to moderate risk of bias by the authors.[1] Combinations of topical steroids plus vitamin D was more effective than vitamin D alone (RR 2.28; 95% CI 1.87 to 2.78; ARR = 19%, NNT = 6; high quality evidence).[1] In three studies (n=1827), overall treatment response favored corticosteroids over vitamin D (RR 2.09; 95% CI 1.80 to 2.41; ARR = 28%, NNT=4; high quality evidence).[1] Treatment of scalp psoriasis with vitamin D appeared to increase study withdrawals due to adverse events when compared with corticosteroids (5% vs. 1%, respectively; four studies, n=2291; ARI = 4%, NNH = 25) although no study reported the nature of the adverse event requiring withdrawal.[1] There was insufficient evidence to assess efficacy and safety of additional topical agents such as salicylic acid, tar, or anthralin-based treatments.

A 2015 Cochrane Collaboration systematic review update compared the effects of topical corticosteroids on pregnancy outcomes in pregnant women.[2] Fourteen observational studies (n=1,601,515) were included in the review of multiple steroid agents with variable potency.[1] Primary outcomes assessed included congenital abnormalities, orofacial clefts, preterm delivery, or low birth weight. The majority of studies failed to find topical steroid use associated with significant increased risk of adverse pregnancy outcomes regardless of potency. Although 3 cohort studies showed an increased risk of low birth weight in women exposed to potent or very potent topical steroids, pooled data from 47,651 patients found no associated risk [RR 1.58, 95% CI 0.96 to 2.58].[2] Based on

variations within the 4 cohort studies and due to 1 study without reports of potent or very potent steroid use, the overall quality of evidence was graded by the authors as low to very low.[2]

A 2015 CADTH Rapid Response Report reviewed the clinical effectiveness of betamethasone valerate (BMV) 0.12% foam compared to BMV topical 0.1% lotion and calcipotriol for scalp psoriasis treatment.[3] The reviewers identified two studies which met inclusion criteria. The clinical measures used to assess primary outcomes were the psoriasis physical signs Sum score and the Investigator's/Physician's Global Assessment (PGA) score. The Sum score assigns a numeric value for physical characteristics of psoriasis as measured by erythema (0-4), scaling (0-4), and induration (0-4) and the total value correlates moderately well with disease severity.[4] The Investigator's/Physician's Global Assessment (IGA/PGA) Score is a reliable assessment tool which commonly exists as a 5, 6, or 7-point ordinal scale which ranges from a lower score of "clear" to a higher score indicative of "very severe psoriasis." In one study (n=241), the Sum score at 28 days was significantly lower for BMV 0.12% foam than of standard treatment, which included BMV 0.1% lotion and calcipotriol (Mean Sum Score BMV foam: 1.5 [95% CI: 1.3 – 1.7] vs. Standard treatment: 3.1 [95% CI: 2.8 – 3.4]) from a baseline value of 7.6 (95% CI: 7.3 – 7.9).[3] The same study demonstrated that BMV foam treatment resulted in a greater proportion of participants with cleared or almost cleared scalp psoriasis compared to standard treatment of corticosteroids plus calcipotriol (88% vs. 66%, p<0.001) as measured by IGA score reductions.[3] A different study demonstrated that a greater proportion of patients were completely or almost completely cleared of disease at 28 days with BMV 0.12% foam compared to BMV lotion or placebo lotion (72 % vs. 47% vs. 21% respectively, p<0.05) as measured by reductions in a 7-point IGA score[3,4] No significant differences were observed in pruritus scores between BMV foam and BMV lotion.

Guidelines:
No new guidelines identified.

New Formulations:
Ultravate® (halobetasol propionate lotion 0.05%) was FDA approved in November 2015 for the topical treatment of moderate plaque psoriasis in patients 18 years of age and older.[5] Approval was based on two identical unpublished, randomized, double-blind, vehicle-controlled studies (n=443) with moderate to severe plaque psoriasis involving 2-12% of body surface area (BSA).[6] Treatment success was defined by the proportion of patients cleared or almost cleared of scaling, erythema and plaque elevation at 2 weeks as determined by a 2-point reduction from baseline in the 5-point Investigator Global Assessment (IGA) score.[6] Overall treatment success for the first trial was 49/110 (44.5%) versus 7/111 (6.3%) (p<0.001, NNT=3) with the second trial showing similar success (49/110 [44.5%] vs. 8/112 [7.1%], p<0.001, NNT=3).[6] The most common adverse reactions were telangiectasia (1.1%) and skin atrophy (1.5%).[6]

In January, 2016 the FDA approved a 0.05% topical spray formulation of betamethasone dipropionate (Sernivo®) for the treatment of adults 18 years or older with mild to moderate plaque psoriasis.[7] Approval for the spray was based on two unpublished, multi-center, double-blind trials in subjects randomized to either Sernivo® Spray (n=352) or placebo vehicle spray (n=180) applied twice daily for 4 weeks.[7] Treatment success was defined by a two-point reduction in IGA score from a baseline of 3 (moderate) to 0 or 1 (clear or almost clear).[7] In both studies at 29 days, treatment success was achieved by a higher proportion of betamethasone diopropionate spray subjects than those on placebo (42.7% vs 11.7% and 34.5% vs 13.6%, P < .001, NNT=4 and 5, respectively).[7] Adverse reactions included pruritus (6%), burning and/or stinging (4.5%), and pain (2.3%).[7]

FDA Safety Alerts:
None identified.

References:

1. Schlager JG, Rosumeck S, Werner RN, et al. Topical treatments for scalp psoriasis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD009687.pub2/abstract. Accessed April 11, 2017.
2. Chi C-C, Wang S-H, Wojnarowska F, Kirtschig G, Davies E, Bennett C. Safety of topical corticosteroids in pregnancy. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2015. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD007346.pub3/abstract. Accessed April 7, 2017.
3. Betamethasone for Adults with Scalp Psoriasis: A Review of the Clinical and Cost-Effectiveness | CADTH.ca. https://www.cadth.ca/betamethasone-adults-scalp-psoriasis-review-clinical-and-cost-effectiveness-0. Accessed May 30, 2017.
4. Spuls PI, Lecluse LLA, Poulsen M-LNF, Bos JD, Stern RS, Nijsten T. How Good Are Clinical Severity and Outcome Measures for Psoriasis?: Quantitative Evaluation in a Systematic Review. Journal of Investigative Dermatology. 2010;130(4):933-943. doi:10.1038/jid.2009.391. Accessed June 9, 2017.
5. Ultravate® (halobetasol propionate lotion 0.05%) Prescribing Information. Ranbaxy Laboratories, Inc., Jacksonville, FL 32257. Nov 2015 http://www.ultravatelotion.com/pdf/ultravatelotionpi.pdf. Accessed May 4, 2017.
6. CDER Evaluation of Ultravate® https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208183Orig1s000MedR.pdf Accessed May 4, 2017.
7. Sernivo® (betamethasone dipropionate) Prescribing Information. DPT Laboratories, Ltd., San Antonio, TX 78215. Feb 2016 http://sernivo.com/documents/sernivo-pi.pdf. Accessed April 27, 2017.

Appendix 1: Current Preferred Drug List

Generic Name	Brand Name	Form	PDL Status
ALCLOMETASONE DIPROPIONATE	ALCLOMETASONE DIPROPIONATE	CREAM (G)	Y
ALCLOMETASONE DIPROPIONATE	ALCLOMETASONE DIPROPIONATE	OINT. (G)	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	CREAM (G)	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	LOTION	Y
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	OINT. (G)	Y
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	CREAM (G)	Y
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	OINT. (G)	Y
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	CREAM (G)	Y
CLOBETASOL PROPIONATE	TEMOVATE	CREAM (G)	Y
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	OINT. (G)	Y
CLOBETASOL PROPIONATE	TEMOVATE	OINT. (G)	Y
DESONIDE	DESONIDE	CREAM (G)	Y
DESONIDE	DESONIDE	OINT. (G)	Y
FLUOCINOLONE ACETONIDE	SYNALAR	CREAM (G)	Y
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	CREAM (G)	Y
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	SOLUTION	Y
FLUOCINOLONE ACETONIDE	SYNALAR	SOLUTION	Y
FLUOCINONIDE	FLUOCINONIDE	CREAM (G)	Y
FLUOCINONIDE	VANOS	CREAM (G)	Y
FLUOCINONIDE	FLUOCINONIDE	SOLUTION	Y
FLUOCINONIDE/EMOLLIENT BASE	FLUOCINONIDE-E	CREAM (G)	Y
HYDROCORTISONE	ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	PROCTOCORT	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-5	CREAM (G)	Y
HYDROCORTISONE	PREPARATION H	CREAM (G)	Y
HYDROCORTISONE	NOBLE FORMULA HC	CREAM (G)	Y
HYDROCORTISONE	NEOSPORIN	CREAM (G)	Y
HYDROCORTISONE	HYDROCREAM	CREAM (G)	Y
HYDROCORTISONE	ECZEMA ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-10 PLUS	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE-10	CREAM (G)	Y
HYDROCORTISONE	CORTIZONE FOR KIDS	CREAM (G)	Y
HYDROCORTISONE	CORTISONE	CREAM (G)	Y
HYDROCORTISONE	CORTAID	CREAM (G)	Y
HYDROCORTISONE	ANTI-ITCH	CREAM (G)	Y
HYDROCORTISONE	HYDROCORT	CREAM (G)	Y
HYDROCORTISONE	RECORT PLUS	CREAM (G)	Y
HYDROCORTISONE	SOOTHING CARE	CREAM (G)	Y
HYDROCORTISONE	HYDROCORTISONE	CREAM (G)	Y

HYDROCORTISONE	HYDROCORTISONE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORTISONE ACETATE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORTISONE	OINT. (G)	Y
HYDROCORTISONE	HYDROCORT	OINT. (G)	Y
HYDROCORTISONE	CORTIZONE-10	OINT. (G)	Y
HYDROCORTISONE	ANTI-ITCH	OINT. (G)	Y
HYDROCORTISONE ACETATE	HYDROCORTISONE ACETATE	CREAM (G)	Y
HYDROCORTISONE ACETATE	DERMAREST DRICORT	CREAM (G)	Y
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	SOLUTION	Y
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	CREAM (G)	Y
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	OINT. (G)	Y
TRIAMCINOLONE ACETONIDE	TRIANEX	OINT. (G)	Y
AMCINONIDE	AMCINONIDE	CREAM (G)	N
AMCINONIDE	AMCINONIDE	LOTION	N
AMCINONIDE	AMCINONIDE	OINT. (G)	N
BETAMETHASONE DIPROPIONATE	BETAMETHASONE DIPROPIONATE	GEL (GRAM)	N
BETAMETHASONE DIPROPIONATE	SERNIVO	SPRAY/PUMP	N
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	FOAM	N
BETAMETHASONE VALERATE	LUXIQ	FOAM	N
BETAMETHASONE VALERATE	BETAMETHASONE VALERATE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE AF	CREAM (G)	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	CREAM (G)	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	LOTION	N
BETAMETHASONE/PROPYLENE GLYC	DIPROLENE	OINT. (G)	N
BETAMETHASONE/PROPYLENE GLYC	BETAMETHASONE DIPROPIONATE	OINT. (G)	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	FOAM	N
CLOBETASOL PROPIONATE	OLUX	FOAM	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	GEL (GRAM)	N
CLOBETASOL PROPIONATE	CLOBEX	LOTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	LOTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SHAMPOO	N
CLOBETASOL PROPIONATE	CLOBEX	SHAMPOO	N
CLOBETASOL PROPIONATE	CLODAN	SHAMPOO	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SOLUTION	N
CLOBETASOL PROPIONATE	CLOBETASOL PROPIONATE	SPRAY	N
CLOBETASOL PROPIONATE	CLOBEX	SPRAY	N
CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMOLLIENT	CREAM (G)	N
CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMULSION	FOAM	N
CLOBETASOL PROPIONATE/EMOLL	OLUX-E	FOAM	N
CLOBETASOL PROPIONATE/EMOLL	CLOBETASOL EMOLLIENT	FOAM	N
CLOBETASOL/SKIN CLEANSER #28	CLODAN	KT SHM CLN	N
CLOCORTOLONE PIVALATE	CLOCORTOLONE PIVALATE	CREAM (G)	N
CLOCORTOLONE PIVALATE	CLODERM	CREAM (G)	N
DESONIDE	DESONATE	GEL (GRAM)	N

DESONIDE	DESONIDE	LOTION	N
DESOXIMETASONE	TOPICORT	CREAM (G)	N
DESOXIMETASONE	DESOXIMETASONE	CREAM (G)	N
DESOXIMETASONE	TOPICORT	GEL (GRAM)	N
DESOXIMETASONE	DESOXIMETASONE	GEL (GRAM)	N
DESOXIMETASONE	DESOXIMETASONE	OINT. (G)	N
DESOXIMETASONE	TOPICORT	OINT. (G)	N
DESOXIMETASONE	TOPICORT	SPRAY	N
DIFLORASONE DIACETATE	DIFLORASONE DIACETATE	CREAM (G)	N
DIFLORASONE DIACETATE	PSORCON	CREAM (G)	N
DIFLORASONE DIACETATE	DIFLORASONE DIACETATE	OINT. (G)	N
DIFLORASONE DIACETATE/EMOLL	APEXICON E	CREAM (G)	N
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	OIL	N
FLUOCINOLONE ACETONIDE	DERMA-SMOOTHE-FS	OIL	N
FLUOCINOLONE ACETONIDE	FLUOCINOLONE ACETONIDE	OINT. (G)	N
FLUOCINOLONE ACETONIDE	SYNALAR	OINT. (G)	N
FLUOCINOLONE ACETONIDE	CAPEX SHAMPOO	SHAMPOO	N
FLUOCINOLONE/EMOL CMB#65	SYNALAR	CMB ONT CR	N
FLUOCINOLONE/EMOL CMB#65	SYNALAR	CREAM (G)	N
FLUOCINOLONE/SHOWER CAP	FLUOCINOLONE ACETONIDE	OIL	N
FLUOCINOLONE/SHOWER CAP	DERMA-SMOOTHE-FS	OIL	N
FLUOCINOLONE/SKIN CLNSR28	SYNALAR TS	KIT	N
FLUOCINONIDE	FLUOCINONIDE	GEL (GRAM)	N
FLUOCINONIDE	FLUOCINONIDE	OINT. (G)	N
FLURANDRENOLIDE	FLURANDRENOLIDE	CREAM (G)	N
FLURANDRENOLIDE	FLURANDRENOLIDE	LOTION	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	CREAM (G)	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	LOTION	N
FLUTICASONE PROPIONATE	CUTIVATE	LOTION	N
FLUTICASONE PROPIONATE	FLUTICASONE PROPIONATE	OINT. (G)	N
HALCINONIDE	HALOG	CREAM (G)	N
HALCINONIDE	HALOG	OINT. (G)	N
HALOBETASOL PROPIONATE	HALOBETASOL PROPIONATE	CREAM (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	CREAM (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	LOTION	N
HALOBETASOL PROPIONATE	HALOBETASOL PROPIONATE	OINT. (G)	N
HALOBETASOL PROPIONATE	ULTRAVATE	OINT. (G)	N
HALOBETASOL/LACTIC ACID	ULTRAVATE X	CMB ONT CR	N
HALOBETASOL/LACTIC ACID	ULTRAVATE X	COMBO. PKG	N
HC/MINERAL OIL/PETROLAT,WHT	HYDROCORTISONE	OINT. (G)	N
HYDROCORTISONE	ANUSOL-HC	CREAM (G)	N
HYDROCORTISONE	HYDRO SKIN	LOTION	N
HYDROCORTISONE	HYDROCORTISONE	LOTION	N
HYDROCORTISONE	SCALPICIN	SOLUTION	N
HYDROCORTISONE	TEXACORT	SOLUTION	N

HYDROCORTISONE ACETATE	MICORT-HC	CRM/PE APP	N
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	CREAM (G)	N
HYDROCORTISONE BUTYRATE	HYDROCORTISONE BUTYRATE	OINT. (G)	N
HYDROCORTISONE BUTYRATE/EMOLL	HYDROCORTISONE BUTYRATE	CREAM (G)	N
HYDROCORTISONE PROBUTATE	PANDEL	CREAM (G)	N
HYDROCORTISONE VALERATE	HYDROCORTISONE VALERATE	CREAM (G)	N
HYDROCORTISONE VALERATE	HYDROCORTISONE VALERATE	OINT. (G)	N
HYDROCORTISONE/ALOE VERA	HYDROCORTISONE PLUS	CREAM (G)	N
HYDROCORTISONE/ALOE VERA	HYDROCORTISONE-ALOE	CREAM (G)	N
HYDROCORTISONE/ALOE VERA	HYDROSKIN	CREAM (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	CREAM (G)	N
MOMETASONE FUROATE	ELOCON	CREAM (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	OINT. (G)	N
MOMETASONE FUROATE	ELOCON	OINT. (G)	N
MOMETASONE FUROATE	MOMETASONE FUROATE	SOLUTION	N
NEOMYCIN SULFATE/FLUOCINOLONE	NEO-SYNALAR	CREAM (G)	N
NEOMYCIN/BACITRA/POLYMYXIN/HC	CORTISPORIN	OINT. (G)	N
NEOMYCIN/FLUOCINOLONE/EMOL #65	NEO-SYNALAR	CREAM (G)	N
PREDNICARBATE	DERMATOP	CREAM (G)	N
PREDNICARBATE	PREDNICARBATE	CREAM (G)	N
PREDNICARBATE	PREDNICARBATE	OINT. (G)	N
PREDNICARBATE	DERMATOP	OINT. (G)	N
TRIAMCINOLONE ACETONIDE	KENALOG	AEROSOL	N
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	AEROSOL	N
TRIAMCINOLONE ACETONIDE	TRIAMCINOLONE ACETONIDE	LOTION	N
HYDROCORTISONE	PROCTOSOL-HC	CRM/PE APP	
HYDROCORTISONE	PROCTOZONE-HC	CRM/PE APP	
HYDROCORTISONE	PROCTO-PAK	CRM/PE APP	
HYDROCORTISONE	HYDROCORTISONE	CRM/PE APP	
HYDROCORTISONE	PROCTO-MED HC	CRM/PE APP	
HYDROCORTISONE ACETATE	MICORT-HC	CRM/PE APP	
NEOMYCIN/POLYMYXIN B SULF/HC	CORTISPORIN	CREAM (G)	

Appendix 2: New Comparative Clinical Trials

A total of 70 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 2 2017

1 aclometasone.mp.1
2 Betamethasone Valerate/ or Betamethasone/ or betamethasone.mp.3158
3 clobetasol.mp. or Clobetasol/1019
4 Fluocinolone Acetonide/ or fluocinolone.mp.444
5 hydrocortisone.mp. or Hydrocortisone/ 29324
6 Triamcinolone Acetonide/ or Triamcinolone/ or triamcinolone.mp.5132
7 fluocortolone.mp. or Fluocortolone/55
8 diflorasone.mp. 16
9 flurandrenolide.mp. or Flurandrenolone/9
10 halobetasol.mp.28
11 prednicarbate.mp.77
12 amcinonide.mp.10
13 clocortolone.mp.8
14 desoximetasone.mp. or Desoximetasone/34
15 Fluticasone/ or fluticasone.mp.3512
16 administration, topical.mp. or Administration, Topical/21895
17 topical corticosteroid.mp.1075
18 topical corticosteroids.mp.2269
19 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 41494
20 16 or 17 or 18 23982
21 19 and 20 1931
22 limit 21 to (english language and humans and (clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews) and last 3 years) 70

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Drug Class Literature Scan: Topical Antipsoriatics

Date of Review: September 2017

Date of Last Review: January 2015
Literature Search: 01/01/15 – 04/30/17

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

Conclusions:
- Since the last review additional evidence has become available with the publication of 1 systematic review. One new combination vitamin D analogue/corticosteroid product has been approved by the Food and Drug Administration (FDA).
- There is insufficient comparative evidence to support differences in safety or efficacy among non-steroidal topical antipsoriatics.
- For scalp psoriasis clearance, one systematic review found that combinations of topical corticosteroids plus vitamin D are more effective than topical vitamin D monotherapy with a NNT of 6.
- For scalp psoriasis clearance, one systematic review found that topical corticosteroid monotherapy is more effective than topical vitamin D monotherapy with a NNT of 4.

Recommendations:
- No changes are recommended to the OHP PDL based on the review of current evidence. Assign coal tar preparations to antipsoriatic class as non-preferred products. Review comparative drug costs in the executive session.

Previous Conclusions:
- First line therapy for psoriasis remains traditional topical therapies, including corticosteroids, vitamin D and vitamin D analogues, dithranol (anthralin), and tar preparations.
- There is no evidence of a significant difference in efficacy/effectiveness or harms between the different vitamin D analogues.
- Combination therapy with a vitamin D analogue and corticosteroid has proved to be more effective than either component alone.
- Calcipotriene is recommended first line in childhood psoriasis.
- There is lower strength of evidence for the efficacy of anthralin and it should be used as alternative therapy after vitamin D analogues and/or corticosteroids.

Previous Recommendations:
- No further review or research needed. Evaluate comparative costs in executive session.

Author: D. Engen

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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:
Cochrane: Topical Treatments for Scalp Psoriasis
A 2016 Cochrane Collaboration systematic review evaluated the efficacy and safety of topical treatments for scalp psoriasis.[1] Main comparators included topical steroids, vitamin D3 analogues, and corticosteroid plus vitamin D combination products. Other comparators included corticosteroid plus salicylic acid combination products, tar-based preparations, anthralin, and salicylic acid monotherapy. Fifty-nine randomized controlled trials in 11,561 participants were included. Data on age of participants were available in 38 of the studies (n=9051) with a mean age of 45.2 years.[1] Few studies included children. Follow-up lasted for a median duration of 2.4 weeks (range: 1-8 weeks).[1] Primary outcomes included either lesion clearance or clinical response as measured by the 5-point Investigator's Global Assessment (IGA) scale.[1] The 5-point IGA scale has been used in evaluation of psoriasis severity in clinical trials and correlates with other common psoriasis assessment tools but is not as well validated.[2] Additional primary outcomes assessed were quality of life improvements and adverse events leading to treatment withdrawal.

Six studies assessed combination vitamin D/steroid preparations versus vitamin D monotherapy for topical psoriatic lesion clearance.[1] Four of the 6 studies (n=2008) addressed IGA clearance as the primary outcome measure.[1] Combinations of topical steroids plus vitamin D were more effective than vitamin D alone (Relative Risk (RR) 2.28; 95% Confidence Interval (CI) 1.87 to 2.78; Absolute Risk Reduction (ARR) = 19%, Number Needed to Treat (NNT) = 6; high quality evidence).[1] However, in three studies (n=1827), overall treatment response favored corticosteroid monotherapy over vitamin D monotherapy (RR 2.09; 95% CI 1.80 to 2.41; ARR = 28%, NNT = 4; high quality evidence).[1] Meta-analysis of 4 studies (n=2291) indicated more participants withdrew due to adverse events for treatment with vitamin D monotherapy versus steroid monotherapy (5% vs. 1%, respectively; Absolute Risk Increase (ARI) = 4%, Number Needed to Harm (NNH) = 25) although no study reported on the nature of the adverse event requiring withdrawal.[1] Data from 4 studies (n=2180) demonstrated that topical steroids improved psoriatic lesion clearance in 29% of patients compared to 16% of patients on calcitriol as measured with the IGA scale (RR 1.82; 95% CI 1.52 to 2.18; ARR = 13%; NNT = 8).[1] All four studies had unclear allocation concealment and 3 of the 4 studies had unclear blinding of outcome assessments which resulted in the quality of evidence downgraded to moderate risk of bias by the authors. There was insufficient evidence to assess efficacy and safety of additional topical agents such as salicylic acid, tar- or anthralin-based treatments.[1]

New Guidelines:
None identified.

New Formulations:
In 2015, the FDA approved Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) topical foam for the treatment of plaque psoriasis in patients 18 years and older.[3] Enstilar® is applied to affected areas once daily for up to 4 weeks.[3] Approval for the foam was based on one phase 2 and one phase 3 multicenter, randomized, double-blind trial (n=728) in subjects with mild to severe psoriasis.[4] Disease severity was graded using a 5-point Investigator's Global Assessment (IGA) and at least 75% of subjects in each study were classified with "moderate" psoriasis at baseline.[4] Successful treatment outcomes were defined as the proportion of subjects at week 4 who were "Clear" to "Almost Clear" of psoriatic lesions.[4] Trial 1 (n=302) compared three treatment groups: Enstilar Foam, betamethasone dipropionate in vehicle, or calcipotriene hydrate in vehicle. The difference in proportion of subjects with successful clearance was higher for Enstilar Foam compared to calcipotriene monotherapy (45% vs. 15%, respectively; p<0.001; ARR = 30%, NNT=4) and versus betamethasone dipropionate alone (45% vs. 31%; p=0.047; ARR = 14%, NNT = 8).[4] Trial 2 (n=426) compared Enstilar Foam to vehicle. For trial 2, the proportion of subjects with treatment success was 53% for Enstilar foam versus 5% for vehicle (p<0.001; ARR = 48%, NNT = 3).[4,5] The most commonly reported adverse events for those treated with Enstilar were nasopharyngitis (2%), increased blood pressure (1%), as well as application site pain (2%), pruritus (1%), and irritation (1%).[5]

New FDA Safety Alerts:
None identified.

References:

1. Schlager JG, Rosumeck S, Werner RN, et al. Topical treatments for scalp psoriasis. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2016. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD009687.pub2/abstract. Accessed April 11, 2017.
2. Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. Journal of Dermatological Treatment. 2015;26(1):23-31. doi:10.3109/09546634.2013.865009. Accessed June 16, 2017.
3. Enstilar® (calcipotriene 0.005%/betamethasone dipropionate 0.064%) Prescribing Information. LEO Pharma Inc. 1 Sylvan Way, Parsippany, NJ 07054. Oct 2015 https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207589s000lbl.pdf. Accessed June 1, 2017.
4. CDER Evaluation of Enstilar® https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207589Orig1s000ClinPharmR.pdf. Accessed June 1, 2017.
5. Leonardi C, Bagel J, Yamauchi P, et al. Efficacy and Safety of Calcipotriene Plus Betamethasone Dipropionate Aerosol Foam in Patients With Psoriasis Vulgaris--a Randomized Phase III Study (PSO-FAST). Journal of Drugs in Dermatology. 2015;14(12):1468-1477.

Appendix 1: Current Preferred Drug List

Antipsoriatic Agents

Formulation	Brand	Generic	PDL
CREAM (G)	CALCIPOTRIENE	CALCIPOTRIENE	Y
SOLUTION	CALCIPOTRIENE	CALCIPOTRIENE	Y
OINT. (G)	CALCIPOTRIENE-BETAMETHASONE DP	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	DOVONEX	CALCIPOTRIENE	Y
OINT. (G)	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	Y
CREAM (G)	TAZAROTENE	TAZAROTENE	Y
CREAM (G)	TAZORAC	TAZAROTENE	Y
GEL (GRAM)	TAZORAC	TAZAROTENE	Y
CREAM (G)	DRITHOCREME HP	ANTHRALIN	N
CREAM (G)	ANTHRALIN	ANTHRALIN	N
SHAMPOO(G)	ZITHRANOL	ANTHRALIN MICRONIZED	N
OINT. (G)	CALCIPOTRIENE	CALCIPOTRIENE	N
OINT. (G)	CALCITRENE	CALCIPOTRIENE	N
FOAM	SORILUX	CALCIPOTRIENE	N
SUSPENSION	TACLONEX	CALCIPOTRIENE/BETAMETHASONE	N
FOAM	ENSTILAR	CALCIPOTRIENE/BETAMETHASONE	N
OINT. (G)	CALCITRIOL	CALCITRIOL	N
OINT. (G)	VECTICAL	CALCITRIOL	N
FOAM	PSORIATAR	COAL TAR	N
FOAM	SCYTERA	COAL TAR	N
OINT. (G)	MG217 PSORIASIS	COAL TAR	N
CREAM (G)	SORBOLENE	GLYCERN/MIN OIL/PETROLAT/C.ALC	N
CREAM (G)	AVAGE	TAZAROTENE	N

Coal Tar Products

FormDesc	Brand	Generic	PDL
SHAMPOO	ANTI-DANDRUFF	COAL TAR	
SHAMPOO	BETATAR	COAL TAR	
SOLUTION	COAL TAR	COAL TAR	
EMULSION	CUTAR	COAL TAR	
SHAMPOO	DHS TAR	COAL TAR	

SHAMPOO	DHS TAR GEL	COAL TAR
SHAMPOO	DUPLEX T	COAL TAR
SHAMPOO	IONIL T	COAL TAR
LOTION	OXIPOR VHC	COAL TAR
SHAMPOO	PC TAR	COAL TAR
SHAMPOO	PENTRAX	COAL TAR
SHAMPOO	PENTRAX GOLD	COAL TAR
SHAMPOO	POLYTAR	COAL TAR
GEL (GRAM)	PSORIASIN	COAL TAR
LOTION	TEGRIN PSORIASIS	COAL TAR
SHAMPOO	TERA-GEL TAR	COAL TAR
SHAMPOO	T-GEL	COAL TAR
SHAMPOO	THERA-GEL	COAL TAR
SHAMPOO	THERAPEUTIC SHAMPOO	COAL TAR
SHAMPOO	T-PLUS	COAL TAR
SHAMPOO	X-SEB T PLUS	COAL TAR

Appendix 2: New Comparative Clinical Trials

A total of 28 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), data collection methods (eg, unblinded), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 4 2017
1 calcipotriene.mp. 773
2 calcipotriene and betamethasone.mp. 194
3 tazarotene.mp. 479
4 Calcitriol/ or calcitriol.mp. 12630
5 anthralin.mp 327
6 coal tar 701
7 psoriasis.mp. or Psoriasis/ 23589
8 1 or 2 or 3 or 4 or 5 or 6 14104
9 7 and 8 1202
limit 9 to (yr="2015 -Current" and english and humans and (clinical study or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or systematic reviews)) 28

Topical Antipsoriasis Drugs

Goal(s):

Restrict topical antipsoriasis drugs only for funded OHP diagnoses. Moderate/Severe psoriasis treatments are funded on the OHP. Treatments for mild psoriasis (L400-404, L408-418, L448), seborrheic dermatitis (L2083,L210-219,L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) and other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985) are not funded.

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis (L2083, L210-219, L303), keroderma (L110, L83, L850-852, L870-872, L900-902, L906, L940, L943) or other hypertrophic and atrophic conditions of skin (L119, L572, L574, L664, L908-909, L918-919, L922, L985)?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis Psoriasis? (ICD-10 L400-404,L408-418, L448)	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as: • At least 10% body surface area involved or with functional impairment • Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No:** Approve for length of treatment; maximum 1 year.
7. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.	**If funded, or clinic provides supporting literature:** Approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/17 (DE); 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*