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, January 28, 2016 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER

A. Roll Call & Introductions	R. Citron (OSU)
B. Conflict of Interest Declaration	R. Citron (OSU)
C. Election of Chair & Vice Chair	R. Citron (OSU)
D. Approval of Agenda and Minutes	Chair
E. Department Update	D. Weston (OHA)

II. DUR ACTIVITIES

A. Quarterly Utilization Reports	R. Citron (OSU)
B. ProDUR Report	R. Holsapple (HP)
C. RetroDUR Report	T. Williams (OSU)
D. Oregon State Drug Reviews	K. Sentena (OSU)

a. "From Antidotes to Edoxaban: An Oral Anticoagulation Update"
b. "Obesity and Related Sequelae: Are Medications the Answer?"
c. "Does Sacubitril/Valsartan Pose a Treatment Conundrum for Management of Heart Failure?"

III. DUR OLD BUSINESS

A. Proton Pump Inhibitor Drug Policy — A. Gibler (OSU)
1. Updated Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

IV. PREFERRED DRUG LIST NEW BUSINESS

A. Antiemetic Drug Class Update — K. Sentena (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

B. Influenza Antiviral Class Update — A. Gibler (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. Drug Class Literature Scans — M. Herink/D. Engen/A. Gibler (OSU)
1. Immunosuppressants
2. Topical Analgesics
3. Inhaled Drugs for Cystic Fibrosis
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

D. Iron Chelators Class Update — A. Gibler (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

E. Hepatitis C Direct-acting Antivirals Class Update — M. Herink (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

F. Phosphate Binders Class Update — S. Willard/A. Gibler (OSU)
1. Auryxia™ (ferric citrate) New Drug Evaluation
2. Phosphate Binders Literature Scan
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

G. ADHD Drug Class Update — A. Gibler (OSU)
1. DERP Summary/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

H. Sodium-glucose Cotransporter 2 Inhibitor Class Update — K. Sentena (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

I. Abbreviated Drug Reviews — D. Engen/A. Gibler (OSU)
1. Cholbam® (cholic acid)
2. Viberzi® (eluxadoline)
3. Addyi® (flibanserin)
4. Saxenda® (liraglutide)
5. Public Comment
6. Discussion of Clinical Recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	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
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
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	Salem	December 2018

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, November 19, 2015 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

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: Cathy Zehrung, RPh; Phillip Levine, PhD; Bill Origer, MD; Rich Clark, MD, MPH; Caryn Mickelson, PharmD;

Members Present by Phone: Dave Pass, MD; Arturo Salazar, MD

Staff Present: Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Shannon Jasper; Dee Weston; Dave Engen, PharmD; Kathy Sentena, PharmD; Kim Wentz, MD;

Staff Present by Phone:

Audience: Devin Dufenhorst (Abbot), Kerry Kostman Bonnila (AstraZeneca), Karen Campbell (Allergan)*, Rick Frees (Vertex), Jamie Tobitt (Vertex)*, Paul Bonham (Novo Nordisk), Venus Holder (Lilly), Bruce Smith (GlaxoSmith Kline), Dr. McCale (Baxacta), Jeana Colabianchi (Sunovion), Brad Clay (Amgen)*, Mark Pledger (Novartis), Anthony Ashtag (Novartis)*, Sylvia Churchill (Amgen), Jennifer Svec (Med Impact), Mary Kemhus (Novartis), Sally Zweber (Novo Nordisk)*, Merrie Kay Alzola (Novo Nordisk), Margaret Olman (AbbVie), Dean Haxby (OSU), Teresa Chiang (Pacific University), Roger Stephen (Mylan), Mike Powers, MD (OHSU)*, Brad Clay (Amgen)*,

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions were made by Committee members and staff.

b. Mr. Citron reported there are no new conflicts of interest to declare.

c. Approval of agenda and minutes presented by Dr. Origer. (pages 5 - 9)

ACTION: Motion, 2nd, All in Favor. Approved.

d. Department updates for OHA.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 10 - 14)
Mr. Citron presented the quarterly utilization report.

b. ProDUR Report (pages 15 – 19)
Mr. Holsapple presented the quarterly ProDUR reports.

c. RetroDUR Report (pages 20 – 24)
Dr. Williams presented the quarterly RetroDUR reports.

d. Oregon State Drug Reviews (pages 25 – 30)
Dr. Sentena presented the following reviews:
   1. Treating UTIs with the Tried and True
   2. Hypertension Guidelines: Do Blood Pressure Goals Change with Age?
   3. Is Long-term Proton Pump Inhibitor Treatment for GERD Worth the Risk?

III. DUR OLD BUSINESS

a. Intranasal Allergy Drug Policy (pages 31 - 32)
Dr. Williams presented the Prior Authorization Criteria.

1. Approve proposed changes to PA criteria.

ACTION: Motion, 2nd, All in Favor. Approved.

b. LABA/ICS Drug Policy (pages 33 - 34)
Dr. Sentena presented the Prior Authorization Criteria.

1. Approve proposed changes to PA criteria.

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

c. LABA/LAMA Drug Policy (pages 35 - 36)
Dr. Sentena presented the Prior Authorization Criteria.

1. Approve proposed changes to PA criteria.

ACTION: Motion, 2nd, All in Favor. Approved.

IV. DUR NEW BUSINESS

a. DURM Methods (pages 37 – 53)
Dr. Herink presented the following review:

   1. Methods for DURM Evidence Summary Reviews. (pages 37 – 48)
   2. Methods for DURM Abbreviated Drug Reviews. (pages 49 – 53)

3. Approve PA for Drugs for Non-funded Conditions.
4. Approve PA criteria for Drugs Selected for Manual Review.
5. Approve PA criteria for New Drug Policy.

ACTION: Motion, 2nd, all in Favor. Approved.

b. Botulinum Toxins Drug Policy (pages 54 – 60)
Dr. Williams presented the following updated policy evaluation:

1. Approve proposed changes to PA criteria.
2. No further review or research needed at this time.
3. Revise step 6 add baseline number of headaches.
4. Revise step 8 to add baseline of urinary episodes.
5. Revise step 2 under Renewal Criteria to reduction in >7 headache days per month.

ACTION: Motion, 2nd, all in favor. Approved.

Public Comment:
Karen Campbell pharmacist from Allergan gave public testimony.

c. Ivabradine (Corlanor®) New Drug Evaluation (pages 61 – 74)
Dr. Herink presented the following drug evaluation:

1. Restrict use of ivabradine to populations where it has demonstrated some efficacy.
2. Approve amended criteria.
3. Change criteria #3 to 35%.
4. Include criteria of hospitalization within the past 12 months.
5. Additional criteria sites patient must be on an aldosterone antagonist.

ACTION: Motion, 2nd, All in Favor. Approved.

Public Comment:
Brad Clay from Amgen gave public testimony.

V. PREFERRED DRUG LIST NEW BUSINESS

a. Ivacaftor/Lumacaftor (Orkambi™) (pages 75 – 91)
Dr. Herink presented the following drug evaluation:

1. Maintain Orkambi™ as non-preferred on PMPDP.
2. Approve updated PA criteria as presented.
3. Continue to monitor for patient adherence and adopt clinical criteria as needed to adequately assess clinical response as further data become available.
4. Changed minimum length of authorization from 60 to 90 days.

ACTION: Motion, 2nd, majority in favor, one opposed. Approved.

Public Comment:
Dr. Michael Powers from OHSU gave public comment.
Dr. Gopal Allada from OHSU gave public comment.
Jamie Tobitt PharmD from Vertex gave public comment.

b. Cross-sex Hormone Class Review (pages 92 – 111)
Dr. Sentena presented the following class review:

1. Include all GnRH analogs in the existing PA criteria for leuprolide and apply to all GnRH treatments for adolescents with GD to ensure they are used appropriately for puberty suppression.
2. Approve changes to testosterone PA criteria to allow approval for patients with GD.
3. Adopt estrogen derivatives PA criteria to allow approval for patients with GD.
4. Amend criteria 3 to include option for any other endocrine disorder.
5. Remove age restriction criteria of 16 years of age and older for testosterone and estrogen derivatives.

ACTION: Motion, 2nd, all in favor. Approved.

c. PCSK9 Inhibitor Class Review (pages 112 – 124)
Dr. Herink presented the following class review:

1. Due to limited evidence of long-term CV benefit and harms designate alirocumab and evolucmab as non-preferred in the "Other Dyslipidemia Drugs" class.
2. Approve proposed PA criteria to restrict use of PCSK9 Inhibitors to the following populations: 1) non-familial hypercholesterolemia unable to achieve at least 50% LCL-C reduction despite high-intensity statin therapy and ezetimibe; 2) familial hypercholesterolemia; or 3) persistent myopathy or myalgia with several adequate trials of statin therapy.
3. Remove CHD risk-equivalent from #3 (patient has to have clinical ASCVD).
4. Remove #7 completely and only approve for patients with documented rhabdomyolysis.

ACTION: Motion, 2nd, All in Favor. Approved.

Public Comment:
Brad Clay pharmacist from Amgen gave public comment.

d. Long-acting Insulin Class update (pages 125 – 133)
Dr. Herink presented the following class update:

1. Make insulin glargine U300 non-preferred and subject to clinical PA.
2. Approve changes to Insulin PA criteria. Maintain at least one preferred long-acting insulin product on the PDL.
3. Review insulin degludec (Tresiba®) and insulin degludec/ aspart (Ryzodeg® 70/30) as separate new drug evaluations at a later time.
4. Evaluate comparative costs in the executive session.

***ACTION:** After executive session. All in favor. Approved.

Public Comment:
Dr. Sally Zweber from Novo Nordisk will come back to give public comment.

e. Antiemetic Drug Class Update (pages 134 – 154)

Review of class deferred.

f. Influenza Antiviral Class Update (pages 155 – 167)

Review of class deferred.

g. Iron Chelator Drug Class Update (pages 168 – 180)

Review of class update deferred.

h. Drug Class Literature Scans

1. Immunosuppressants (pages 181 – 189)

Review of class deferred.

2. Topical Analgesics (pages 190 – 194)

Review of class deferred.

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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Pharmacy Utilization Summary Report: July 2014 - June 2015

Eligibility	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Total Members (FFS & Encounter)	981,835	997,487	1,008,231	1,021,045	977,740	998,873	1,027,655	1,043,479	1,059,499	1,081,244	1,078,839	1,049,644	1,027,131
FFS Members	132,379	140,158	134,462	132,913	140,236	139,950	157,174	140,889	134,463	130,455	132,476	126,047	136,800
OHP Basic with Medicare	28,468	28,659	28,804	29,015	29,111	29,136	29,283	29,328	29,255	29,480	29,794	29,983	29,193
OHP Basic without Medicare	24,836	24,911	24,494	23,833	21,350	18,720	18,429	17,581	16,680	16,978	16,784	16,112	20,059
ACA	79,075	86,588	81,164	80,065	89,775	92,094	109,462	93,980	88,528	83,997	85,898	79,952	87,548
Encounter Members	849,456	857,329	873,769	888,132	837,504	858,923	870,481	902,590	925,036	950,789	946,363	923,597	890,331
OHP Basic with Medicare	38,419	38,620	38,770	38,810	38,812	38,946	39,105	39,244	39,267	39,566	39,496	39,527	39,049
OHP Basic without Medicare	220,955	219,511	215,256	205,287	164,063	131,637	120,645	116,957	116,321	116,337	113,941	97,164	153,173
ACA	590,082	599,198	619,743	644,035	634,629	688,340	710,731	746,389	769,448	794,886	792,926	786,906	698,109

Gross Cost Figures for Drugs	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	YTD Sum
Total Amount Paid (FFS & Encounter)	$53,132,675	$50,738,874	$54,183,983	$56,958,136	$49,846,206	$58,946,093	$59,084,337	$55,410,289	$63,177,719	$64,496,363	$64,325,249	$65,353,173	$695,653,096
Mental Health Carve-Out Drugs	$10,921,674	$10,588,025	$11,072,974	$11,558,114	$10,236,122	$11,028,779	$10,867,982	$10,383,893	$11,641,970	$11,318,098	$10,685,463	$10,932,174	$131,235,269
OHP Basic with Medicare	$4,573	$5,442	$2,452	$5,630	$6,949	$10,422	$10,229	$10,140	$10,995	$12,864	$11,878	$13,598	$105,171
OHP Basic without Medicare	$6,348,075	$6,058,902	$6,191,009	$6,281,657	$5,362,128	$5,468,698	$5,353,506	$5,004,952	$5,537,722	$5,341,997	$5,035,491	$5,094,826	$67,078,962
ACA	$4,470,302	$4,438,711	$4,785,138	$5,188,930	$4,801,929	$5,505,669	$5,471,797	$5,337,784	$6,062,170	$5,931,107	$5,610,494	$5,800,507	$63,404,539
FFS Physical Health Drugs	$3,394,260	$3,222,584	$3,477,819	$3,449,164	$3,306,505	$3,792,580	$3,882,805	$3,271,947	$3,124,784	$3,066,242	$2,851,572	$3,214,188	$40,054,451
OHP Basic with Medicare	$270,866	$240,008	$244,614	$246,416	$228,081	$251,397	$249,861	$227,167	$239,793	$226,257	$228,379	$231,835	$2,884,674
OHP Basic without Medicare	$1,360,975	$1,254,951	$1,444,294	$1,375,246	$1,212,628	$1,292,974	$1,294,806	$1,153,246	$1,167,300	$1,049,536	$949,531	$1,008,689	$14,564,176
ACA	$1,665,913	$1,640,058	$1,706,537	$1,744,438	$1,792,657	$2,168,255	$2,266,304	$1,816,390	$1,647,620	$1,718,366	$1,605,528	$1,904,562	$21,676,628
FFS Physician Administered Drugs	$1,379,064	$1,525,864	$1,848,586	$1,669,336	$1,356,975	$1,384,121	$1,847,099	$1,497,883	$1,762,528	$1,605,040	$1,534,197	$1,609,799	$19,020,492
OHP Basic with Medicare	$182,939	$154,986	$155,504	$177,379	$134,520	$178,784	$283,549	$244,319	$222,804	$287,769	$236,883	$260,871	$2,520,308
OHP Basic without Medicare	$425,879	$443,656	$531,028	$423,735	$500,987	$282,212	$367,856	$299,642	$344,386	$404,892	$246,595	$384,866	$4,655,733
ACA	$561,857	$676,180	$940,237	$869,638	$556,360	$752,134	$951,848	$807,595	$996,404	$692,242	$862,166	$716,750	$9,383,412
Encounter Physical Health Drugs	$30,274,471	$29,412,182	$31,254,252	$32,951,469	$28,975,978	$35,588,090	$35,471,264	$33,790,468	$38,778,414	$40,844,739	$41,879,974	$41,906,629	$421,127,929
OHP Basic with Medicare	$193,686	$195,549	$201,593	$199,118	$196,335	$196,602	$247,740	$233,504	$246,608	$275,631	$267,828	$274,480	$2,728,671
OHP Basic without Medicare	$13,846,045	$12,792,727	$13,269,767	$13,430,639	$10,864,216	$12,333,488	$11,793,921	$10,829,095	$12,129,408	$12,308,283	$12,412,245	$12,188,374	$148,198,209
ACA	$15,901,806	$16,121,818	$17,480,482	$19,038,154	$17,643,983	$22,871,059	$23,213,627	$22,580,771	$26,234,040	$28,096,711	$29,023,539	$29,317,042	$267,523,032
Encounter Physician Administered Drugs	$7,163,205	$5,990,217	$6,530,351	$7,330,054	$5,970,626	$7,152,523	$7,015,187	$6,466,097	$7,870,024	$7,662,244	$7,374,044	$7,690,382	$84,214,954
OHP Basic with Medicare	$202,856	$175,051	$154,676	$191,303	$146,010	$143,961	$229,468	$194,507	$178,817	$177,113	$166,472	$146,832	$2,107,067
OHP Basic without Medicare	$3,429,246	$2,440,759	$2,441,705	$2,600,487	$2,120,459	$2,270,033	$2,253,099	$2,003,784	$2,487,907	$2,321,129	$2,086,643	$2,286,584	$28,741,832
ACA	$3,308,490	$3,165,076	$3,680,274	$4,277,813	$3,540,664	$4,555,709	$4,356,636	$4,143,670	$5,014,773	$5,033,785	$5,006,386	$5,068,657	$51,151,934

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: January 20, 2016

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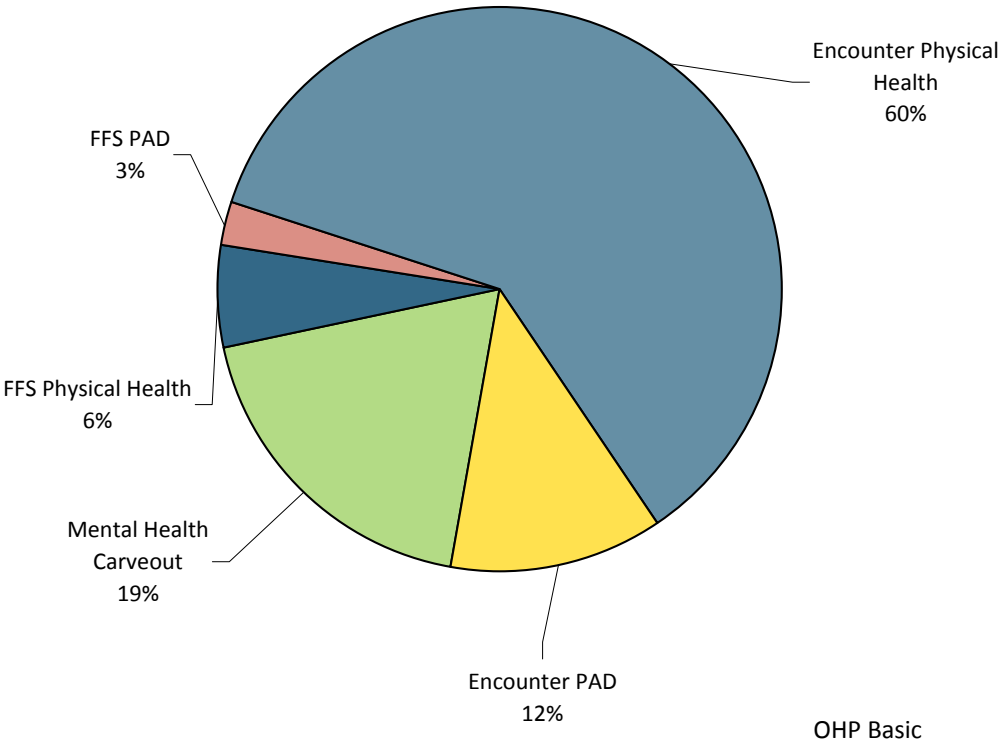
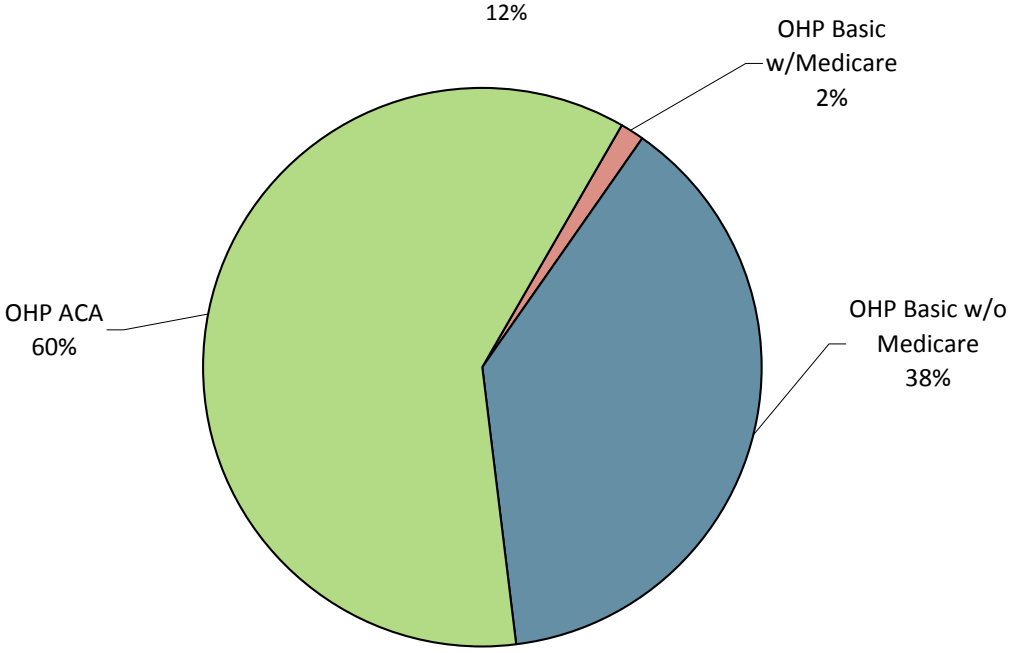
Pharmacy Utilization Summary Report: July 2014 - June 2015

YTD Percent Paid Amounts





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

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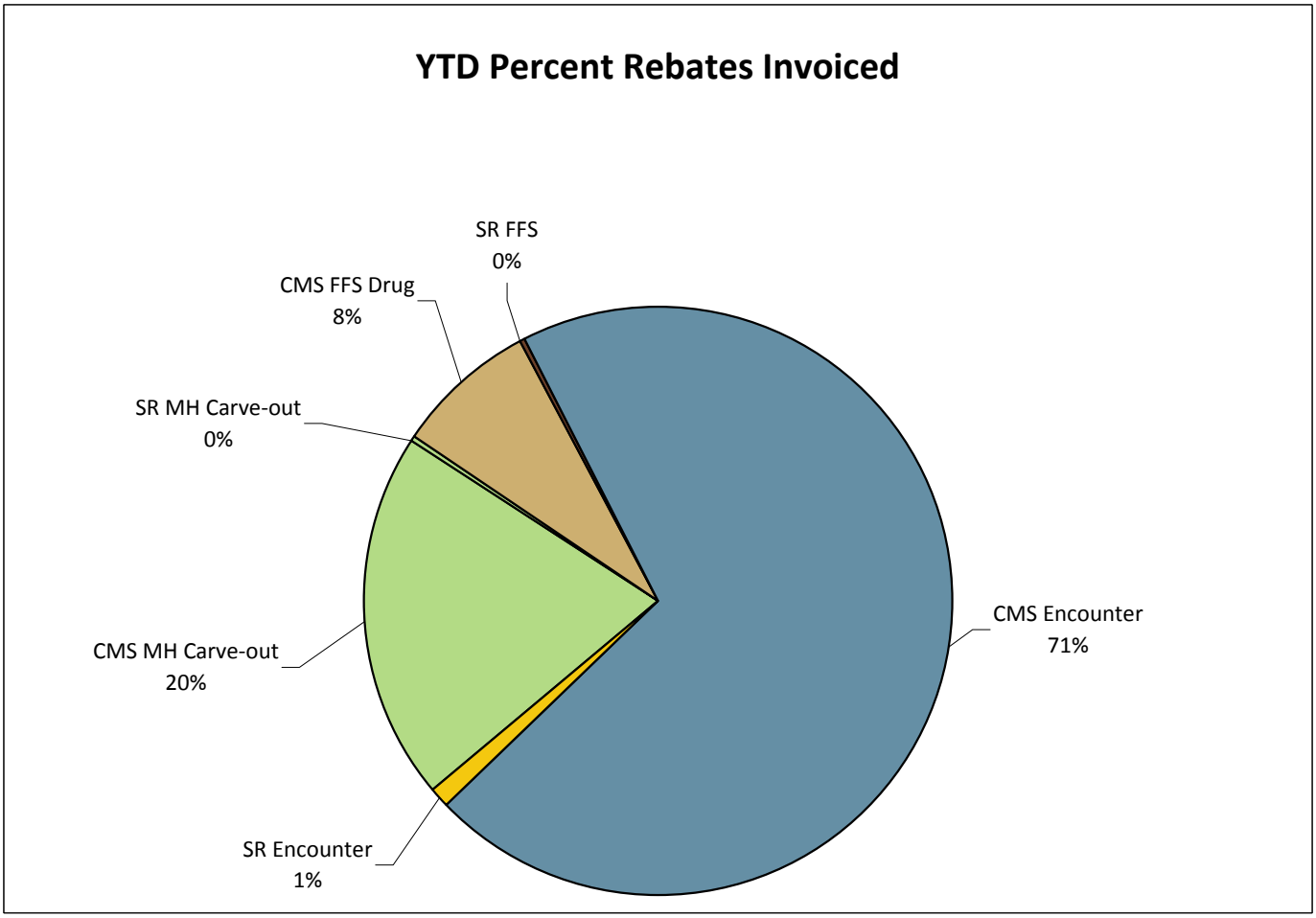
Pharmacy Utilization Summary Report: July 2014 - June 2015

Quarterly Rebates Invoiced	2014-Q3	2014-Q4	2015-Q1	2015-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$69,307,450	$75,634,200	$90,278,955	$97,055,567	$332,276,173
CMS MH Carve-out	$15,135,883	$15,228,555	$18,457,271	$18,998,120	$67,819,829
SR MH Carve-out		$64,807			$64,807
CMS FFS Drug	$6,062,304	$6,560,269	$7,222,149	$6,163,605	$26,008,326
SR FFS	$229,999	$257,828	$255,055	$222,795	$965,677
CMS Encounter	$47,080,661	$52,460,278	$63,463,184	$70,382,583	$233,386,706
SR Encounter	$798,603	$1,062,464	$881,296	$1,288,465	$4,030,828

Quaterly Net Drug Costs	2014-Q3	2014-Q4	2015-Q1	2015-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$88,748,081	$90,116,236	$87,393,389	$97,119,218	$363,376,923
Mental Health Carve-Out Drugs	$17,446,790	$17,529,654	$14,436,574	$13,937,616	$63,350,633
FFS Phys Health + PAD	$8,555,877	$8,140,584	$7,909,842	$7,494,638	$32,100,940
Encounter Phys Health + PAD	$62,745,414	$64,445,998	$65,046,973	$75,686,965	$267,925,350



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

Last Updated: January 20, 2016

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Pharmacy Utilization Summary Report: July 2014 - June 2015

PMPM Drug Costs (Rebates not Included)	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$54.12	$50.87	$53.74	$55.78	$50.98	$59.01	$57.49	$53.10	$59.63	$59.65	$59.62	$62.26	$56.36
Mental Health Carve-Out Drugs	$11.12	$10.61	$10.98	$11.32	$10.47	$11.04	$10.58	$9.95	$10.99	$10.47	$9.90	$10.42	$10.65
FFS Physical Health Drugs	$25.64	$22.99	$25.86	$25.95	$23.58	$27.10	$24.70	$23.22	$23.24	$23.50	$21.53	$25.50	$24.40
FFS Physician Administered Drugs	$10.42	$10.89	$13.75	$12.56	$9.68	$9.89	$11.75	$10.63	$13.11	$12.30	$11.58	$12.77	$11.61
Encounter Physical Health Drugs	$35.64	$34.31	$35.77	$37.10	$34.60	$41.43	$40.75	$37.44	$41.92	$42.96	$44.25	$45.37	$39.30
Encounter Physician Administered Drugs	$8.43	$6.99	$7.47	$8.25	$7.13	$8.33	$8.06	$7.16	$8.51	$8.06	$7.79	$8.33	$7.88

Claim Counts	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Total Claim Count (FFS & Encounter)	944,871	914,947	958,673	1,008,538	874,488	978,481	1,020,493	954,654	1,067,872	1,061,541	1,030,378	1,017,396	986,028
Mental Health Carve-Out Drugs	140,589	136,822	142,387	148,426	132,301	151,810	148,733	139,254	154,433	154,138	148,623	152,182	145,808
FFS Physical Health Drugs	78,357	76,610	79,062	80,070	75,779	80,910	83,875	70,269	72,714	70,828	68,340	72,107	75,743
FFS Physician Administered Drugs	13,231	13,450	12,418	13,142	11,973	12,160	15,975	13,016	13,708	14,103	13,664	14,640	13,457
Encounter Physical Health Drugs	635,528	615,702	650,358	687,792	587,284	660,255	694,946	660,283	743,675	737,425	716,363	695,214	673,735
Encounter Physician Administered Drugs	77,166	72,363	74,448	79,108	67,151	73,346	76,964	71,832	83,342	85,047	83,388	83,253	77,284

Amount Paid per Claim (Rebates not Included)	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$56.23	$55.46	$56.52	$56.48	$57.00	$60.24	$57.90	$58.04	$59.16	$60.76	$62.43	$64.24	$58.70
Mental Health Carve-Out Drugs	$77.69	$77.39	$77.77	$77.87	$77.37	$72.65	$73.07	$74.57	$75.39	$73.43	$71.90	$71.84	$75.08
FFS Physical Health Drugs	$43.32	$42.06	$43.99	$43.08	$43.63	$46.87	$46.29	$46.56	$42.97	$43.29	$41.73	$44.58	$44.03
FFS Physician Administered Drugs	$104.23	$113.45	$148.86	$127.02	$113.34	$113.83	$115.62	$115.08	$128.58	$113.81	$112.28	$109.96	$118.00
Encounter Physical Health Drugs	$47.64	$47.77	$48.06	$47.91	$49.34	$53.90	$51.04	$51.18	$52.14	$55.39	$58.46	$60.28	$51.93
Encounter Physician Administered Drugs	$92.83	$82.78	$87.72	$92.66	$88.91	$97.52	$91.15	$90.02	$94.43	$90.09	$88.43	$92.37	$90.74

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$26.72	$26.88	$26.89	$26.87	$27.07	$27.03	$26.54	$26.85	$26.84	$27.23	$27.76	$27.78	$27.04
Mental Health Carve-Out Drugs	$61.73	$61.30	$61.38	$61.69	$60.78	$54.71	$56.11	$57.38	$57.81	$55.54	$54.16	$53.47	$58.00
FFS Physical Health Drugs	$22.26	$22.10	$21.97	$21.46	$21.68	$22.00	$23.14	$22.58	$22.30	$21.46	$21.48	$20.90	$21.95
Encounter Physical Health Drugs	$19.27	$19.56	$19.65	$19.67	$19.88	$21.07	$20.39	$20.65	$20.64	$21.68	$22.71	$22.68	$20.65

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$414.92	$405.47	$387.42	$371.19	$399.85	$451.42	$419.61	$435.33	$445.58	$477.39	$498.35	$517.71	$435.35
Mental Health Carve-Out Drugs	$461.31	$458.94	$457.61	$452.85	$461.02	$472.86	$470.34	$471.48	$479.63	$481.64	$479.19	$493.84	$470.06
FFS Physical Health Drugs	$308.82	$298.61	$309.90	$301.38	$313.54	$353.42	$318.89	$344.87	$303.66	$321.36	$298.95	$345.81	$318.27
Encounter Physical Health Drugs	$422.77	$412.14	$388.53	$369.94	$403.32	$460.65	$426.32	$440.84	$455.59	$492.09	$519.96	$538.52	$444.22

Multi-Source Drug Use Percentage	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Multi-Source Drug Use Percentage	93.4%	93.3%	92.9%	92.6%	92.9%	93.1%	93.0%	93.2%	93.2%	93.3%	93.3%	93.2%	93.1%
Mental Health Carve-Out Drugs	96.0%	96.0%	95.9%	95.9%	95.9%	95.7%	95.9%	95.8%	95.8%	95.8%	95.8%	95.8%	95.9%
FFS Physical Health Drugs	92.7%	92.8%	92.4%	92.3%	92.5%	92.5%	92.2%	92.6%	92.7%	92.7%	92.7%	92.7%	92.5%
Encounter Physical Health Drugs	93.0%	92.8%	92.3%	91.9%	92.3%	92.5%	92.4%	92.7%	92.8%	92.8%	92.8%	92.7%	92.6%

Preferred Drug Use Percentage	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Avg Monthly
Preferred Drug Use Percentage	86.13%	86.08%	86.40%	86.49%	86.42%	86.47%	86.71%	86.58%	86.56%	86.51%	86.45%	86.50%	86.4%
Mental Health Carve-Out Drugs	73.12%	73.05%	75.82%	77.03%	77.11%	76.83%	76.97%	76.76%	76.94%	76.81%	76.70%	76.56%	76.1%
FFS Physical Health Drugs	94.36%	94.57%	94.46%	94.60%	94.83%	94.63%	95.00%	94.81%	94.60%	94.62%	94.59%	94.89%	94.7%
Encounter Physical Health Drugs	88.15%	88.08%	87.91%	87.76%	87.57%	87.79%	87.88%	87.87%	87.83%	87.82%	87.74%	87.86%	87.9%

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: January 20, 2016

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2015

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$11,388,407	25.2%	11,741	$970	V
2	LATUDA	Antipsychotics, 2nd Gen	$2,765,821	6.1%	3,232	$856	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,796,636	4.0%	3,102	$579	V
4	STRATTERA	ADHD Drugs	$1,659,030	3.7%	4,715	$352	Y
5	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,134,057	2.5%	753	$1,506	V
6	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$738,950	1.6%	1,076	$687	V
7	INVEGA	Antipsychotics, 2nd Gen	$712,407	1.6%	742	$960	V
8	DULOXETINE HCL	Antidepressants	$689,579	1.5%	24,156	$29	V
9	FLUOXETINE HCL	Antidepressants	$552,535	1.2%	31,224	$18	Y
10	ABILIFY MAINTENA	Antipsychotics, Parenteral	$500,238	1.1%	324	$1,544	V
11	SAPHRIS	Antipsychotics, 2nd Gen	$464,039	1.0%	845	$549	V
12	BUPROPION XL	Antidepressants	$452,289	1.0%	16,723	$27	V
13	SERTRALINE HCL	Antidepressants	$443,584	1.0%	38,083	$12	Y
14	PRISTIQ ER	Antidepressants	$419,413	0.9%	1,579	$266	V
15	RISPERDAL CONSTA	Antipsychotics, Parenteral	$414,379	0.9%	598	$693	Y
16	Factor Viii Recombinant Nos	Physican Administered Drug	$404,128	0.9%	12	$33,677	
17	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$382,575	0.8%	1,082	$354	V
18	TRAZODONE HCL	Antidepressants	$356,551	0.8%	37,413	$10	
19	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$354,014	0.8%	4,211	$84	Y
20	AMITRIPTYLINE HCL	Antidepressants	$333,354	0.7%	17,173	$19	Y
21	VENLAFAXINE HCL ER	Antidepressants	$298,658	0.7%	1,822	$164	V
22	LAMOTRIGINE	Antiepileptics (oral & rectal)	$288,868	0.6%	20,189	$14	Y
23	CITALOPRAM HBR	Antidepressants	$268,297	0.6%	30,650	$9	Y
24	VIIBRYD	Antidepressants	$259,190	0.6%	1,308	$198	V
25	LANTUS	Diabetes, Insulins	$258,730	0.6%	794	$326	Y
26	VENLAFAXINE HCL ER	Antidepressants	$248,712	0.6%	14,465	$17	Y
27	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$246,129	0.5%	580	$424	Y
28	ESCITALOPRAM OXALATE	Antidepressants	$244,116	0.5%	18,544	$13	Y
29	ENBREL	Biologicals for RA, Psoriasis and Crohn's Disease	$232,088	0.5%	83	$2,796	Y
30	BUPROPION HCL SR	Antidepressants	$223,549	0.5%	11,335	$20	Y
31	METHYLPHENIDATE ER	ADHD Drugs	$212,627	0.5%	1,662	$128	N
32	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$212,473	0.5%	3,964	$54	Y
33	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$212,362	0.5%	12,562	$17	
34	NUVIGIL	ADHD Drugs	$211,925	0.5%	386	$549	V
35	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$208,996	0.5%	11,442	$18	Y
36	HARVONI	Hepatitis C	$207,978	0.5%	8	$25,997	Y
37	LORAZEPAM	Benzodiazepine Anxiolytics	$200,750	0.4%	20,996	$10	
38	Infliximab Injection	Physican Administered Drug	$197,932	0.4%	106	$1,867	
39	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$197,275	0.4%	2,059	$96	
40	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$190,217	0.4%	224	$849	V
		Top 40 Aggregate:	**$30,582,860**		**351,963**	**$1,919**	
		All FFS Drugs Totals:	**$45,174,889**		**692,913**	**$463**	

Notes
- FFS Drug Costs only, rebates excluded
- 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: January 20, 2016

ProDUR Report for October through December 2015

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	58	14	0	44	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,991	448	1	1,542	1.73%
DD (Drug/Drug Interaction)	Set alert/Pay claim	213	36	0	177	0.13%
ER (Early Refill)	**Set alert/Deny claim**	**76,776**	**13,549**	**199**	**62,969**	**68.90%**
ID (Ingredient Duplication)	Set alert/Pay claim	20,343	4,919	50	15,350	18.20%
LD (Low Dose)	Set alert/Pay claim	885	134	0	746	0.77%
LR (Late Refill/Underutilization)	Set alert/Pay claim	108	69	0	39	0.07%
MC (Drug/Disease Interaction)	Set alert/Pay claim	795	296	0	499	0.67%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,051	254	9	788	0.87%
PG (Pregnancy/Drug Interaction)	**Set alert/Deny claim**	**2,131**	**1,268**	**0**	**863**	**1.83%**
TD (Therapeutic Duplication)	Set alert/Pay claim	6,976	1,939	3	5,022	6.20%
	Totals	**111,327**	**22,926**	**262**	**88,039**	**99.37%**

ProDUR Report for October through December 2015

Top Drugs in Early Refill

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden	% Claims Screened Override Alert
DC	Diazepam	125	36	11,988	1.0%	28.8%	0.30%
	Haloperidol	266	69	2,756	9.7%	25.9%	2.50%
	Wellbutrin (Bupropion)	899	147	42,000	2.1%	16.4%	0.35%
DD	Geodon (Ziprasidone)	84	24	4,430	1.9%	28.6%	0.54%
	Celexa (Citalopram)	47	4	39,122	0.1%	8.5%	0.01%
ER	Remeron (Mirtazapine)	1,055	160	9,963	10.6%	15.2%	1.61%
	Hydrocodone/APAP	250	81	7,966	3.1%	**32.4%**	1.02%

Clarification Code & Description	# of Paid Claims	# of Recipients	# of Drugs
01 - No Override	1,313	841	164
02 - Other Override	148	82	85
03 - Vacation Supply	578	429	120
04 - Lost Prescription	782	579	145
05 - Therapy Change	3,590	3,065	317
06 - Starter Dose	83	64	46
07 - Medically Necessary	4,860	3,291	451
14 - Long Term Care Leave of Absence	5	4	5
16 - Long Term Care Emergency box (kit) or automated dispensing machine	2	1	1
18 - Long Term Care Patien Admit/Readmit Indicator	19	16	16

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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

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	26			
		Profiles Sent	10			
		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	61			
		Profiles Sent	60			
		Members With Response	0			
		Response Rate	0%			
		Newly Scheduled	0			
		Provider Contacted	55			
		Provider Agreed with Recommendation	0			
		Patient Not With Office	0			

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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

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	Profiles Reviewed	87			
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	14			
	Children under age 18 on any psychotropic	Profiles Reviewed	99			
	Children under age 6 on any psychotropic	Profiles Reviewed	14			
	Lock-In	Profiles Reviewed	88			
		Locked In	14			

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Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	13	1		
		Disqualified - TPL coordination issue	5			
		Disqualified - Other	1			
		Disqualified - No Provider Info	3			
		Disqualified - Erroneous denial	4	1		
		Faxes Sent	7	4		
		Fax Sent - SABA		2		
		Fax Sent - Controller	2			
		Fax Sent - Combination Inhaler	2			
		No Subsequent Pulmonary Claims	3	2		

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From Antidotes to Edoxaban: An Oral Anticoagulation Update

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Anticoagulation is required for a multitude of indications, from atrial fibrillation (AF) to pulmonary embolism (PE) and deep vein thrombosis (DVT). Four new oral agents, now being referred to as "direct oral anticoagulants (DOACs)" are available for patients whom warfarin is not a preferred option. The newest drug to enter the market is edoxaban (Savaysa®) an oral direct factor Xa inhibitor.[1] The focus of this newsletter will be to highlight the evidence for the use of edoxaban and how it compares to the already approved agents. An update on the development of antidotes for the DOACs will also be discussed.

Edoxaban (Savaysa®)

Edoxaban is approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of DVT and PE in patients already treated with a parenteral anticoagulant.[1] Unlike the other DOACs, edoxaban is not recommended in NVAF patients with high functioning renal clearance (CrCl >95 mL/min) due to an increased risk of ischemic stroke, compared to warfarin, found in this subgroup.[1]

Atrial Fibrillation

The NVAF trial (ENGAGE AF-TIMI 48) was a good quality study comparing edoxaban 30 mg daily and edoxaban 60 mg daily to warfarin in over 21,000 patients for approximately 2.5 years.[2] Patients had a $CHADS_2$ score of ≤3, putting them at low to moderate risk of embolism. Patients randomized to warfarin were in therapeutic range an average of 65% of the time. Both doses of edoxaban were found to be noninferior to warfarin (table 1). Similar to the other factor Xa inhibitors the incidence of intracranial hemorrhages was lower in both edoxaban groups compared to warfarin, which was driven by hemorrhagic stroke reduction. All-cause mortality was lower in the low dose edoxaban group compared to warfarin (p=0.006) and similar between high dose edoxaban and warfarin [hazard ratio (HR) 0.92, 95% CI 0.83 to 1.01, p=0.08].[2]

Table 1. Key Efficacy Outcomes of ENGAGE-TIMI 48 Trial.[2]

Outcome†	Edoxaban 30 mg (E30)	Edoxaban 60 mg (E60)	Warfarin (W)	Hazard Ratios and P-values
Composite of stroke or systemic embolism	253 (3.6%)	182 (2.6%)	232 (3.3%)	**E30 vs. W:** 1.07 (97.5% CI, 0.87 to 1.31; p=0.005*) **E60 vs. W:** 0.79 (97.5% CI, 0.63 to 0.99; P<0.001*)
Ischemic stroke	333 (4.73%)	236 (3.35%)	235 (3.33%)	**E30 vs. W:** 1.41 (95% CI 1.19 to 1.67; p<0.001) **E60 vs. W:** 1.00 (95% CI 0.83 to 1.19, p=0.97)
Hemorrhagic stroke	30 (0.43%)	49 (0.70%)	90 (1.3%)	**E30 vs W:** 0.33 (95% CI 0.22 to 0.50; p<0.001) **E60 vs W:** 0.54 (95% CI 0.38 to 0.77; p<0.001)
All-cause mortality	737 (11%)	773 (11%)	839 (12%)	**E30 vs W**: 0.87 (95% CI 0.79 to 0.96; P=0.006) **E60 vs W**: 0.92 (0.83 to 1.01; p=0.08)

* For noninferiority analysis; † data from overall study period

VTE Treatment

The approval of edoxaban for the use in VTE treatment was based on a good quality, phase 3, randomized controlled trial that compared edoxaban 60 mg daily to warfarin (adjusted INR of 2-3).[3] Edoxaban 30 mg daily was given to subjects with the following characteristics: CrCl 30-50 mL/min, body weight ≤60 kg and/or use of potent P-glycoprotein inhibitors. Patients were required to have been treated with at least 5 days of parenteral anticoagulant to be included. The median treatment duration was 7 days. Patients taking warfarin were therapeutic 64% of the time, which is consistent with other studies. The primary endpoint was occurrence of adjudicated symptomatic recurrent VTE, which included DVT or fatal or non-fatal PE. Edoxaban was found to be noninferior to warfarin for the primary endpoint, HR 0.89 (95% CI 0.70 to 1.13, p<0.001 for noninferiority).[3] Mortality rates were similar between groups.

Safety

Bleeding and anemia were the most common adverse effects seen with edoxaban use in clinical trials.[1] As with other DOACs used in patients with AF, major bleeding rates were significantly less in edoxaban groups compared to warfarin.[2] Intracranial bleeding was also significantly less in edoxaban treated subjects. The incidence of gastrointestinal bleeds (GI) was similar between low dose edoxaban and warfarin but significantly higher in the high dose edoxaban group compared to warfarin (HR 1.23; 95% 1.02 to 1.50; p=0.03, NNT 167) in the ENGAGE trial.[2] Major bleeding rates were similar between edoxaban and warfarin in patients treated for VTE.[3]

Place in Therapy

Anticoagulation is a delicate balance between embolism prevention and bleeding while also preventing mortality. All the DOACs have been shown to be non-inferior to warfarin for the prevention of stroke and systemic embolism in patients with NVAF, with dabigatran and apixaban also demonstrating superiority.[4-6] DOACs have been shown to perform significantly better than warfarin for preventing hemorrhagic strokes. No significant differences in ischemic stroke rates have been demonstrated between the DOACs and warfarin, except for dabigatran which was found to be superior to warfarin (p=0.03).[4] Evidence has shown edoxaban and apixaban to have significantly less major bleeding compared to warfarin, however, warfarin is associated with less risk of GI bleeds compared to all DOACs.[2,4-6] Only apixaban is associated with lower all-cause mortality rates compared to warfarin (when comparing high dose treatment regimens).[6]

When evaluating indirect treatment comparisons, it is important to consider key trial differences that may have impacted the results. Studies of DOACs in patients with NVAF were blinded trials, except the RE-LY study.[2,4-6] RE-LY compared dabigatran to warfarin using an open-label design. Open-label studies may bias results in favor of the study treatment. The time in therapeutic range (TTR) can greatly influence the efficacy of treatment in patients randomized to warfarin. TTRs were consistent between the studies except for the ROCKET-AF study which had a mean TTR of 55% compared to an average of 65% for the other studies.[2,4-6] TTR variability can translate into fewer patients taking an effective dose of warfarin which may worsen outcomes and bias the results in favor of the comparator. The $CHADS_2$ score estimates the risk of stroke based on patient comorbidities. The $CHADS_2$ score was similar between the studies (2.1-2.8) except for the ROCKET-AF trial.[2,4-6] In ROCKET-AF rivaroxaban and warfarin patients had a higher $CHADS_2$ score, with a mean score of 3.5.[5] A higher $CHADS_2$ score puts patients in a higher risk category for stroke and consequently more likely to experience a higher incidence of stroke or systemic emboli compared to other DOACs. Clinical trials directly comparing the DOACs is be the only way to determine the true differences between efficacy outcomes.

For VTE treatment, systematic reviews and meta-analyses have found no significant difference between efficacy of the DOACs compared to standard therapy (enoxaparin and warfarin).[7,8] Major bleeding rates were found to be less with the DOACs compared to standard therapy, with the lowest rates seen with rivaroxaban and apixaban.[7,8]

Antidotes

Clinical studies have not recognized the lack of a reversal agent as a major barrier to the use of DOACs. However, having access to an antidote in the event of a bleeding emergency is desired. Effectiveness of potential antidotes depends on the specific pharmacokinetics of each individual DOAC. Activated charcoal can be considered in the event of an acute dabigatran ingestion.[9] It is unclear if it would be helpful for edoxaban or apixaban and not likely to work for rivaroxaban. Dialysis may be useful for dabigatran in an emergency situation. The efficacy of dialysis for apixaban and edoxaban drug removal is unknown. The highly protein bound nature of rivaroxaban would make is not dialyzable.[9] The use of prothrombin complex concentrate (PCC) and activated PCC (aPCC) as a dabigatran and rivaroxaban antidote has been contradictory. Some studies have demonstrated improvement in lab parameters (i.e., prothrombin and thrombin potential) and exogenous thrombin potential while other studies showed no benefit. PCC and aPCC have not shown to be effective in the reversal of apixaban in animal studies. Limited evidence has demonstrated PCC and aPCC to be helpful as an edoxaban antidote.[9] Supportive care and removal of antithrombotic is the standard of care in a bleeding emergency until an antidote becomes available.

There are three new DOAC antidotes being studied in trials. Idarucizumab (aDabi-Fab) is being developed to inactivate dabigatran and is currently being studied in a phase 3 trial (RE-VERSE AD).[9] A phase 3 trial of an antidote to inactivate rivaroxaban, by binding to factor Xa inhibitors and heparin-activated antithrombin, is in the recruitment stage.[9] This recombinant protein, andexanet alfa (Annexa), has also proven to be useful in apixaban reversal and may have a role in edoxaban reversal but no studies have been reported. A universal anticoagulant reversal agent in development is PER977 (arapazine/ciraparantag). PER977 binds to the anticoagulant and causes inactivation. In addition to antidote concerns, there is no standardized, reproducible way to measure coagulation effects of the DOACs.[9]

Change in Oregon Health Plan (OHP) Policy

A review of the oral anticoagulant class was presented to The Oregon Pharmacy and Therapeutics Committee in May of 2015.[10] The Committee recommended that Oregon Health Plan (OHP) Fee-For-Service patients have access to all DOACs by discontinuing the clinical prior authorization (PA) requirement. A Retrospective DUR program will be conducted to monitor appropriate use.

Removal of the PA requirement was done as a result of findings of a recent policy evaluation of the anticoagulants.[11] The evaluation found <10% of patients with claims for anticoagulants were for DOACs. But, there was a low rate of (56.3%) of PAs requested by providers and 41 patients encountering a PA did not receive subsequent anticoagulation, putting them at risk for thrombosis. The potential safety risk to members prompted revisions to the PA policy. These changes were also supported by evidence from guidelines and systematic reviews that demonstrated similar efficacy and safety results for most anticoagulants, when used for their approved indications.[12-18] Tolerability, dosing, route of elimination, drug/food interactions and monitoring requirements are just a few of the characteristics that differentiate the anticoagulants from each other. Clinical relevance of these differences still needs to be determined.

Conclusion

With the approval of the fourth new oral anticoagulant, there are an increasing number of alternatives to warfarin for patients requiring anticoagulation. Studies have demonstrated similar efficacy between the DOACs and warfarin when used in patients with NVAF and VTE. Clinically relevant differences between the agents remain small. The optimal anticoagulant choice is influenced by patient specific characteristics, which will be aided by additional studies as the DOACs are prescribed on a broader scale.

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Obesity and Related Sequelae: Are Medications the Answer?

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Obesity, and its related morbidities, is a major health concern worldwide.[1] In the U.S., approximately 69% of people are overweight and 35% of these are obese.[2] Oregon fares better than the national average but the numbers are still alarming: 60% of the adult population is overweight and 26% of these are obese.[3] Obesity is linked with many chronic diseases and staggeringly high medical costs.[4] Obesity increases the risk of several health conditions including type 2 diabetes mellitus (T2DM), cardiovascular diseases, stroke, and some cancers.[4,5] Relative to the non-obese weight population, persons with obesity incur 46% greater inpatient costs and an 80% increase in prescription medications costs.[4] In 2008, costs associated with obesity and its complications cost $147 billion nationwide.[4]

Definitions of Overweight, Obesity, and Weight Loss Success

The International Obesity Task Force defines obesity as a body mass index (BMI) of 30 kg/m^2 or greater.[1] The U.S. Food and Drug Administration (FDA) subdivides obesity into 3 classes based on BMI: class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2), and class III ($\geq$40 kg/m^2).[6,7] Industry guidance for obesity treatment by the FDA considers treatments to be effective if: 1) there is a statistically significant difference in mean weight loss of 5% or more between the drug and placebo, or 2) at least 35% of subjects lose at least 5% body weight and the difference in weight loss between the drug and placebo is statistically significant.[6]

Treatment Modalities for Obesity

An increasing number of treatment options are available for obese patients unable to successfully lose weight and keep weight off with behavioral interventions alone. Bariatric surgery can lead to body weight reductions of 30-40% as well as a reduction in obesity-related comorbidities.[5] Historically, bariatric surgery was reserved for patients with extreme obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidities), but recent research has led to FDA approval of bypass surgery for an expanded subset of the population (BMI ≥35 kg/m^2 or ≥30 kg/m^2 with at least one obesity-related comorbidity).[1,5,11] Nevertheless, surgery is expensive, and not without risks, so there is continued interest in less invasive treatment options; medications are an attractive option for clinicians and patients looking for weight loss aids that are simple to administer and minimally invasive.

Weight Loss Medication History

Sympathomimetic agents were some of the first available weight loss medications.[9] However, many formerly approved sympathomimetics were removed from the market due to increased risk for cardiac events and other adverse effects.[9] Two sympathomimetics, phentermine and diethylpropion, are still approved, but their use is limited to less than 12 weeks and both carry safety concerns for abuse potential and risk for cardiovascular events.[5,8] Serotonergic agents also act centrally but reduce appetite by affecting other neurotransmitters.[8] Two serotonergic medications, fenfluramine and dexfenfluramine, were removed from the market due to pulmonary hypertension and risk for cardiovascular events.[10] Orlistat is a peripherally-acting medication for long-term use that prevents uptake of fatty substances through the gastrointestinal tract but is minimally effective and associated with gastrointestinal adverse effects.[1,8] Besides orlistat, long-term health outcomes data are still not available and there is no evidence these drugs decrease morbidity outcomes associated with obesity.

Guideline Recommendations

Current guidelines recommend behavioral and lifestyle interventions as first-line treatment for weight loss in obese patients.[1,4,5,7,8,11] If comprehensive lifestyle changes fail to promote durable weight loss, the American Association of Clinical Endocrinologists, The Obesity Society, the American Society for Metabolic & Bariatric Surgery, the American Heart Association, and the American College of Cardiology all recommend bariatric surgery over pharmacologic agents.[4,11] Bariatric surgery demonstrates greater weight loss, improved durability of weight loss, and improved surrogate markers of metabolic disease as compared to weight loss drugs.[4,11] The Canadian Task Force on Preventive Health Care advises practitioners to not routinely prescribe medications for weight loss due to unfavorable harms and unknown long-term benefit.[7] The World Gastroenterology Organization and the Endocrine Society also suggest reserving these drugs for patients who cannot lose weight by lifestyle interventions alone, with both organizations acknowledging that these drugs are only modestly effective.[1,8] Finally, a 2015 Institute for Clinical and Economic Review report calls into question the utility and safety of all weight loss drugs.[5]

Current FDA-Approved Medications for Weight Loss

Four weight loss drugs have gained popularity in recent years.[5] These drugs are approved for adults with a BMI of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more with an obesity-associated comorbidity.[5,8] In general, patients on a weight loss drug should be monitored every 3 months, and the drug should be discontinued if there is less than 5% weight loss or an adverse event occurs.[8]

Lorcaserin (Belviq®)

Lorcaserin is a selective serotonin 2c agonist previously reviewed in the December 2012 newsletter.[10] Lorcaserin was approved based on 3 placebo-controlled trials, each about one year in duration.[10] Combined data (n=6139) demonstrated a modest percent reduction in body weight compared to placebo (-4.5 to -5.8% vs. -1.5 to -2.8%, p<0.001).[5] It is still unknown whether this modest reduction is sustained over time and whether use of the drug improves comorbidities associated with obesity.[10] Lorcaserin is also associated with a number of adverse effects and precautions such as adverse psychiatric effects, headache, dizziness, and nausea.[10]

Phentermine/Topiramate (Qsymia®)

Phentermine/topiramate was also reviewed in the December 2012 newsletter.[10] Drug approval was based on two 56-week placebo-controlled trials that demonstrated a moderate reduction in body weight with both the high (15/92 mg) and low (7.5/46 mg) doses as compared to placebo (-10.9% and -5.1%, respectively vs. -1.6%, p<0.0001 for all comparisons). It is unknown whether this weight reduction is sustained over time and there is insufficient evidence that the drug improves comorbidities associated with obesity.[10] The agents are also associated with a number of adverse effects and precautions, such increased heart rate, paresthesias, and anxiety.[10]

Naltrexone/Bupropion (Contrave®)

Bupropion is an antidepressant that inhibits dopamine and norepinephrine reuptake and may promote satiety. Naltrexone augments the appetite suppressant effects of bupropion.[5,8] Approval for naltrexone/bupropion was based on four 56-week randomized, placebo-controlled trials (n=4468).[12-15] Results revealed statistically significant weight loss compared to placebo (-5.0 to -9.3% vs. -1.2 to -5.1%).[12-15] The proportion of patients who lost more than 5% and 10% of body weight with naltrexone/bupropion was significantly higher than with placebo (52% and 28%, respectively, vs. 24% and 10% with placebo).[12-15]

Only one trial reported the impact of naltrexone/bupropion on an obesity-related comorbidy.[12] The trial studied the effect of the drug combination on A1C in patients with T2DM and found a higher percentage of patients who took naltrexone/bupropion achieved an A1C of less than 7% compared with placebo (44.1% vs. 26.3%; p<0.001).[12] The Light Study was another highly

anticipated designed to assess the impact of naltrexone/bupropion on cardiovascular events.[16] However, amidst much controversy the study was suddenly halted. Interim analysis indicated that naltrexone/bupropion did not offer any protection from cardiovascular events.[16] In fact, more patients on naltrexone/bupropion experienced cardiovascular events than patients on placebo (55 vs. 43 events, respectively).[16] The manufacturer warns of potential for increased heart rate and blood pressure with use.[17]

Common adverse effects associated with bupropion/naltrexone include nausea, vomiting, headache, constipation, dizziness and dry mouth.[17] Adverse events were reported in 83-90% of patients in clinical trials and between 20-30% of patients stopped the drug early due to an adverse event.[12-15] There is a black boxed warning for the drug combination because of increased risk of suicidal behaviors and neuropsychiatric reactions observed in patients who use bupropion.[17] Other contraindications include seizure disorders and uncontrolled hypertension.[17]

Liraglutide (Saxenda®)

Liraglutide is an injectable glucagon-like peptide-1 agonist approved for T2DM that can promote satiety.[8] The FDA approved liraglutide for weight loss based on three 56-week randomized, placebo- and active-controlled trials with up to 2 years of follow-up.[18-20] Data from these 3 trials (n=4999) demonstrated statistically significant weight loss compared to placebo or orlistat (-6 to -8% vs. -2.4 to -2.9%, respectively).[18-20] The proportion of patients who lost more than 5% and 10% of body weight with liraglutide was significantly higher than with placebo or orlistat (63-73% and 26-27% respectively with liraglutide, vs. 27-28% and 6-11% with placebo and 44% and 14% with orlistat).[18-20] Not surprisingly, liraglutide delayed the diagnosis of T2DM in nondiabetics and reduced the onset of pre-diabetes versus placebo at week 56 (30.8% vs. 67.3%; p<0.001).[18,21]

Common adverse effects include nausea, vomiting, diarrhea, constipation, and headache.[22] Adverse events were reported in 80-96% of patients in clinical trials and between 8-10% of patients stopped the medication early due to an adverse event.[18-20] Liraglutide may interact with other medications by slowing the rate and extent of gastric emptying.[22] The long-term safety data of liraglutide has not been established; concerns about thyroid tumors observed in animal models led the FDA to issue a black boxed warning.[22] Users of liraglutide may also be at increased risk for pancreatitis, pancreatic cancer and immunogenicity-related events.[22]

Discussion & Conclusions

The primary goals of weight loss are improved health outcomes. Bariatric surgery has demonstrated superior health outcomes as compared to weight loss drugs and is covered by the Oregon Health Plan (OHP) in patients with a BMI of 35 or greater.[23] Even though some weight loss drugs have been on the market for several years, none have demonstrated a reduction in obesity-related comorbidities, such as cardiovascular events, nor have they been shown to improve daily functioning, symptom-relief, or quality of life.[5,16] In addition, currently available weight loss drugs are associated with multiple adverse effects and several safety warnings.[5,10] Most medical societies do not consider the benefits of weight loss medications to exceed the potential harms[4,5,7,11] and use of a drug for weight loss is not covered by OHP.[23] Current recommendations for treatment of obesity continue to be diet and physical activity, as well as bariatric procedures in certain populations.[4,5,7,11]

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Does Sacubitril/Valsartan Pose a Treatment Conundrum for Management of Heart Failure?

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Characteristics and Classifications of Heart Failure

Progression of heart failure (HF) results in unfavorable symptoms, such as dyspnea, fatigue or peripheral edema due to abnormal cardiac structure or function.[1] Etiology of HF is primarily ischemic but can also be non-ischemic, such as from long-standing hypertension.[1] About 50% of the population with HF have reduced ejection fraction (HFrEF), which is associated with an important prognosis: lower ejection fraction (EF) is associated with higher mortality.[1] In clinical trials, HFrEF is often defined as an EF of 40% or less, and it is only in these patients that drug therapy is consistently effective.[2] However, HF with preserved EF (HFpEF) is also associated with significant mortality and has become increasingly prevalent. HFpEF rates now approach 50% of all cases of HF and is difficult to manage with drug therapy.[2] If HFpEF is suspected, presence for structural heart disease should be investigated.[1]

Investigators routinely use the New York Heart Association (NYHA) functional classification, which is based on patient symptoms, to select subjects for clinical HF drug trials. For example, patients with NYHA class I have no symptoms, whereas patients with NYHA class IV may have symptoms at rest.[2] Independent of EF, there is a strong correlation between symptom severity and risk for hospitalization or death.[1,2]

Drug Management of Heart Failure with Reduced Ejection Fraction

In patients with HFrEF, pathological 'remodeling' of the ventricle occurs with increasing ventricle enlargement and decline in EF.[1] This maladaptive progression is thought to be largely due to neurohormonal activation by the renin-angiotensin system (RAAS) and the sympathetic nervous system – systems, when activated long-term, detrimentally remodel heart tissue.[1] The basis of standard HFrEF treatment is to stop this remodeling process.

The goals of treatment in patients with HF are to relieve symptoms, prevent hospitalization admission and decrease mortality.[1] No drug therapy has shown to effectively improve health-related quality of life.[2] For years, 3 classes of disease-modifying therapies – ACE-inhibitors (or angiotensin receptor blockers [ARB]), beta-blockers, and aldosterone antagonists – have been fundamentally important in modifying the course of HFrEF and should be strongly considered in each patient with HFrEF. Recently, the neprilysin inhibitor sacubitril, combined with a maximally dosed ARB, was added to this medley of drug classes.[3] All 4 types of drugs are neurohormonal antagonists and are complementary in the management of HFrEF.

Pivotal Heart Failure Drug Trials

ACE-inhibitors should be prescribed to all patients with HFrEF.[2] Landmark clinical trials of ACE-inhibitors demonstrated early and significant *absolute* risk reduction in all-cause mortality versus placebo of 4.5%[4] and 15%[5] in patients with mild and severe symptomatic HFrEF, respectively. Target doses of ACE-inhibitors are convincingly correlated with greater mortality reduction.[6] Further trials of ACE-inhibitors have consistently proven significant mortality benefit.[7] The landmark beta-blocker trials were conducted in patients with mild to severe symptomatic HFrEF already on an ACE-inhibitor.[8–10] These trials showed an additional *absolute* reduction in all-cause mortality by another 5-7% within 1 year when a beta-blocker was added to an ACE-inhibitor relative to an ACE-inhibitor alone.[8–10] Strong and consistent evidence demonstrates that an ACE-inhibitor and beta-blocker should be initiated in all patients with HFrEF without contraindications.[8–11]

Aldosterone antagonists also have a major role in the management of HFrEF. Both spironolactone and eplerenone have demonstrated significant mortality benefit when added to an ACE-inhibitor.[12,13] Evidence for use of spironolactone came before beta-blockers were widely used and was studied in patients with more severely symptomatic HFrEF.[12] Spironolactone resulted in an *absolute* risk reduction in all-cause mortality of 11% within 2 years.[12] Eplerenone also provides additional reduction in cardiovascular (CV) mortality and hospital admissions for HF when it is added to an ACE-inhibitor (or ARB) and beta-blocker in patients with mildly symptomatic HFrEF.[13] The addition of an aldosterone antagonist to an ACE-inhibitor and beta-blocker in symptomatic HFrEF is recommended and guidelines provide clear recommendations for mitigating risk for hyperkalemia with these agents.[1,2]

There is also some evidence for use of an ARB in HFrEF. However, the evidence of benefit is more clear when an ARB is substituted for an ACE-inhibitor in patients intolerant to an ACE-inhibitor.[14–16] Similar to target doses of ACE-inhibitors, target doses of ARBs are more effective than lower doses at reducing HF-associated mortality and morbidity outcomes.[17] ARBs are strongly recommended in patients with HFrEF who are intolerant to an ACE-inhibitor, though guidelines also detail circumstances in which the addition of an ARB to an ACE-inhibitor and beta-blocker (but not aldosterone antagonist) may be reasonable.[1,2] Table 1 lists the drugs and target doses that have demonstrated reduction in mortality and morbidity outcomes.

Table 1. Doses of Drugs with Mortality Benefit in Patients with HFrEF.[1]

ACE-inhibitor	**Target Dose**
Captopril	50 mg t.i.d.
Enalapril	10-20 mg b.i.d.
Lisinopril	20-35 mg once daily
Ramipril	5 mg b.i.d.
Trandolapril	4 mg once daily
Aldosterone Antagonist	**Target Dose**
Eplerenone	50 mg once daily
Spironolactone	25-50 mg b.i.d.
Angiotensin Receptor Blocker (ARB)	**Target Dose**
Candesartan	32 mg once daily
Valsartan	160 mg b.i.d.
Beta-blocker	**Target Dose**
Bisoprolol	10 mg once daily
Carvedilol	25-50 mg b.i.d.
Metoprolol Succinate (ER/XL)	200 mg once daily
Neprilysin Inhibitor/ARB	**Target Dose**
Sacubitril/Valsartan	200 mg b.i.d.

Abbreviations: b.i.d. = twice daily; ER/XL = extended-release; t.i.d. three times daily

With the exception of diuretics, the therapeutic value of other drugs periodically used for HFrEF is less well defined. Digoxin may be useful to reduce risk of hospitalizations for HFrEF but has consistently demonstrated no effect on mortality.[18,19] The therapeutic niche for ivabradine is still uncertain after only one trial found it reduced hospitalizations, but not mortality, in HFrEF patients in normal sinus rhythm with a resting heart rate of 70 beats-per-minute or more.[20] Evidence for use of hydralazine combined with isosorbide dinitrate is well documented in Black patients already on standard HFrEF therapy[21] and is a reasonable fourth-line option in any HFrEF patient without contraindications.[1,2]

A New Neurohormonal Antagonist: Sacubitril/Valsartan

Sacubitril/valsartan is the first HF drug approved in years that demonstrates mortality benefit in HFrEF. However, evidence for its use is limited to only one trial that compared sacubitril/valsartan 200 mg twice daily (n=4,187) with enalapril 10 mg twice daily (n=4,212).[22] A careful, step-wise approach was used to maximize safety in the study. First, a single-blind run-in period was

used to determine which eligible patients could tolerate enalapril 10 mg twice daily; then a second single-blind run-in period was utilized to determine which of those patients could tolerate sacubitril/valsartan 200 mg twice daily.[22] Over 20% of eligible patients were not eligible for randomization into the clinical trial, mostly because of intolerance to the target doses.[22]

Randomized patients had stable, mildly symptomatic HFrEF (NYHA II or III) and were on a concomitant beta-blocker and diuretic.[22] The mean EF was 29%.[22] Most patients were white males. Females, Blacks, and U.S. citizens were largely under-represented in the study.[22]

There was a 4.7% absolute risk reduction in the primary endpoint, which was a composite of death from CV causes or first hospitalization for HF, with use of sacubitril/valsartan (enalapril 26.5% vs. sacubitril/valsartan 21.8%; hazard ratio [HR] 0.80; 95% CI, 0.73 to 0.87; p<0.001).[22] Thus, 22 patients need to be treated (NNT) for 27 months with sacubitril/valsartan instead of enalapril to prevent one hospitalization for HF or one death from a CV cause.[22] All-cause mortality was also significantly reduced with sacubitril/valsartan compared to enalapril (17.0% vs. 19.8%, respectively; HR 0.84; 95% CI, 0.76 to 0.93; p<0.001; NNT 36).[22] During the trial, 19.8% of patients stopped sacubitril/valsartan prematurely and 17.8% of patients stopped enalapril prematurely.[22] There was a higher incidence of symptomatic hypotension (14.0% vs. 9.2%; p<0.001) and angioedema (0.45% vs. 0.24%) with sacubitril/valsartan than with enalapril.[22]

Conclusion

The results from this new trial are certainly promising. Time will tell how safe and tolerable sacubitril/valsartan is in real-world settings. But before prescribers start replacing ACE-inhibitors with sacubitril/valsartan, some limitations should be considered. First, the specific order of the single-blind run-in phases likely introduced bias early in the trial. Second, about 20% of patients in each arm discontinued the study prematurely, which is concerning after accounting for the additional 20% of eligible patients who were not randomized due to intolerability of either drug in the initial run-in phases. It is unclear how many patients in real world settings will be able to tolerate the dose studied in the trial; lower doses may be better tolerated but may not be any more effective than far less costly ACE-inhibitor or ARB. Third, it is unclear if the efficacy seen with sacubitril/valsartan can be attributed to the addition of sacubitril to bioequivalent 320 mg daily dose of valsartan used in the trial,[3] or if it can be attributed to the high valsartan dose alone. Both valsartan and enalapril doses studied were optimal,[4,14,23] but a 40 mg daily dose of enalapril may have been a more reasonable comparator.[24–27] A comparison of sacubitril/valsartan to valsartan 320 mg daily would be helpful to explain its place in therapy in HFrEF. In time, these limitations may be adequately addressed. However, with the plethora of time-tested evidence for use of ACE-inhibitors, a selective and cautious approach is reasonable before ACE-inhibitors are indiscriminately substituted for a new and more costly drug.

Peer Reviewed By: Bill Origer, MD, Medical Director, Samaritan Health Services, Corvallis, OR and Harleen Singh, PharmD, BCAP, Clinical Associate Professor at OSU College of Pharmacy, Portland, OR.

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Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 60 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a preferred PPI?	Yes: Go to 5	No: Go to 3
3. Is the treating diagnosis an OHP-funded condition (see **Table**)?	Yes: Go to 4	No: Pass to RPh; deny, not funded by OHP.
4. Will the prescriber consider changing to a preferred PPI product? Message: 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.	No: Go to 5
5. Has the patient already received 68 days of PPI therapy for either of the following diagnoses: • GERD [esophageal reflux (K219), esophagitis (K200 - K210)] or • *H. pylori* infection (B9681)?	Yes: Go to 6	No: Go to 7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	Yes: Approve for 1 year	No: Pass to RPh; not funded by OHP. RPh may approve a quantity limit of 30 doses (not to exceed the GERD dose in the **Table**) over 90 days if time is needed to taper off PPI. Note: No specific PPI taper regimen has proven to be superior. H2RAs may be helpful during the taper. Preferred H2RAs are available without PA.

7. Does the patient have a history of gastrointestinal ulcer or bleed and have one or more of the following risk factors? • Age 65 years or older • Requires at least 3 months of continuous daily: i. Anticoagulant, ii. Aspirin or non-selective NSAID, or iii. Oral corticosteroid	Yes: Approve for 1 year	No: Go to 8
8. Are the indication, daily dose and duration of therapy consistent with criteria outlined in the **Table**? Message: OHP-funded conditions are listed in the **Table**.	Yes: Approve for recommended duration.	No: Pass to RPh. Deny; medical appropriateness or not funded by OHP Message: Patient may only receive 8 weeks of continuous PPI therapy.

Table. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	**Maximum Duration**	**Maximum Daily Dose**
GERD: Esophageal reflux (K219) Esophagitis (K200-K210)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection (B9681)	2 weeks	Dexlansoprazole 60 mg Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg
Achalasia and cardiospasm (K220) Barrett's esophagus (K22.70; K22.71x) Duodenal Ulcer (K260-K269) Dyskinesia of esophagus (K224) Esophageal hemorrhage (K228) Gastritis and duodenitis (K2900-K2901; K5281) Gastroesophageal laceration-hemorrhage syndrome (K226) Gastric Ulcer (K250-K259) Gastrojejunal ulcer (K280-K289) Malignant mast cell tumors (C962) Multiple endocrine neoplasia [MEN] type I (E3121) Neoplasm of uncertain behavior of other and unspecified endocrine glands (D440; D442; D449) Peptic ulcer site unspecified (K270-K279) Perforation of Esophagus (K223) Stricture & Stenosis of Esophagus (K222) Zollinger-Ellison (E164)	1 year	

*A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

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Class Update with New Drug Evaluation: Antiemetics

Date of Review: January 2016
Generic Name: netupitant/palonosetron
rolapitant

End Date of Literature Search: September 2015
Brand Name (Manufacturer): Akynzeo® (Eisai)
Varubi™ (Tesaro, Inc.)
Dossiers Received: yes (Akynzeo)/ no (Varubi)

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

Purpose for Class Update:
The antiemetic drug class will be reviewed to determine if there is any relevant, updated evidence to be incorporated into the recommendations provided to the Oregon Health Plan (OHP). Evidence identified since the last review in November of 2014 will be included.

Research Questions:
1. What is the comparative efficacy and effectiveness of different antiemetic treatments in reducing nausea or vomiting (n/v) in patients with cancer, post-operatively, during pregnancy, or in patients with severe n/v who require rescue treatment (i.e., emergency department visit or hospitalization)?
2. What are the comparative harms of different antiemetic treatments used in patients with cancer, post-operatively, or during pregnancy?
3. Are there subpopulations of patients in which a particular antiemetic treatment would be more effective or associated with less harm?

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.[1] Key recommendations from clinical practice guidelines include up to 3 days of an antiemetic for patients beyond length of the chemotherapy regimen or radiation.[1,2]
- 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, which reduced post-operative nausea (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) based on 3 randomized controlled trials (RCTs) (n=224).[3]
- 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.[4] 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.[5,6] 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.[6] 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%.[5]
- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (VARUBI™). Currently, only prescribing information could be found.[7]

Recommendations:

- No changes are recommended to the PDL based on review of the clinical data. Evaluate drug costs in the executive session.
- Recommend that patients receiving chemotherapy or radiation are allowed 3 days of antiemetic therapy beyond length of treatment (Appendix 5).
- Recommend that doxylamine/pyridoxine be added to the Antiemetic PA criteria to allow coverage for pregnancy-induced n/v.
- Recommend that NEPA and rolapitant also be added to the Antiemetic PA.

Previous Conclusions and Recommendations:

- There is evidence that palonosetron may be superior to other 5HT3 antagonists for management of CINV due to moderately emetogenic chemotherapy; however, ondansetron, dolasetron, and granisetron are equally effective for CINV and PONV.[8]
- In pregnancy, ondansetron is not superior to promethazine for effectiveness but is less sedating. Long-term studies show no difference in number of live births, proportion of infant deformities, or birth weight between ondansetron and active control groups. There is low quality evidence that doxylamine/pyridoxine led to significantly greater improvement in n/v symptoms compared to placebo but there is insufficient comparative evidence with other antiemetic therapy.[8]
- Ondansetron is superior to granisetron for complete response rates in subpopulations with a predisposition to n/v, such as motion sickness or previous treatment with emetogenic chemotherapy.[8]
- No changes were recommended to the PMPDP.

Background:

Antiemetics are commonly prescribed for CINV, PONV, and pregnancy-related n/v. A multitude of medical conditions can also cause n/v which are often treated with promethazine, metoclopramide, prochlorperazine, and ondansetron.[9] Risk factors for n/v are female gender, history of motion sickness, and non-smoking history.[10] In addition to these risk factors, patients undergoing surgery are at increased risk if they have a previous history of PONV; receive post-operative opioids; receive general (versus regional) anesthesia, volatile anesthetics or nitric oxide; and certain types of surgery.[10,11] Newer antiemetics used at minimal doses are well tolerated and are associated with a low incidence of adverse effects.[11] Important outcomes for evaluating effectiveness of antiemetics are incidence of n/v, need for rescue therapy and quality-of-life assessments. For CINV, the Functional Living Index-Emesis (FLIE) is used to determine the effect of n/v on patients' daily lives. The Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status is also used to describe patient functioning (ability to care for them self, daily activities, and physical ability) on a scale of 1-5 (Table 1).[12]

Table 1. ECOG Scale of Performance Status[12]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Pregnancy-related n/v requires treatment in 10% of females. Pyridoxine, a form of vitamin B6, is recommended as a first-line therapy by the American Congress of Obstetricians and Gynecologists (ACOG).[13] The combination of pyridoxine with doxylamine, a first-generation antihistamine, is recommended for pregnant patients who fail pyridoxine alone. The 5HT3 receptor antagonists (RA) are frequently prescribed for pregnancy-related n/v, despite limited evidence to support their use.[13]

PONV occurs in 25-30% patients undergoing surgery and in up to 70-80% patients at high-risk who do not receive antiemetic prophylaxis.[10] In addition, post-discharge nausea and vomiting (PDNV) occurs in 30-50% patients discharged from surgery.[11] Antiemetics recommended by the Society for Ambulatory Anesthesiology (SAA) recommend 5HT3 RA, NK1 RA, corticosteroids, butyrophenones (e.g., droperidol), antihistamines, and anticholinergics.[11] Patients at medium to high risk for PONV should receive one or two antiemetics to prevent PONV.[11] There is no evidence of clinically significant difference in effectiveness between antiemetics used for PONV and guidelines do not prefer one treatment over another.[10,11,14]

CINV is highly dependent upon the chemotherapeutic agent used, dose of therapy, schedule and route of treatment. Radiation-induced nausea and vomiting (RINV) varies dependent upon area of the body and the amount exposed to treatment.[1] Patient variables, such as age, sex, prior chemotherapy, and alcohol use may also influence degree of CINV. Young female patients are at highest risk for CINV. Incidence of vomiting can be reduced by about 60% when prophylactic antiemetics are used; however, nausea is much more difficult to control. CINV is classified into acute (0-24 hours), delayed (24-170 hour), anticipatory, breakthrough or refractory.[1]

Guidelines for CINV recommend antiemetic therapy based on emetogenic potential (Table 2).[2] Antiemetic regimens should be guided by the chemotherapeutic agent with the greatest emetic risk in the regimen.[2] In pediatric patients recommendations are the same for MEC and HEC regimens: a 5-HT3 RA plus a corticosteroid. For patients undergoing high-dose chemotherapy with stem cell or bone marrow transplant, a 5-HT3 RA with dexamethasone is recommended.[2] The addition of lorazepam, alprazolam or olanzapine may be considered in patients with breakthrough n/v. High-dose intravenous metoclopramide can be substituted for a 5HT3 RA or a dopamine antagonist can be considered. Lorazepam and diphenhydramine are only used as adjunctive therapy.[2]

Table 2. American Society of Clinical Oncology (ASCO) Guideline Recommendations for Antiemetics[2]

Regimen	Recommendation
Highly Emetogenic Chemotherapy (HEC)	- Three-drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist and dexamethasone
Moderately Emetogenic Chemotherapy (MEC)	- Two-drug combination of palonosetron and dexamethasone - If palonosetron is not available, substitute a first generation 5-HT3 receptor antagonist, preferably granisetron or ondansetron - Limited evidence also supports adding aprepitant to the combination
Low Emetogenic Chemotherapy	- A single 8 mg dose of dexamethasone
High-dose Chemotherapy	- 5-HT3 antagonists and dexamethasone
High-risk Radiation-induced nausea and vomiting	- 5-HT3 antagonist before each fraction and 24 hours following and dexamethasone during fractions 1-5
Moderate-risk Radiation-induced nausea and vomiting	- 5-HT3 antagonist before each fraction and may consider dexamethasone during fractions 1-5
Low-risk Radiation-induced nausea and vomiting	- 5-HT3 antagonist alone as prophylaxis or rescue
Minimal-risk Radiation-induced nausea and vomiting	- Rescue therapy with a dopamine receptor antagonist or a 5-HT3 antagonist
Multi-day chemotherapy	- Antiemetics appropriate for emetogenic risk class of chemotherapy be given during treatment and for 2 days after

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 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.

Systematic Reviews:

COCHRANE – Interventions for Nausea and Vomiting in Early Pregnancy

Studies in patients in early pregnancy with n/v and retching were reviewed. Both pharmacological and non-pharmacological therapies were included.[15] Forty-one studies met inclusion criteria. Limited data suggested ginger products may be helpful but evidence was not consistent. Evidence for the use of pharmacotherapy was limited. Studies with vitamin B6, doxylamine-pyridoxine and other antiemetics were identified but pooling of the data was not possible due to heterogeneity of patients and interventions. Low-quality evidence for important outcomes prevent conclusions based on effectiveness of antiemetic treatments.[15]

Canadian Agency for Drugs and Technology in Health (CADTH)

CADTH released a rapid response review on the long-term use (>5 days) of ondansetron, dolasetron and granisetron in prevention of n/v in patients who are receiving chemotherapy or are postoperative.[16] Literature was searched from January 1, 2009 to March 24, 2014. No evidence was found for long-term use of these agents.

Antiemetics for opioid-induced nausea was the focus of a second CADTH rapid response report.[17] Nineteen studies met inclusion criteria for the review. Antiemetic drugs reviewed were found to be similar in effectiveness and combining antiemetics may improve outcomes. Both ondansetron and dimenhydrinate are recommended by guidelines for PONV.

Liu, et al – Neuorkinin-1 Receptor Antagonists in Preventing Postoperative Nausea and Vomiting

A systematic review and meta-analysis of NK-1 RA treatment was evaluated for PONV.[3] Methodology followed PRISM guidelines and evidence was graded using a modified Jadad scale. The primary outcome of the review was the incidence of PONV. Complete response (defined as no need for rescue medication and absence of vomiting) was a secondary outcome. Treatments were evaluated 24 hours after surgery. Fourteen studies met inclusion criteria. NK-1 RAs included were the following: aprepitant, fosaprepitant, casopitant, ezlopitant, netupitant, rolapitant and vaestipitant.[3] Evidence was found for aprepitant, rolapitant, and casopitant (not available in the US). Three RCTs including 224 patients found aprepitant to be effective for PONV versus placebo. Aprepitant 80 mg reduced post-operative nausea (RR 0.60, 95% CI 0.47 to 0.75, p<0.001) and vomiting (RR 0.13, 95% CI 0.04 to 0.37; p<0.001) compared to placebo. Aprepitant 40 mg was also superior to placebo for preventing incidence of vomiting. In a dose comparison study of aprepitant, there was no difference in efficacy between 80 mg and 125 mg doses (35% incidence of nausea for both groups). Aprepitant 40 mg and 125 mg doses were superior to ondansetron 4 mg at preventing n/v (RR 0.47, 95% 0.37 to 0.60; p<0.001 and RR 0.32, 95% CI 0.13 to 0.78; p=0.01, respectively).[3] Incidence of vomiting was significantly reduced in a dose-dependent manner with rolapitant 20 mg, 70 mg and 200 mg doses compared to placebo. Significantly less patients were likely to require rescue therapy when they received 80 mg of aprepitant versus placebo; however, no difference was found in patients who received 40 mg of aprepitant versus placebo.[3] No significance difference was found between ondansetron 4 mg and aprepitant 40 mg or 125 mg in requirement for rescue therapy or complete response rates. Limitations of the review include small sample size, inclusion of different surgery types, patients with varying susceptibility to PONV, and varying degrees of study quality.

New Guidelines:

NCCN Clinical Practice Guideline in Oncology

The NCCN guideline for use of antiemetics in supportive care in oncology was recently updated.[1] The NCCN guidelines are based on evidence and committee consensus. The primary treatment goal is prevention of CINV. Choice of antiemetic should be based on patient specific factors, emetic risk of chemotherapy, and prior antiemetic experience. Treatment recommendations based on chemotherapy are presented in Table 3.[1] Recommendations for intravenous HEC, MEC, LEC, oral chemotherapy regimens and RINV are based on low-quality evidence and consensus from the committee that the treatment is appropriate. The exceptions are for NK1 RA use in HEC regimens, which is supported by high-quality evidence and uniform consensus for use, and use of rolapitant, which is recommended for MEC based on high-quality evidence and uniform consensus for use. If breakthrough treatment is needed, an additional agent from a different class from the original regimen prescribed is recommended. Dexamethasone, 5HT3 RA, and IV palonosetron can be used for multi-day chemotherapy regimens. Aprepitant (with a 5HT3 RA and dexamethasone) and fosaprepitant (with dexamethasone) can also be used for multi-day HEC regimens.[1]

Table 3. NCCN Guideline Recommendations for Antiemetics[1]

Chemotherapy Regimen	Antiemetic Options - Day 1	Additional Antiemetic Therapy
High Emetic IV Chemotherapy Agents	1. NK1 RA (days 1-3) *AND* 5-HT3 RA *AND* dexamethasone	- Days 2-3: continue NK1 RA (exception is rolapitant which is given as one dose on day 1) *AND* - Days 2-4: continue dexamethasone
	2. NEPA *AND* dexamethasone	- Days 2-4: continue dexamethasone
	3. Olanzapine *AND* palonosetron IV *AND* dexamethasone	- Days 2-4: continue olanzapine
Moderate Emetic IV Chemotherapy Agents	1. 5-HT3 RA *AND* dexamethasone ± NK1 RA	- Days 2-3: 5HT3 RA *OR* dexamethasone OR NK1 RA with or without dexamethasone
	2. NEPA *AND* dexamethasone	- Days 2-3: continue dexamethasone
	3. Olanzapine *AND* palonosetron *AND* dexamethasone	- Days 2-3: continue olanzapine
Low Emetic IV Chemotherapy Agents	1. Dexamethasone *OR* 2. Metoclopramide *OR* 3. Prochlorperazine *OR* 4. 5HT3 RA	- Additional doses only if needed for breakthrough n/v
High to Moderate Emetic Oral Chemotherapy	1. 5HT3 RA	- Continue daily
Low to Minimal Emetic Oral Chemotherapy	1. As needed	- Continue daily if required
Upper abdominal radiation (pretreatment)	1. Ondansetron *OR* 2. Granisetron ± dexamethasone	- Additional only if needed for breakthrough n/v
Total body irradiation (pretreatment)	1. Ondansetron *OR* 2. Granisetron ± dexamethasone	- Additional only if needed for breakthrough n/v
Multi-day Emetogenic Chemotherapy Regimens	- Dependent upon chemotherapy regimen and emetogenic potential Options: • Dexamethasone for 2-3 days after chemotherapy • 5HT3 RA – frequency dependent on drug and	- Give antiemetic to cover both acute and delayed n/v

	route • Palonosetron • NK 1 RA for 2 days after chemotherapy	

New Safety Alerts:
No new safety alerts identified.

New Formulations or Indications:
None identified.

Randomized Controlled Trials:
A total of 185 citations were manually reviewed from the literature search. After further review, four trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining four trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 4: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Oliveira, et al[13]	Ondansetron 4 mg every 8 hours vs. pyridoxine 25mg plus doxylamine 12.5 mg every 8 hours x5 days	Pregnant females with n/v (n=36)	Improvement in nausea as reported on a 100-mm VAS	Ondansetron was associated with more improvement of baseline nausea compared to pyridoxine/doxylamine (median VAS decrease 51 mm vs. 20 mm, p=0.019).
Roila, et al[18]	Dexamethasone 4 mg twice daily vs. aprepitant 80 mg once daily on days 2-3 after chemotherapy (All patients received IV palonosetron, dexamethasone and aprepitant before chemotherapy)	580 patients with breast cancer treated with anthracyclines plus cyclophosphamide	Rate of complete response (no vomiting or no rescue therapy) on day 2-5 after chemotherapy	Complete response rates were the same for both groups of antiemetic prophylaxis, 79.5%.
Kang H, et al[19]	Aprepitant vs. control regimen (placebo for 3 days -All patients received ondansetron on day 1 and allowed use of dexamethasone	Children (6 mo. to 17 years) with malignancy and scheduled to receive MEC or HEC (n=307) during the delayed phase (25-120 h) after chemotherapy	Proportion who achieved complete response (no vomiting, no retching, and no use of rescue medication)	Aprepitant was superior to placebo during the delayed phase with 51% experiencing a complete response compared to 26%. Use of dexamethasone was similar between patients treated with aprepitant and the control regimen, 28% and 29%, respectively.

Schmitt T, et al[20]	Aprepitant regimen vs. placebo control regimen <u>Aprepitant regimen</u> Day 1: Aprepitant 125 mg + granisetron 2 mg + dexamethasone 4 mg Days 2-3: Aprepitant 80 mg + granisetron 2 mg + dexamethasone 2 mg Day 4: Aprepitant 80 mg + granisetron 2 mg <u>Placebo regimen</u> Day 1: Placebo + granisetron 2 mg + dexamethasone 8 mg Days 2-3: Placebo + granisetron 2 mg + dexamethasone 4 mg Day 4: Placebo + granisetron 2 mg	Patients (≥ 18 years) with multiple myeloma undergoing autologous transplant after high-dose melphalan conditioning (n=362)	No emesis and no rescue therapy within 120 hours of melphalan administration	Aprepitant was superior to control (OR 1.92, 95% CI 1.23 to 3.00; p=0.0042).

<u>NEW DRUG EVALUATION:</u>

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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.

<u>Netupitant and Palonosetron (Akynzeo®)</u>

Clinical Efficacy:

The fixed-dose combination product NEPA was approved in October of 2014 for the prevention of acute and delayed CINV associated with initial and repeat courses of chemotherapy, including HEC regimens.[21] Palonosetron was previously approved in 2008 (but never marketed in the US) and netupitant is a new molecular entity.[22] NEPA is administered as a single dose 1 hour before chemotherapy.[4] FDA approval was based on four studies, three phase 3 studies and one phase 2 study.[4-6] The phase 2 study did not meet our inclusion crieteria.[23] The three phase 3 trials will be discussed below.

In a phase 3, double-dummy, double-blind randomized controlled trial a single oral dose of NEPA was compared to palonosetron 0.50 mg along with a dose of oral dexamethasone (12 mg for NEPA and 20 mg for palonosetron).[4] All patients (n=1449) received MEC consisting of an anthracycline and cyclophosphamide. At the time of the study the chemotherapy regimen was considered moderately emetogenic, however, in 2011 ASCO guidelines recommended that this regimen now be considered highly emetogenic. Based on this change the FDA agreed that NEPA was appropriate for MEC and HEC regimens.[21] Most patients were female (98%) with breast cancer (97%). The primary endpoint was complete response (defined as no emesis and no rescue medication) during the delayed phase (25-120 hours) in cycle 1. Secondary endpoints were complete response during the acute phase and incidence of emesis and "significant" nausea (not defined) during acute and delayed phases. The impact of CINV was assessed via FLIE.[4]

Results showed NEPA was superior to palonosetron alone for complete response during the delayed phase (p=0.001) with a number needed to treat (NNT) of 14. NEPA was also significantly better for complete response in the acute phase (0-24 hours) and overall phase (0-120 hours).[4] NEPA demonstrated significantly higher FLIE scores compared to palonosetron, indicating that n/v had less impact on the daily lives of patients. Participants were invited to participate in a multiple-cycle extension study that has not yet been published.

A trial by Boccia, et al determined the noninferiority of oral palonosetron to IV palonosetron. The phase 3, double-blind, double-dummy randomized controlled trial compared a single dose of oral palonosetron 0.25 mg, 0.50 mg or 0.75 mg to IV palonosetron 0.25 mg in patients receiving MEC.[5] Patients were also randomized to receive one dose of IV dexamethasone 8 mg or placebo. Patients were predominately females (63%) with breast cancer (82%) and a mean age of 57 years old. The primary endpoint was complete response during the acute phase (0-24 hours) with key secondary endpoints being complete response in the delayed phase (24-120) and the complete response overall (0-120).[5] A complete response was defined as no emesis and no rescue therapy. During the acute phase all oral doses of palonosetron were noninferior to IV palonosetron, with a complete response percentage ranging from 70-76%. The palonosetron 0.50 mg oral dose was found to be noninferior to IV palonosetron 0.25 mg for the overall phase. None of the oral palonosetron doses achieved noninferiority to IV formulation for the delayed phase. The efficacy of the all the formulations was similar in the ability to prevent emesis and nausea. The addition of dexamethasone improved complete response rates by at least 15% for all groups during the acute phase, except for oral palonosetron 0.25 mg. These patients had an improvement of approximately 7% during the acute phase. Limitations to the study are the lack of details related to methodology, making the risk of bias unclear. The high percentage of females with breast cancer in the patient population limits the external validity.

In a safety study, NEPA was given in a phase 3, double-dummy, double-blind, randomized controlled trial to 413 chemotherapy naïve patients.[6] NEPA day 1 was studied with aprepitant (125 mg on day 1, 80 mg days 2-3) + palonosetron (0.50 mg day 1) (AP) as a control. Both regimens were given with open label dexamethasone dose dependent on emetogenicity of chemotherapy regimen; 12 mg day 1 for MEC and 12 mg day 1 and 8 mg days 2-4 for HEC. No formal efficacy comparison was done. An equal number of males and females were enrolled and scheduled to receive multiple rounds of chemotherapy for a malignant tumor diagnosis. Seventy percent were prescribed a MEC regimen and patients had an ECOG performance status of 0-2. NEPA treated patients were found to have a higher number of poorer cancer prognostic variables compared to the AP study arm.[6] A complete response (no emesis, no rescue mediation) and no significant nausea were key efficacy endpoints. Treatment emergent adverse events and clinical evaluations were used for safety endpoints.

A complete response was seen in 81-91% of patients taking NEPA compared to 76-86% taking AP for chemotherapy cycles 1-6. Patients experienced no significant nausea in 84-92% patients taking NEPA and 81-87% of patients taking AP. This study provided a descriptive analysis of efficacy for NEPA in MEC and HEC regimens over multiple cycles. Limitations were that the focus of this study was safety, not efficacy, therefore, there was no formal efficacy comparison and patients had a variable cancer diagnoses and chemotherapy regimens.

Clinical Safety:
NEPA was well tolerated in short-term clinical studies (Table 5).[20] Constipation, erythema and dyspepsia was associated with NEPA in 3-4% of patients on a HEC regimen. A safety study in patients receiving multiple rounds of chemotherapy found no cardiac abnormalities with NEPA treatment.[20] One patient developed acute psychosis that was thought to be linked to NEPA. No other severe adverse events were seen. Less than 1% of patients in studies discontinued NEPA due to treatment related adverse events.[4, 22]

Table 5. Adverse Reactions Occurring in ≥3% of Patients Receiving NEPA[20]

Adverse Event	NEPA (n=725)	Palonosetron 0.50 mg (n=725)
Headache	9%	7%
Asthenia	8%	7%
Fatigue	7%	5%

Rolapitant (Varubi®)

Clinical Efficacy:
Rolapitant was approved in September 2015 to be used in combination with other antiemetic agents for the prevention of delayed CINV associated with initial and repeat courses of chemotherapy, including HEC regimens, in adults. Rolapitant 180 mg (2 tablets) is administered as a single dose 1-2 hours before chemotherapy with dexamethasone and a 5-HT3 RA.[7] No studies have been published and no trial results are available on Clinicaltrials.gov.

Prescribing information for rolapitant provides data from 2 RCTs.[7] Studies 1 and 2 were double-blind, parallel-group RCTs (n=1,076) that compared rolapitant 180 mg to placebo in patients also on oral dexamethasone (20 mg on day 1 and 8 mg twice daily on days 2-4) and 10 mcg/kg IV granisetron. Rolapitant and placebo were given 1 to 2 hours prior to HEC (cisplatin, with 84% on an additional concomitant chemotherapy agents), and dexamethasone and granisetron were given 30 minutes prior to treatment on Day 1. The studies included 65% males and a mean age of 58 years. The primary endpoint was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25-120 hours).[7] In study 1, complete response was seen in 72.7% of patients on rolapitant compared to 58.4% on placebo (95% CI 6.3 to 22.4; $p<0.001$). In study 2, a complete response occurred in 70.1% on rolapitant compared to 61.9% on placebo (95% CI 0.3 to 16.1; $p=0.043$).

Rolapitant was also studied in patients taking MEC regimens (n=1,369) with the same design as in Studies 1 and 2. Patients were randomized to rolapitant 180 mg or placebo on background oral granisetron 2 mg and oral dexamethasone 20 mg on Day 1. Oral granisetron 2 mg was also given on day 2 and 3. At least 50% of patients were on combination chemotherapy consisting of an anthracycline and cyclophosphamide. Included patients were a mean age of 57 years and 80% were female. The primary endpoint was the same as in studies 1 and 2. Rolapitant was superior to placebo in terms of complete response (71.3% vs. 61.6%, respectively; treatment difference 9.8; 95% CI 4.7 to 14.8; $p<0.001$).[7]

Clinical Safety:
In HEC regimens, rolapitant was more commonly associated with neutropenia and hiccups; in MEC, more decreased appetite, neutropenia and dizziness was observed.[5]

Table 6. Adverse Reactions Occurring in ≥3% of Patients Receiving Rolapitant on HEC Regimens[7]

Adverse Event	Rolapitant* (n=624)	Control (n=627)
Neutropenia	9%	8%
Hiccups	5%	4%
Abdominal Pain	3%	2%
* Rolapitant was given with dexamethasone and 5-HT3 receptor antagonist Control therapy: placebo, dexamethasone and 5-HT3 receptor antagonist		

Pharmacology and Pharmacokinetic Properties:

Parameter	Netupitant (N) and Palonosetron (P)[20]	Rolapitant[5]
Mechanism of Action	P/neurokinin 1 (NK_1) receptor antagonist and a serotonin-3 ($5HT_3$) receptor antagonist	P/neurokinin 1 (NK_1) receptor antagonist
Oral Bioavailability	97%	Not reported
Distribution and Protein Binding	Distribution is 8.3 ± 2.5 L/kg 62% protein bound	Vd: 460 L 99.8% protein bound
Elimination	86.5% feces and 4.7% urine	73% feces and 14.2% urine
Half-Life	N: 96 hours and P: 44 hours	169 to 183 hours
Metabolism	Predominately CYP2D6 and lesser extent CYP3A4 and CYP1A2	CYP3A4

Abbreviations: VD = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Vomiting
2) Nausea
3) Retching
4) Need for rescue medication
5) Quality of life

Primary Study Endpoint:
1) Complete Response (no emesis and no rescue medication)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Aapro, et al[4] Phase 3, PG, DB, DD, RCT	1. NEPA* 300mg/0.50 mg single oral dose + dexamethasone 12 mg single oral dose 2. Palonosetron (P) 0.5 mg single oral dose + dexamethasone 20 mg single oral dose *NEPA= netupitant 300mg and palonosetron 0.5 mg	Demographics: Female: 98% Age: 54 years White: 80% EGOG PS of 0: 70% Key Inclusion Criteria: - Age ≥ 18 years - Naïve to chemotherapy - Receiving first course of AC MEC - solid malignant tumor -ECOG status of 0-2 Key Exclusion Criteria: - HEC from day 1-5 - Additional MEC from day 2-5 following chemo - radiation to abdomen or pelvis - bone marrow or stem cell transplant - nausea or vomiting within 24 hours of day 1. - strong or moderate CYP3A4 inhibitors - Cardiac abnormalities	FAS: NEPA= 724 P=725 PP: NEPA= 719 (99%) P=719 (99%) Attrition: NEPA=7 (1%) P=10 (1%)	Complete response during delayed phase: NEPA 557 (76.9%) P 504 (69.5%) P=0.001 Complete response during acute phase: NEPA 640 (88.4%) P 616 (85%) P=0.047 Complete response during overall phase: NEPA 538 (74.3%) P 483 (66.6%) P=0.001 No emesis overall: NEPA 578 (79.8%) P 523 (72.1%) P<0.001 No significant nausea overall: NEPA 540 (74.6%) P 501 (69.1%) P=0.020	7.4/14 3.4/29 7.7/13 7.7/13 5.5/18	Serious AE: NEPA 13 (1.8%) P 12 (1.7%) p=NR AE leading to D/C: NEPA 0 (0%) P 2 (0.1%) p=NR Headache: N 24 (3.3%) P 22 (3.0%) p=NR	N/A N/A N/A	**Risk of Bias (low/high/unclear)**: Selection: (unclear) No details on randomization provided. Performance :(low) Blinding maintained by double-dummy design. No details on patient or provider blinding. Detection :(unclear) No details provided on outcome assessment blinding. Attrition :(low) Low attrition; FAS used for efficacy analysis. **Applicability**: Patient: 98% female, 97% breast cancer; may limit applicability. However, young females are at highest risk of CINV, requiring triple therapy. Intervention: single dose appropriate. Comparator: Palonosetron; only demonstrates efficacy for netupitant. Outcomes: Outcome of complete response (no emesis and no rescue medication) appropriate. Setting: Conducted in 177 outpatient sites in 15 countries.
2. Boccia, et al[5] Phase 3, PG, DB, DD, RCT	1. Palonosetron 0.25 mg single oral dose (P25) 2. Palonosetron 0.50 mg single oral	Demographics: Female: 63% Age: 57 years Key Inclusion Criteria:	FAS: P25 = 157 P50 = 161 P75 =	Complete response during acute phase: P25 114 (73.5%) P50 122 (76.3%) P75 117 (74.1%) P 114 (70.4%)	NA	AE leading to D/C: P25 0 (0%) P50 1 (0.6%) P75 2 (1.3%) P 0 (0%) no p-value provided	NA	**Risk of Bias (low/high/unclear)**: Selection: (unclear) No details on randomization provided. Performance :(low) Blinding maintained by double-dummy design. No details on patient or provider blinding.

	dose (P50) 3. Palonosetron 0.75 mg single oral dose (P75) 4. Palonosetron 0.25 mg single IV dose (P)	- Age ≥ 18 years - Naïve or non-naïve to chemotherapy - Receiving MEC - malignant disease Key Exclusion Criteria: - HEC - previous palonosetron use within the previous 2 weeks - irradiation to upper abdomen, cranium or total body days 1-5 - Low-level emetogenic chemotherapy - hepatic, renal or CV conduction interval abnormalities	158 P = 163 PP: P25 = 155 (99%) P50 = 161 (100%) P75 = 157 (99%) P = 161 (99%) Attrition: P25 = 2 (1%) P50 = 0 (0%) P75 = 1 (1%) P = 2 (1%)	no p-value provided Complete response during delayed phase: P25 92 (59.4%) P50 100 (62.5%) P75 95 (60.1%) P 106 (65.4%) no p-value provided Complete response overall: P25 83 (53.5%) P50 94 (58.8%) P75 84 (53.2%) P 96 (59.3%) no p-value provided	NA NA	Treatment related adverse events: P25 11 (7%) P50 13 (8.1%) P75 12 (7.6%) P 26 (16.0%) no p-value provided		Detection :(unclear) No details provided on outcome assessment blinding. Attrition :(low) Low attrition; FAS used for efficacy analysis. **Applicability**: Patient: A higher number of females and breast cancer diagnosis were represented in population. Intervention: oral palonosetron comparative doses appropriate. Comparator: IV Palonosetron; appropriate comparator for non-inferiority of oral product Outcomes: Outcome of complete response (no emesis and no rescue medication) appropriate. Setting: Conducted in 46 sites in 3 countries.
3. Gralla, et al[6] Phase 3, PG, DB, DD, RCT, safety study	1. NEPA* 300mg/0.50 mg single oral dose + dexamethasone∞ (NEPA) 2. Aprepitant** + Palonosetron 0.50 mg on day 1 + dexamethasone∞ (AP) *NEPA= netupitant 300mg and palonosetron 0.5 mg ∞ Dexamethasone was given open	Demographics: Female: 50% Age: 58 years MEC: 76% HEC: 24% ECOG PS of 0: 48% ECOG PS of 1: 51% Key Inclusion Criteria: - age ≥ 18 years - naïve to chemotherapy - scheduled to receive repeat courses of MEC or HEC chemotherapy - malignant tumor diagnosis -ECOG status of 0-2	FAS: NEPA= 309 AP = 104 PP: NEPA= 198 (64%) AP = 61 (59%) Attrition: NEPA= 111 (36%) AP=43 (41%)	Complete response over 6 cycles of chemotherapy: NEPA 81-91% AP 76-86% p-value not calculated No significant nausea: NEPA 84-92% AP 81-87% p-value not calculated	NA NA	Serious AE: NEPA 1 (0.3%) APR 0 (0%) p=NR AE leading to D/C: NEPA 1 (0.3%) APR 0 (0%) p=NR	N/A N/A	**Risk of Bias (low/high/unclear)**: Selection :(unclear) Randomized 3:1. No details on randomization provided. Performance: (low) Blinding maintained by double-dummy design. No details on patient or provider blinding. Detection :(unclear) No details provided on outcome assessment blinding. Attrition :(high) High attrition; FAS used for efficacy analysis. **Applicability**: Patient: Men and women patients predominately treated with MEC (76%) and to a lesser extent with HEC (24%). Intervention: single dose appropriate. Comparator: Aprepitant; used as a control for safety study. Outcomes: Outcome of complete response (no emesis and no rescue medication) is appropriate.

	label and dose was dependent on emetogenicity of chemotherapy regimen: MEC – 12 mg day 1 HEC – 12 mg day 1 and 8 mg days 2-4 ** Aprepitant given as 125 mg on day 1, 80 mg on days 2-3	Key Exclusion Criteria: - breast cancer diagnosis scheduled to receive anthracycline-cyclophosphamide HEC from day 1-5 - MEC or HEC on days 2-5 - bone marrow transplant or stem cell rescue - prior NK1 RA use - cardiac abnormalities - Drugs with CYP3A4 interactions						Setting: Conducted in 59 sites in 10 countries.
AC= Anthracycline-cyclophosphamide; AE= adverse event; CINV= chemotherapy-induced nausea and vomiting; D/C = discontinuation; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FAS= full analysis set; HEC=highly emetogenic chemotherapy; MEC= moderately emetogenic chemotherapy; number needed to harm; NNT = number needed to treat; NR= not reported; PP = per protocol								

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Appendix 1: Current Status on 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

Appendix 2: Abstracts of Clinical Trials

Aapro M, Rugo H, Rossi G, et al. A randomized phase IIII study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Annals of oncology 2014; 25: 1328-1333.

BACKGROUND: Antiemetic guidelines recommend co-administration of agents that target multiple molecular pathways involved in emesis to maximize prevention and control of chemotherapy-induced nausea and vomiting (CINV). NEPA is a new oral fixed-dose combination of 300 mg netupitant, a highly selective NK1 receptor antagonist (RA) and 0.50 mg palonosetron (PALO), a pharmacologically and clinically distinct 5-HT3 RA, which targets dual antiemetic pathways. PATIENTS AND METHODS: This multinational, randomized, double-blind, parallel group phase III study (NCT01339260) in 1455 chemotherapy-naïve patients receiving moderately emetogenic (anthracycline-cyclophosphamide) chemotherapy evaluated the efficacy and safety of a single oral dose of NEPA versus a single oral dose (0.50 mg) of PALO. All patients also received oral dexamethasone (DEX) on day 1 only (12 mg in the NEPA arm and 20 mg in the PALO arm). The primary efficacy end point was complete response (CR: no emesis, no rescue medication) during the delayed (25-120 h) phase in cycle 1. RESULTS: The percentage of patients with CR during the delayed phase was significantly higher in the NEPA group compared with the PALO group (76.9% versus 69.5%; P = 0.001), as were the percentages in the overall (0-120 h) (74.3% versus 66.6%; P = 0.001) and acute (0-24 h) (88.4% versus 85.0%; P = 0.047) phases. NEPA was also superior to PALO during the delayed and overall phases for all secondary efficacy end points of no emesis, no significant nausea and complete protection (CR plus no significant nausea). NEPA was well tolerated with a similar safety profile as PALO. CONCLUSIONS: NEPA plus a single dose of DEX was superior to PALO plus DEX in preventing CINV following moderately emetogenic chemotherapy in acute, delayed and overall phases of observation. As a fixed-dose antiemetic drug combination, NEPA along with a single dose of DEX on day 1 offers guideline-based prophylaxis with a convenient, single-day treatment.

Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. *J Clin Oncol* 2014;32:3413-3420.

PURPOSE: The optimal regimen to prevent chemotherapy-induced nausea and vomiting (CINV) for patients undergoing high-dose chemotherapy and autologous stem-cell transplantation (ASCT) is unclear. To evaluate the effect of aprepitant in addition to a standard regimen, we conducted this randomized, placebo-controlled phase III trial. PATIENTS AND METHODS: Patients with multiple myeloma were randomly assigned at a one-to-one ratio to receive either aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4), granisetron (2 mg orally on days 1 to 4), and dexamethasone (4 mg orally on day 1 and 2 mg orally on days 2 to 3) or matching placebo, granisetron (2 mg orally on days 1 to 4), and dexamethasone (8 mg orally on day 1 and 4 mg orally on days 2 to 3). Melphalan 100 mg/m(2) was administered intravenously on days 1 to 2. ASCT was performed on day 4. The primary end point (complete response) was defined as no emesis and no rescue therapy within 120 hours of melphalan administration. Quality of life was assessed by modified Functional Living Index-Emesis (FLIE) questionnaire on days -1 and 6. RESULTS: Overall, 362 patients were available for the efficacy analysis (181 in each treatment arm). Significantly more patients receiving aprepitant reached the primary end point (58% v 41%; odds ratio [OR], 1.92; 95% CI, 1.23 to 3.00; P = .0042). Absence of major nausea (94% v 88%; OR, 2.37; 95% CI, 1.09 to 5.15; P = .026) and emesis (78% v 65%; OR, 1.99; 95% CI, 1.25 to 3.18; P = .0036) within 120 hours was increased by aprepitant. Mean total FLIE score (± standard deviation) was 114 ± 18 for aprepitant and 106 ± 26 for placebo (P < .001). CONCLUSION: The addition of aprepitant resulted in significantly less CINV and had a positive effect on quality of life.

Kang H, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:385-94.

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 pediatric 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, multicenter, 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. Randomization 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 pediatric 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 ($p<0·0001$). 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), anemia (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 pediatric patients being treated with moderately or highly emetogenic chemotherapy.

Oliveira L, Capp S, You W, et al. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. *Obstet and Gynec* 2014; 124: 735-742.

OBJECTIVE: To evaluate whether ondansetron or the combination of doxylamine and pyridoxine was superior for the treatment of nausea and vomiting of pregnancy. METHODS: This was a double-blind, randomized, controlled trial in which women with nausea and vomiting of pregnancy were assigned to 4 mg of ondansetron plus a placebo tablet or 25 mg pyridoxine plus 12.5 mg of doxylamine for 5 days. The primary outcome was an improvement in nausea as reported on a 100-mm visual analog scale (VAS). Secondary outcomes were a reduction in vomiting on the VAS and the proportion of patients reporting sedation or constipation while using either study regimen. RESULTS: Thirty-six women (18 in each group) were randomized to either ondansetron or pyridoxine and doxylamine, of whom 13 (72%) and 17 (94%) completed follow-up, respectively. There were no differences among the groups with regard to demographic characteristics or baseline nausea. Patients randomized to ondansetron were more likely to have an improvement in their baseline nausea as compared with those using pyridoxine and doxylamine over the course of 5 days of treatment (median VAS score decreased 51 mm [interquartile range 37-64] compared with 20 mm [8-51]; P=.019). Furthermore, women using ondansetron reported less vomiting (median VAS decreased 41 [interquartile range 17-57] compared with

17 [-4 to 38]; P=.049). There was no significant difference between the groups regarding sedation or constipation. CONCLUSION: Our investigation showed ondansetron to be superior to the combination of pyridoxine and doxylamine in the treatment of nausea and emesis in pregnancy.

Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. J Clin Oncol 2014; 32: 101-106.

PURPOSE: A combination of aprepitant, a 5-HT3 receptor antagonist, and dexamethasone is recommended for the prophylaxis of acute or delayed emesis induced by chemotherapy containing anthracyclines plus cyclophosphamide in patients with breast cancer. The aim of this study was to verify whether dexamethasone is superior to aprepitant in preventing delayed emesis in patients receiving the same prophylaxis for acute emesis. PATIENTS AND METHODS: A randomized double-blind study comparing aprepitant versus dexamethasone was completed in chemotherapy-naive patients with breast cancer treated with anthracyclines plus cyclophosphamide. Before chemotherapy, all patients were treated with intravenous palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg. On days 2 and 3, patients randomly received oral dexamethasone 4 mg twice per day or aprepitant 80 mg once per day. Primary end point was rate of complete response (i.e., no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. RESULTS: Of 580 enrolled patients, 551 were evaluable: 273 received dexamethasone, and 278 received aprepitant. Day 1 complete response rates were similar: 87.6% for dexamethasone and 84.9% for aprepitant (P < .39). From days 2 to 5, complete response rates were the same with both antiemetic prophylaxes (79.5%; P < 1.00), as were results of secondary end points (i.e., complete protection, total control, no vomiting, no nausea, score of Functional Living Index-Emesis; P < .24). Incidences of insomnia (2.9% v 0.4%; P < .02) and heartburn (8.1% v 3.6%; P < .03) were significantly greater with dexamethasone on days 2 to 5. CONCLUSION: In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to aprepitant but instead had similar efficacy and toxicity in preventing delayed emesis.

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

AKYNZEO® (netupitant and palonosetron) capsules, for oral use
Initial U.S. Approval: 2014

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

AKYNZEO is a fixed combination of netupitant, a substance P/neurokinin 1 (NK_1) receptor antagonist, and palonosetron, a serotonin-3 ($5\text{-}HT_3$) receptor antagonist indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. (1)

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

One AKYNZEO capsule administered approximately 1 hour prior to the start of chemotherapy. (2)
AKYNZEO can be taken with or without food. (2)

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

Capsule: 300 mg netupitant/0.5 mg palonosetron (3)

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

None (4)

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

- Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving palonosetron with or without known hypersensitivity to other $5\text{-}HT_3$ receptor antagonists (5.1)
- Serotonin syndrome has been reported with $5\text{-}HT_3$ receptor antagonists alone but particularly with concomitant use of serotonergic drugs (5.2)

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

Most common adverse reactions (incidence ≥3% and greater than palonosetron) are headache, asthenia, dyspepsia, fatigue, constipation and erythema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EISAI at 1-888-422-4743 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- CYP3A4 Substrates: inhibition of CYP3A4 by netupitant can result in increased plasma concentrations of the concomitant drug that can last at least 4 days and may last longer after single dosage administration of AKYNZEO; use with caution (7.1)
- CYP3A4 Inducers (e.g., rifampin): decreased plasma concentrations of netupitant; avoid use (7.2)

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

- Hepatic Impairment: Avoid use in patients with severe hepatic impairment (8.6)
- Renal Impairment: Avoid use in patients with severe renal impairment or end-stage renal disease (8.7)

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

Revised: 4/2015

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

VARUBI™ (rolapitant) tablets, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

VARUBI™ is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 180 mg rolapitant administered approximately 1 to 2 hours prior to the start of chemotherapy (2)
- Administer in combination with dexamethasone and a 5-HT3 receptor antagonist, see full prescribing information for dosing information (2)
- No dosage adjustment for dexamethasone is required. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg of rolapitant (3)

CONTRAINDICATIONS

Concurrent use with thioridazine, a CYP2D6 substrate (4)

WARNINGS AND PRECAUTIONS

Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index: The inhibitory effect of a single dose of VARUBI on CYP2D6 lasts at least 7 days and may last longer. Avoid use of pimozide; monitor for adverse reactions if concomitant use with other CYP2D6 substrates with a narrow therapeutic index cannot be avoided (4, 5.1, 7.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are:

- Cisplatin Based Highly Emetogenic Chemotherapy: neutropenia and hiccups (6.1)
- Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide: decreased appetite, neutropenia and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tesaro at 1-844-4-TESARO or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- BCRP and P-gp Substrates with a Narrow Therapeutic Index: inhibition of BCRP and P-gp by VARUBI can increase plasma concentrations of the concomitant drug and potential for adverse reactions. See full prescribing information for specific examples. (7.1)
- Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of VARUBI; avoid use of VARUBI in patients who require chronic administration of such drugs. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to September Week 2 2015
Search Strategy:

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to September Week 2 2015
Search Strategy:

#	Searches	Results
1	antiemetics.mp. or Antiemetics/	5652
2	neurokinin-1 receptor antagonist.mp. or Neurokinin-1 Receptor Antagonists/	1630
3	NEPA.mp.	52
4	netupitant.mp.	23
5	palonosetron.mp.	299
6	ondansetron.mp. or Ondansetron/	2664
7	aprepitant.mp.	530
8	fosaprepitant.mp.	40
9	dolasetron.mp.	242
10	granisetron.mp. or Granisetron/	1019
11	doxylamine.mp. or Doxylamine/	173
12	pyridoxine.mp. or Pyridoxine/	2293
13	rolapitant.mp.	5
14	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	11193
15	limit 14 to english language	10213
16	limit 15 to yr="2014 -Current"	612
17	limit 16 to (clinical trial, all 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)	185

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.
- Restrict inappropriate chronic use (>3 days per week).
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy (criteria specific)

Requires PA:

- Non-preferred drugs will be subject to PA criteria and quantity limits (**Table 1**)
- Preferred drugs will deny only when quantity limit exceeded

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal Generic oral	1 patch / 7 days 1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

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

2. Is the requested drug preferred?	**Yes:** Go to #4	**No:** Go to #3
3. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA unless they exceed dose limits in table 1. • Preferred products do not require a co-pay. • 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 and dose limits. If dose exceeds limits, continue to #4.	**No:** Go to #4
4. Is the request if for Diclegis® (doxylamine/pyridoxine) for pregnancy-related nausea or vomiting?	**Yes:** Approve for up to 3 months	**No:** Go to #5
5. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	**Yes:** Approve for 3 days beyond length of chemotherapy regimen or radiation (not subject to dose limits above)	**No:** Go to #6
6. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months	**No:** Go to #7
7. RPh only: All other indications need to be evaluated as to whether they are funded under the Oregon Health Plan. [ ] Funded: Deny for medical appropriateness [ ] Non-funded: Deny; not funded by the OHP		

P&T / DUR Review: *1/16 (KS); 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03*
Implementation: *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*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Class Update with New Drug Evaluation: Influenza Antiviral Agents

Date of Review: September 2015
Generic Name: peramivir injection

Date of Last Review: January 2012
Brand Name (Manufactuer): Rapivab™ (BioCryst Pharmaceuticals)
Dossier Received: no

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

Purpose for Class Update:
Rapivab™ (peramivir) is a neuraminidase inhibitor approved by the United States (U.S.) Food and Drug Administration (FDA) to treat uncomplicated influenza in adults. This class has not been reviewed since 2012 and both updated systematic reviews and guidelines are available.

Research Questions:
1. What is the comparative efficacy/effectiveness between antiviral agents to treat and prevent influenza?
2. What are the comparative harms between antiviral agents?
3. Are there any populations in which a specific antiviral agent for influenza is more effective or associated with greater harms than other agents?

Conclusions:
- There is insufficient comparative evidence between neuraminidase inhibitors to assess relative safety and efficacy between these drugs.
- There is moderate quality evidence that influenza symptoms are alleviated sooner with neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) compared to placebo in previously healthy adults if the drug is started within 48 hours of onset of symptoms.[1–5] Time to alleviation of symptoms were reduced by 14 to 21 hours (a 10% reduction in time to alleviation) depending on the drug.[1–5] However, the clinical significance of such a modest effect is not well defined.
- In previously healthy children, there is moderate quality evidence that oseltamivir can reduce the time to alleviation of influenza symptoms by about 1 day relative to placebo; however, oseltamivir does not appear to have any effect in children with asthma.[2,3] There is moderate quality evidence that treatment with zanamivir is ineffective in children.[1,3] There is insufficient evidence for peramivir in this population.[5]
- There is low quality evidence that treatment with oseltamivir and zanamivir do not reduce complications from influenza in children or adults.[1–3] There is insufficient evidence to determine if peramivir can reduce complications from influenza.
- There is low quality evidence that treatment with oseltamivir may not reduce risk for hospitalization.[2,3] There is insufficient evidence to determine if treatment with zanamivir or peramivir can decrease rates of hospitalizations.[1,3,5]

- There is moderate quality evidence that prophylactic use of oseltamivir or zanamivir in previously healthy adults and children can reduce risk of developing influenza symptoms, but by only 2% to 4% compared to placebo. These drugs do not reduce complications of influenza if it develops.[1–4]
- There is moderate quality evidence that the prophylactic use of oseltamivir does not reduce rates of hospitalizations.[2,3] There is insufficient evidence to determine if prophylactic use of zanamivir can reduce hospitalizations.[1,3] Peramivir for prophylaxis of influenza is not recommended.
- Use of amantadine and rimantadine for prevention or treatment of influenza is not recommended. Safety concerns with amantadine, inactivity of both drugs against influenza B virus, and complete resistance to influenza A virus preclude use of these drugs for influenza.[6,7]
- The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, and psychiatric effects in adults and vomiting in children.[1–3] Zanamivir and peramivir were well tolerated in clinical trials.[1,3,5]

Recommendations:
- Designate amantadine and rimantadine non-preferred because of lack of efficacy for influenza and insufficient evidence for use in other conditions (eg, dyskinesias, Parkinson's disease), and possible increased harms with amantadine.
- Move amantadine from the Influenza Antiviral drug class to the Parkinson's Drug Class. Two drugs used for dyskinesias, benztropine and trihexyphenidyl, are already preferred within the Parkinson's Drugs Class.
- Designate peramivir non-preferred at this time due to limited evidence.
- No other changes to the PDL are recommended at this time. Review comparative drug costs in the executive session.
- Approve modified prior authorization (PA) criteria (see **Appendix 4**). Restrict PA to neuraminidase inhibitors only.

Previous Conclusions:
- Vaccination is the primary method of preventing influenza infection.
- Amantadine or rimantadine are not recommended for the treatment or prophylaxis of influenza A due to high prevalence of resistance.
- Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders.

Previous Recommendations:
- Recommend taking into account current public health recommendations for appropriate populations, duration and dosing schedules.

Background:
Influenza is a respiratory infection caused by influenza viruses A and B, the primary viruses that result in influenza epidemics in humans.[8] Influenza can be described as uncomplicated or complicated influenza, and can also become a progressive disease.[8] Persons with uncomplicated influenza may present with influenza-like symptoms (e.g., fever, cough, sore throat, muscle pain, malaise, etc.) but without shortness of breath (SOB). Though it can be a self-limited disease, there can be serious complications. Persons with complicated influenza may present with sinusitis, otitis media, or pneumonia (SOB, tachypnea, hypoxia and/or radiologic signs), which can also be associated with altered mental status, severe dehydration, secondary complications (e.g., multiorgan failure, septic shock), or exacerbation of an underlying chronic disease.[8]

The current report of influenza activity in the U.S. can be found online at CDC Weekly FluView.[9] During the 2014-15 influenza season, 83.5% of circulating influenza viruses were influenza A (nearly all subtyped were H3N2) and 16.5% were influenza B.[10] Hospitalizations for influenza were double the incidence seen

in the 2013-14 season with 65.5 hospitalizations per 100,000 persons.[10] Deaths from pneumonia or influenza were at or above epidemic level for 8 consecutive weeks.[10]

The annual influenza vaccine is the primary method to prevent influenza.[11] The vaccination is recommended for all persons 6 months of age and older who do not have contraindications.[11] No vaccine is preferred over any other in adults for whom multiple versions are appropriate, including trivalent or quadrivalent inactivated influenza vaccines, live attenuated influenza vaccines, or recombinant influenza vaccines.[11] Five influenza antiviral medications are also available in the U.S. However, only 3 are recommended for use: oral oseltamivir (Tamiflu®) and inhaled zanamivir (Relenza®) are recommended for acute treatment of influenza or prevention of influenza in susceptible individuals (eg, severe immune deficiency); injectable peramivir (Rapivab™), approved in December 2014, is recommended for the treatment of acute uncomplicated influenza in adults.[7,12] Each of these drugs are known as neuraminidase inhibitors and have activity against both influenza A and B.[7] Amantadine and rimantadine are antiviral drugs known as adamantanes, which are not active against influenza B, but are also not recommended for treatment of prevention of currently circulating influenza A viruses.[7] Since the 2005-06 season, resistance to amantadine and rimantadine have been widespread.[8] In the 2014-15 season, circulating viruses remained highly resistant (>99%) to amantadine and rimantadine.[10]

Oseltamivir, zanamivir and peramivir are approved by the U.S. Food and Drug Administration treatment of acute, uncomplicated influenza in patients who have had symptoms for up to 48 hours.[13–15] Treatment effects in controlled clinical trials showed improvement in time to alleviation of a constellation of symptoms rated as “none” or “mild” including: nasal congestion, sore throat, headache, aches, or chills.[5] Oseltamivir received FDA approval for patients as young as 14 days, while zanamivir is limited to patients aged 7 years and older and peramivir is limited to adult use only.[13,14] Oseltamivir and zanamivir are also FDA-approved for prophylaxis of influenza.[13,14] Oseltamivir is approved in patients 1 year and older and zanamivir is approved in patients 5 years and older.[13,14] Neuraminidase inhibitors may reduce symptoms duration by about 1 day in adults and by 0.5-3 days in children.[8] Oseltamivir is the most studied drug and does not appear to reduce likelihood of hospitalization or pneumonia in adults and adolescents with influenza-like illness; however, oseltamivir may reduce complications and hospitalization in children with influenza and chronic medical conditions.[8] At the time these drugs were last reviewed in January 2012, there was no evidence these drugs reduced mortality.

Amantadine has been used as an antiparkinsonian agent in the past but there is insufficient evidence of efficacy for its use.[8] Besides high rates of resistance, use of amantadine and rimantadine are limited by high rates of adverse events, particularly central nervous system adverse events.[8]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:

Zanamivir

A Cochrane systematic review with meta-analysis of zanamivir for influenza in adults and children was conducted.[1,3] Eligible studies were published or unpublished and limited to randomized, placebo-controlled trials testing the effects of zanamivir for prophylaxis, post-exposure prophylaxis, and treatment of influenza in previously healthy adults and children.[1,3] Trial registries and several electronic databases were searched, in addition to regulatory archives and correspondences with the manufacturer.[1,3] The effects of zanamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalizations and adverse events in the intention-to-treat (ITT) population were analyzed.[1,3] Twenty-eight studies were identified that met explicit inclusion criteria: 6 compared zanamivir with usual care in the prevention of influenza A and B among populations exposed to a local epidemic, 2 studies for the prevention of transmission of influenza among households, and 20 trials for the treatment of influenza A and B.[1,3] All trials identified were sponsored by the manufacturer.[1,3] Quality of the studies varied and posed large threats that introduce biases: only 1 study showed adequate randomization technique; adequate blinding of participants and personnel was reported in only 2 studies, and 24 studies showed adequate blinding of outcome assessors.[1,3]

For treatment of influenza, zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% Confidence Interval [CI], 0.39 to 0.81 days; $p<0.001$; $I^2=9\%$), which translated to an average 14.4-hour time reduction, or a 10% reduction in the mean duration of symptoms from 6.6 days to 6.0 days.[1,3] However, the treatment effect of zanamivir in children was not significant (mean difference -1.08 days; 95% CI, -2.32 to 0.15 days).[1,3] In subgroup analysis, there was no significant difference in treatment effects by infection status for time to first alleviation of symptoms in adults.[1,3] The treatment effect was an improvement by 0.67 days in patients with confirmed influenza (95% CI, 0.35 to 0.99 days) compared to 0.52 days (0.18 to 0.86 days) in patients without confirmed influenza.[1,3] Zanamivir treatment reduced the risk of bronchitis in adults (Relative Risk [RR]=0.75; 95% CI, 0.61 to 0.91: $I^2=3\%$; NNT=56), but there were no significant reduction found for serious complications of influenza, nor in incidence of otitis media (RR=0.81; 95% CI, 0.54 to 1.20; $I^2=0\%$) and sinusitis (RR=1.12; 95% CI, 0.84 to 1.48; $I^2=30\%$).[1,3] No data were reported on the effect of zanamivir treatment on rates of hospitalizations.[1,3] No studies specifically defined pneumonia, but self-reported, investigator-mediated verified and unverified pneumonia was not reduced with zanamivir (RR=0.90; 95% CI, 0.58 to 1.40; $I^2=0\%$).[1,3]

For prevention of influenza, zanamivir reduced the risk of symptomatic influenza by 2% versus placebo (RR=0.39; 95% CI, 0.22 to 0.70; $I^2=45\%$; Number Needed-to-Treat [NNT]=51), as well as in post-exposure prophylaxis of households by 14.84% (RR=0.33; 95% CI, 0.18 to 0.58; $I^2=40\%$; NNT=7).[1,3] No data were reported on the effect of zanamivir prophylaxis on prevention of hospitalizations.[1,3] Zanamivir prophylaxis had no effect on reduction of complications from influenza in adults or children.[1,3]

Studies reported zanamivir was well tolerated with no evidence of increased risk of adverse events.[1,3]

Oseltamivir

A systematic review with meta-analysis[2,3] of oseltamivir for influenza in adults and children was also conducted by the same Cochrane Collaboration group that conducted the review of zanamivir[1,3]. The same methodology applied to the previous systematic review was also applied to this review.[1–3] Studies of previously healthy adults and children and patients with a chronic illnesses (e.g., asthma, diabetes, etc.) were included; however, patients with immunosuppression were excluded from the analysis.[2,3] About 48% (11/23) of studies adequately reported random sequence generation, and 65% showed adequate allocation concealment.[2,3] Forty-eight percent showed adequate blinding of outcome assessors.[2,3] There was high risk of bias for included outcomes as a result of missing data, selective reporting, potentially active placebo, lack of outcome definitions, suboptimal measurement, and incomplete reporting in the study reports.[2,3]

There were inadequate measures in place to protect 11 studies from performance bias due to non-identical placebo products, which may have included active substances. In addition, attrition bias was high across the studies.[2,3]

In treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.7 hours (95% CI, 8.4 to 25.1 hours; p<0.001).[2,3] This difference represents a 10% reduction in time to first alleviation of symptoms from 7 days to 6.3 days in the oseltamivir group versus the placebo group.[2,3] In previously healthy children, oseltamivir reduced the time to first alleviation of symptoms by 29 hours (95% CI, 12 to 27 hours; p=0.001), but there was no significant effect for children with asthma (p=0.53).[2,3] Because of strong selection bias in treatment trials, an analysis was not performed by influenza-infected status.[2,3] In treatment of adults, there was a non-significant difference of 0.15% in rate of hospitalization between oseltamivir and placebo groups (RR=0.92; 95% CI, 0.57 to 1.50; I^2=0%; p=0.84).[2,3] Oseltamivir treatment also did not affect hospitalizations in children.[2,3] Oseltamivir had no significant treatment effect in adults or adults or children for sinusitis, bronchitis, otitis media, or any serious complications.[2,3] Oseltamivir reduced unverified pneumonia by 1% versus placebo when used as treatment in adults (95% CI, 0.22 to 1.49%; NNT=100).[2,3] There was no significant difference in studies that used more detailed definitions of pneumonia (e.g., radiologically confirmed pneumonia).[2,3]

In prophylaxis trials, oseltamivir reduced symptomatic influenza in subjects by 3.05% versus placebo (95% CI, 1.83 to 3.88; NNT=33) and in households by 13.6% (95% CI, 9.52 to 15.47%; NNT=7).[2,3] In these trials, oseltamivir did not reduce incidence of pneumonia in children or adults versus placebo.[2,3] In addition, prophylaxis with oseltamivir did not reduce rates of hospitalizations in adults or children.[2,3]

Treatment of oseltamivir was associated with increased risk of nausea in adults (RR=1.57; 95% CI, 1.14 to 2.51) and children (RR=1.70; 95% CI, 1.23 to 2.35).[2,3] Other adverse effects that occurred significantly more with oseltamivir use in adults were headache and vomiting.[2,3] In addition, oseltamivir appeared to be associated with increased risk of 1.06% for psychiatric adverse events (including depression, confusion, hallucinations, and psychosis) versus placebo in prophylaxis trials (RR=1.80; 95% CI, 1.05 to 2.08; Number Needed to Harm =94). this observation was not found at treatment doses.[2,3]

Neuraminidase Inhibitors Oseltamivir and Zanamivir

A systematic review of high-quality reviews of neuraminidase inhibitors (oseltamivir, zanamivir) using the Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Database of Abstracts of Reviews of Effects, and Medline (January 2006 to July 2012) was also conducted.[4] Nine systematic reviews were identified and were based on randomized controlled trials restricted to ITT results and assessed review (AMSTAR) and study quality (GRADE).[4] In healthy adults given oseltamivir as prophylaxis, risk of developing influenza symptoms by reduced by an absolute risk reduction (ARR) of 3.6% compared to placebo (95% CI, 2.0 to 4.3%) (GRADE moderate).[4] Prophylaxis with zanamivir reduced risk of developing influenza symptoms by an ARR of 4.4% (95% CI, 2.3 to 5.1%) versus placebo (GRADE moderate).[4] Similar efficacy was also observed for post-exposure prophylaxis in adults who received oseltamivir.[4] In children, only post-exposure prophylaxis studies were performed, which found and ARR of 12.1% (95% CI, 3.0 to 16.1%) with oseltamivir.[4] In at-risk adults and adolescents, prophylaxis with zanamivir reduced risk of influenza (ARR 4.0%; 95% CI, 1.6 to 4.4%) (GRADE moderate); however, no effect in elderly patients was observed.[4] Similar to the Cochrane analyses previously noted,[1–3] treatment with oseltamivir or zanamivir in adults and children alleviated symptoms of influenza less than 1 day sooner than with placebo (GRADE moderate).[4] No evidence was available on the treatment benefits of neuraminidase inhibitors in elderly and at-risk groups and their effects on hospitalization and mortality.[4] In oseltamivir trials, nausea, vomiting and diarrhea were significant adverse effects.[4] Zanamivir was well tolerated.[4]

Amantadine and Rimantidine

A Cochrane review did not find sufficient evidence for the use of amantadine and rimantadine for the prevention or treatment of influenza A in children and the elderly.[6] The lack of knowledge about the safety of amantadine and the limited benefit of rimantadine were of particular concern to the reviewers.[6]

New Guidelines:

The CDC antiviral recommendations were last published in January 2015.[7,12] The CDC recognizes clinical trials and observational data that show early antiviral treatment can shorten the duration of fever and symptoms, and may reduce the risk of complications from influenza. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.[7] Oral oseltamivir (Tamilfu®), inhaled zanamivir (Relenza®) and intravenous peramivir (Rapivab™) are the antiviral medications recommended by the CDC for treatment against influenza A and B for the 2014-15 season. Amantadine and rimantadine are not recommended for treatment or prevention of influenza due to high levels of resistance (>99%).[7] **Table 1** lists the antiviral drugs recommended by the CDC, which may not reflect official labeling of the drugs.

Table 1. Centers for Disease Control and Prevention (CDC) Recommendations for Antiviral Use in Influenza (2014-2015 Season).[7]

Antiviral Agent	Use	Recommended	NOT Recommended	Dose
Oseltamivir #	Treatment	Any age	N/A	75 mg BID** x5 days
	Chemo-prophylaxis	Age ≥3 months	N/A	75 mg once daily** x7 days
Zanamivir *	Treatment	Age ≥7 years	Patients with underlying respiratory disease (e.g., asthma, COPD)	10 mg BID x5 days
	Chemo-prophylaxis	Age ≥5 years		10 mg once daily x7 days
Peramivir ^	Treatment	Age ≥18 years	N/A	One dose
	Chemo-prophylaxis	N/A	N/A	N/A

Abbreviations: COPD = chronic obstructive pulmonary disease; N/A = not applicable.

Oseltamivir is the preferred treatment of pregnant women.

* Relenza is contraindicated in patients with history of allergy to milk protein.

^ Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

**See current prescribing information for dosing in patients ≤40 kg or in patients with renal impairment.

Briefly, any of the following patients with suspected or confirmed influenza should be treated as early as possible, without laboratory confirmation of influenza, after illness onset with a neuraminidase inhibitor[7]:

1. All hospitalized patients
2. Severe, complicated or progressive illness (e.g., prolonged progressive symptoms or pneumonia complications)
3. High risk for influenza complications
    - Children <2 years of age
    - Adults ≥65 years of age
    - Chronic pulmonary, cardiovascular, renal, hepatic, hematologic, and neurologic/neurodevelopment conditions
    - Immunosuppression
    - Pregnancy or immediate post-partum
    - Persons ≤18 years on long-term aspirin
    - American Indians/Alaskan Natives

- Morbid obesity (body mass index ≥40)
- Residents of nursing homes and other chronic care facilities

A history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms of influenza.[7] Antiviral treatment can also be considered in previously healthy, symptomatic outpatients not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.[7]

The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis due to risk of emergence of antiviral resistant viruses.[7] Antiviral medications for chemoprophylaxis are 70-90% effective in preventing influenza and may be useful adjuncts to the vaccine.[7] The CDC suggests patients with severe immune deficiencies or at high risk for complications of influenza who cannot receive the influenza vaccine, or during the first 2 weeks following vaccination, may be appropriate for chemoprophylaxis with antiviral agents.[7]

New Safety Alerts:
None identified.

New Formulations or Indications:
No new formulations or indications were identified. However, a new neuraminidase inhibitor was identified. Rapivab™ (peramivir) for injection was approved in December 2014 for treatment of influenza.[15]

Randomized Controlled Trials:
Two hundred fifty-five potentially relevant clinical trials or systematic reviews were evaluated from the literature search (see **Appendix 2**). After further review, none of the trials were randomized, head-to-head trials that compared one antiviral drug to another, and were therefore excluded.

NEW DRUG EVALUATION:
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Peramivir is the third drug in the neuraminidase class and is recommended for use in adult patients with acute uncomplicated illness based primarily on data from the 4 placebo-controlled Phase 2 or 3 trials in adults with acute uncomplicated influenza (studies 621, 211, 212 and 311).[5] The analysis of safety was based chiefly on data from Study 621,[16] with supplemental data from the other studies.[5] Study 621 was a 3-arm randomized, multi-centered, blinded trial conducted in Japan that evaluated a single intravenous (IV) dose of peramivir 300 mg, peramivir 600 mg, or placebo administered over 30 minutes in previously healthy patients 20 to 64 years of age (n=297) with acute uncomplicated influenza that had developed within the previous 48 hours.[5] Patients were eligible if they had fever greater than 38 ^{o}C, a positive rapid antigen test for influenza virus, with at least 2 symptoms (cough, nasal symptoms, sore throat, myalgia, chills/sweats, malaise, fatigue, or headache) of moderate severity.[5] All enrolled patients were allowed to take medication for fever during the study.[5] The primary endpoint was time to alleviation of symptoms (TTAS), defined as the number of hours from initiation of study drug until the start of the 24-hour period in which all 7 symptoms of influenza (cough, sore throat, nasal congestion, headache, fever, myalgia and fatigue) were either absent or present at a level no greater than "mild" for at least 21.5 hours.[5] The group assigned to 600 mg of peramivir demonstrated significant improvement.[5] In the group assigned to peramivir 600 mg

(n=98), alleviation of symptoms occurred a median of 21 hours sooner than those receiving placebo.[5] The median time to recover to normal temperature in the 600 mg group was approximately 12 hours sooner compared to placebo.[5] In the 600 mg peramivir group, 55% were male; 34% were smokers; and 99% were infected with influenza A virus (1% were infected with influenza B virus).[5] Pooled analysis of all the placebo-controlled trials in acute uncomplicated influenza are described in **Table 2**, which shows the duration of influenza symptoms was shortest in patients treated with peramivir 300 mg and 600 mg.[5]

Table 2. Median Time to Alleviation of Symptoms by Treatment Group in Subjects with Confirmed Influenza.[5]

	Paramivir 150 mg	Paramivir 300 mg	Paramivir 600 mg	Paramivir Overall	Placebo
N (number censored)	100 (17)	255 (33)	256 (22)	611 (72)	399 (41)
Median TTAS in hours (95% CI)	120.7 (96.1 to 148.1)	81.7 (68.1 to 102.0)	79.4 (68.1 to 91.6)	87.6 (78.3 to 96.1)	107.3 (95.7 to 115.2)

Abbreviations: CI = confidence interval; N = number of patients; TTAS = time to alleviation of symptoms.

Clinical Safety:

Across controlled clinical trials in adults with uncomplicated influenza, a total of 1,399 patients were exposed to at least 1 dose of peramivir.[5] Among the 664 patients who received peramivir 600 mg, the most commonly observed adverse reaction was diarrhea (8% vs. 7% with placebo).[5] No serious adverse events were reported in the trials.[5] One death due to meningitis occurred in the clinical trials and was deemed unlikely to be related to the study drug.[5] Clinically significant laboratory abnormalities that occurred more frequently with peramivir 600 mg than placebo are listed in **Table 3**.[5]

Table 3. Laboratory Abnormalities Occurring in ≥2% of Patients Treated with Peramivir 600 mg.[5]

Laboratory Parameter	Peramivir 600 mg	Placebo
Alanine Aminotransferase (>2.5 x ULN)	3%	2%
Serum Glucose (>160 mg/dL)	5%	3%
Creatine Phosphokinase (≥ 6.0 x ULN)	4%	2%
Neutrophils (<1.000 $x10^9$/L)	8%	6%

Abbreviations: dL = deciliters; L = liters; ULN = upper limit of normal range.

References:

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3. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database of Systematic Reviews*. 2014;(Issue 4. Art. No.: CD008965). doi:10.1002/14651858.CD008965.pub4.

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8. DynaMed [internet database]. Ipswich, MA: EBSCO Information Services. Updated periodically. Registration and login required.

9. Situation Update: Summary of Weekly FluView. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/flu/weekly/summary.htm. Accessed July 27, 2015.

10. Influenza Activity - United States, 2014-15 Season and Composition of the 2015-16 Influenza Vaccine; June 5, 2015. Morbidity and Mortality Weekly Report (MMWR), Centers for Disease Control and Prevention. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6421a5.htm. Accessed July 27, 2015.

11. Key Facts About Seasonal Flu Vaccine. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/flu/protect/keyfacts.htm. Accessed July 27, 2015.

12. CDC Health Update Regarding Treatment of Patients with Influenza with Antiviral Medications - January 2015. Health Alert Network, Centers for Disease Control and Prevention. Available at http://emergency.cdc.gov/han/han00375.asp. Accessed July 24, 2015.

13. TAMIFLU (oseltamivir phosphate) [prescribing information]. South San Francisco, CA: Genentech, Inc., November 2014.

14. RELENZA (zanamivir) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, October 2013.

15. RAPIVAB (peramivir injection) [prescribing information]. Durham, NC: BioCryst Pharmaceuticals, Inc., December 2014.

16. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrobial Agents and Chemotherapy*. 2010;54:4568-4574. doi:10.1128/AAC.00474-10.

Appendix 1: Current Status on Preferred Drug List

Generic Name	Brand Name	Form	PDL Status	Current Drug Use Criteria
AMANTADINE HCL	AMANTADINE	CAPSULE	Y	
AMANTADINE HCL	AMANTADINE	SOLUTION	Y	
AMANTADINE HCL	AMANTADINE	TABLET	Y	
OSELTAMIVIR PHOSPHATE	TAMIFLU	CAPSULE	Y	Quantity Limit
OSELTAMIVIR PHOSPHATE	TAMIFLU	SUSP RECON	Y	Quantity Limit
RIMANTADINE HCL	RIMANTADINE HCL	TABLET	Y	
RIMANTADINE HCL	FLUMADINE	TABLET	Y	
ZANAMIVIR	RELENZA	BLST W/DEV	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2015
1 exp Amantadine/ 2973
2 exp Rimantadine/ 259
3 exp Oseltamivir/ 2154
4 exp Zanamivir/ 816
5 peramivir.mp. 210
6 1 or 2 or 3 or 4 or 5 5501
7 limit 6 to (yr="2012 -Current" and (clinical trial, all 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 pragmatic clinical trial or randomized controlled trial or systematic reviews)) 255

Appendix 3: Highlights of Prescribing Information

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

RAPIVAB™ (peramivir injection), for intravenous use
Initial U.S. Approval: [2014]

----------INDICATIONS AND USAGE----------
RAPIVAB is an influenza virus neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. (1)

Limitations of Use:
- Efficacy based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1)
- Efficacy could not be established in patients with serious influenza requiring hospitalization. (1)

----------DOSAGE AND ADMINISTRATION----------
- Administer as a single dose within 2 days of onset of influenza symptoms (2.1)
- Recommended dose is 600 mg, administered by intravenous infusion for a minimum of 15 minutes (2.1)
- Renal Impairment:: Recommended dose for patients with creatinine clearance 30-49 mL/min is 200 mg and the recommended dose for patients with creatinine clearance 10-29 mL/min is 100 mg (2.2)
- Hemodialysis: Administer after dialysis. (2.2)
- RAPIVAB must be diluted prior to administration (2.3)
- See the Full Prescribing Information for drug compatibility information (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 200 mg in 20 mL (10 mg/mL) in a single-use vial (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
- Serious skin/hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme have occurred with RAPIVAB. (5.1)
- Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reaction (incidence >2%) is diarrhea (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-844-273-2327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Live attenuated influenza vaccine (LAIV), intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB, unless medically indicated (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Use if benefit outweighs risk.(8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

Appendix 4: Proposed Prior Authorization Criteria

Neuraminidase Inhibitors

Goal:

- Restrict use of extended prophylactic influenza antiviral therapy to high risk populations recognized by the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA).

Length of Authorization:

- Up to 30 days

Requires PA:

- Non-preferred neuraminidase inhibitors
- Oseltamivir therapy for greater than 5 days

Covered Alternatives:

Preferred alternatives listed at http://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 antiviral agent to be used to treat a current influenza infection (ICD10 J1100, J129, J111-112, J1181, J1189; J09X1-J09X9)?	Yes: Go to #4	No: Go to #5
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives in class and approve for length of therapy or 5 days, whichever is less.	No: Approve for length of therapy or 5 days, whichever is less.
5. Is the antiviral prescribed oseltamivir or zanamivir?	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness.

Approval Criteria		
6. Does the patient have any of the following CDC[1] and IDSA[2] criteria that may place them at increased risk for complications requiring chemoprophylaxis? • Persons at high risk of influenza complications during the first 2 weeks following vaccination after exposure to an infectious person (6 weeks in children not previously vaccinated and require 2 doses of vaccine) • Persons with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person • Persons at high risk for complications from influenza who cannot receive influenza vaccine after exposure to an infectious person • Residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution. • Pregnancy and women up to 2 weeks postpartum who have been in close contact with someone suspected or confirmed of having influenza	Yes: Approve for duration of prophylaxis or 30 days, whichever is less. Current recommended duration of prophylaxis: 7 days (after last known exposure; minimum 2 weeks to control outbreaks in institutional settings and hospitals, and continue up to 1 week after last known exposure. .	No: Pass to RPh. Deny for medical appropriateness.

References:
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P&T/DUR Review: *1/16 (AG); 1/12; 9/10*
Implementation: *1/11*

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Literature Scan: Immunosuppressants

Date of Review: November 2015

Date of Last Review: May 2013
Literature Search: January 2013 to October 2015

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

Conclusions:
- There is low quality evidence of no difference between tacrolimus and cyclosporine in mortality or acute rejection in lung transplant recipients. Tacrolimus may be result in less harms compared to cyclosporine for certain adverse event outcomes such as the incidence of bronchiolitis obliterans syndrome (Relative Risk [RR] 0.46; 95%, CI 0.29 to 0.74). [1]
- There are insufficient data to assess the effects of immunosuppressant drugs in preventing rejection following lung transplantation in patients with Cystic Fibrosis. [2]
- Adequate immunosuppression is needed to support graft function following organ transplant and needs to be balanced against the risk of potential adverse effects from the medications. Although there is no standard of care for dose and regimen, calcineurin inhibitors remain the primary treatment to prevent rejection following transplantation. Monitoring of adequate immunosuppression levels and graft function remains essential.
- There is insufficient evidence for a difference in efficacy/effectiveness or harms between agents. Agents are often used concomitantly. Side effect profile, monitoring requirements and patient specific factors determine therapy of choice.

Recommendations:
- No changes to the PDL recommended at this time.

Previous Conclusions and Recommendations:
- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- Recommend coverage of all entities.
- Recommend preference of generic products.

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 Cochrane Collaboration systematic review compared the benefits and harms of tacrolimus versus cyclosporine for primary immunosuppression in lung transplant recipients.[1] Three studies (n=413) that compared tacrolimus with cyclosporine were included; all of which had a high risk of bias. Tacrolimus was significantly better than cyclosporine regarding the incidence of bronchiolitis obliterans syndrome (RR 0.46; 95% CI 0.29 to 0.74), lymphocytic bronchitis score (mean difference [MD] -0.60; 95% CI -1.04 to -0.16), treatment withdrawal (RR 0.27; 95% CI 0.16 to 0.46), and arterial hypertension (RR 0.67; 95% CI 0.50 to 0.89). The finding for arterial hypertension was not confirmed using the random-effects model. Diabetes mellitus occurred more frequently in the tacrolimus group compared with cyclosporine (RR 4.24; 95% CI 1.58 to 11.40), but no difference was seen when the random-effects model was used for the analysis. There was low quality evidence of no significant difference between the two groups in mortality, acute rejection, infections, cancer, kidney failure, neurotoxicity, and hyperlipidemia. Trial sequential analysis showed the required information thresholds were not reached for any of the outcome measures. Overall, the authors concluded that tacrolimus may be superior to cyclosporine for certain adverse event outcomes. However, there were few studies comparing these agents after lung transplantation, the included studies were at a high risk of bias, and more RCTS are needed to assess the results of the review.

Another systematic review from the Cochrane Collaboration assessed the effects of immunosuppressant drugs in preventing rejection following lung transplantation in patients with Cystic Fibrosis (CF).[2] Only two RCTs were identified in the literature search and because they did not report any information specific to patients with CF, the authors decided not to include them in the systematic review. Therefore, there was insufficient evidence to make conclusions about the comparative efficacy and safety of the various immunosuppressive drugs among patients with CF following lung transplantation.

A third systematic review from the Cochrane Collaboration aimed to compare mycophenolate versus methotrexate for prevention of acute graft-versus-host disease (GVHD) in people undergoing an allogeneic hematopoietic stem cell transplantation (allo-HCT).[3] A literature search for RCTs identified 3 trials (n=177); two trials included background therapy with cyclosporine and one with tacrolimus. There was low quality evidence of no difference seen between mycophenolate and methotrexate for the incidence of acute GVHD (RR 1.25; 95% CI 0.75 to 2.09), overall survival (HR 0.73; 95% CI 0.45 to 1.17), and incidence of chronic GVHD (RR 0.92; 95% CI 0.65 to 1.30). There was low quality evidence that mycophenolate was associated with decreased incidence of severe mucositis, use of parenteral nutrition, and medication for pain control. There was insufficient evidence to evaluate quality of life. The authors concluded that mycophenolate compared with methotrexate (in combination with a calcineurin inhibitor) appears to be associated with a more favorable toxicity profile, without an apparent compromise on disease relapse, transplant-associated mortality, or overall survival. However, the overall quality of the evidence was low and there remains a need for high quality studies evaluating the best approach to prevention of GVHD. [3]

A high-quality systematic review by Su, et al. evaluated everolimus-based calcineurin-inhibitor sparing regimens for kidney transplant recipients.[4] Seven RCTs (n=2067) were identified and included in the meta-analysis. Six of the seven trials included cyclosporine as the calcineurin inhibitor; only one used tacrolimus.

There was no significant difference in death or graft-loss (RR 1.07; 95% CI 0.73-1.58) between everolimus-based calcineurin inhibitor sparing and the standard calcineurin group. However, elimination of calcineurin inhibitor was associated with more acute rejection compared to the standard group (RR 2.51; 95% CI 1.63 to 3.87) while there was no difference between calcinerin inhibitor minimization. Lastly, patients on everolimus-based regimens had more discontinuations (RR 1.69; 95% CI 1.44 to 1.99).

New Guidelines:
2013 guidelines for the long-term medical management of the pediatric patient after liver transplantation were released by the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation.[5] Recommendations are focused on the prevention of acute rejection and management of side effects and complications. There are no recommendations or conclusions on the comparative efficacy or safety on different oral immunosuppressant and no specific therapy recommendations are provided.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
Tacrolimus extended-release (Astagraf XL) was approved by the FDA in July 2013.[6] This formulation was developed with interest in possible improvement in immunosuppressive medication adherence.

Pharmacokinetic trials demonstrated bioequivalence of the XL product with the immediate-release tacrolimus with a delayed time to maximum concentration. Many trials have been published regarding the conversion of immediate-release to extended-release tacrolimus in renal, liver and heart transplant patients. Four of the trials demonstrated bioequivalence of the products, but this was not duplicated in all clinical trials.[7–14] Trials in stable transplant patients showed statistically significant decreases in maximal plasma concentrations, requiring dose increases to maintain therapeutic blood levels (1:1.25). Data demonstrates a continued need to monitor drug levels while transitioning between formulations.

A systematic review evaluated 6 RCTs and 15 observational studies that compared daily versus twice-daily tacrolimus in patients with kidney transplant.[15] Overall, there was no difference in acute rejection (RR 1.24; 95% CI 0.93-1.65), patient survival (RR 0.99; 95% CI 0.97-1/02), and graft survival (RR 0.99; 95% CI 0.97-1.02) between the two formulations. Mean trough levels among those who received extended-release tacrolimus was at least 40% lower than patients on immediate-release tacrolimus. The additional dose required to achieve therapeutic targets varied between 10-25%. Additional observational and randomized trials have studied the conversion from immediate-release to extended-release tacrolimus; overall, studies demonstrated the conversion was safe and effective as long as appropriate therapeutic drug monitoring was provided, patients are educated about the conversion and that the same pharmaceutical manufacturer is utilized after conversion.[16]

Tacrolimus extended-release is indicated for the prophylaxis of acute organ rejection in patients receiving a kidney transplant with mycophenolate mofetil and corticosteroids, with or without basiliximab induction. [6] Limitations of use include: 1) it is not interchangeable with tacrolimus immediate-release and 2) it should not be used simultaneously with cyclosporine.

New FDA Safety Alerts:
None identified.

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17. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood*. 2014;124(8):1372-1377. doi:10.1182/blood-2014-04-567164.

18. Levy G, Villamil FG, Nevens F, et al. REFINE: a randomized trial comparing cyclosporine A and tacrolimus on fibrosis after liver transplantation for hepatitis C. *Am J Transplant*. 2014;14(3):635-646. doi:10.1111/ajt.12620.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	CAPSULE	CYCLOSPORINE	CYCLOSPORINE	Y
ORAL	CAPSULE	CYCLOSPORINE MODIFIED	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	GENGRAF	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	CAPSULE	NEORAL	CYCLOSPORINE, MODIFIED	Y
ORAL	CAPSULE	PROGRAF	TACROLIMUS	Y
ORAL	CAPSULE	SANDIMMUNE	CYCLOSPORINE	Y
ORAL	CAPSULE	TACROLIMUS	TACROLIMUS	Y
ORAL	SOLUTION	CYCLOSPORINE	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	GENGRAF	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	NEORAL	CYCLOSPORINE, MODIFIED	Y
ORAL	SOLUTION	RAPAMUNE	SIROLIMUS	Y
ORAL	SOLUTION	SANDIMMUNE	CYCLOSPORINE	Y
ORAL	SUSP RECON	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	SUSP RECON	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	AZATHIOPRINE	AZATHIOPRINE	Y
ORAL	TABLET	CELLCEPT	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	IMURAN	AZATHIOPRINE	Y
ORAL	TABLET	MYCOPHENOLATE MOFETIL	MYCOPHENOLATE MOFETIL	Y
ORAL	TABLET	RAPAMUNE	SIROLIMUS	Y
ORAL	TABLET	SIROLIMUS	SIROLIMUS	Y
ORAL	TABLET	ZORTRESS	EVEROLIMUS	Y
ORAL	TABLET DR	MYCOPHENOLIC ACID	MYCOPHENOLATE SODIUM	Y
ORAL	TABLET DR	MYFORTIC	MYCOPHENOLATE SODIUM	Y
ORAL	CAP ER 24H	ASTAGRAF XL	TACROLIMUS	N
ORAL	TABLET	AZASAN	AZATHIOPRINE	N

Appendix 2: New Clinical Trials

A total of 45 citations were manually reviewed from the literature search. After further review, 43 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 2 trials are 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
Cutler, et al.[17]	Tacrolimus + Sirolimus (T/S) vs. Tacrolimus + methotrexate (T/M)	<60 y/o undergoing transplantation for acute leukemia, myelodysplastic disorder, or chronic myeloid leukemia (n=304)	Day 144 acute GVHD-free survival	GVHD-free surivival: T/S: 67% (95% CI 59-74) T/M: 62% (95% CI 54-70) P=0.38
REFINE[18]	Cyclosporine vs. tacrolimus	HCV-positive adult recipients of a first liver transplant (n=356)	Rate of fibrosis stage ≥2 by 12 months after liver transplantation	Fibrosis score ≥2 Cyc: 63/88 (71.6%) Tac: 62/77 (67.5%) P=0.759 OR 1.11 (95% CI 0.56-2021)

Appendix 3: Abstracts of Clinical Trials

1. Cutler C et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood.* 2014 Aug 21;124(8):1372-7. doi: 10.1182/blood-2014-04-567164. Epub 2014 Jun 30.

Abstract
Grades 2-4 acute graft-versus-host disease (GVHD) occurs in approximately 35% of matched, related donor (MRD) allogeneic hematopoietic cell transplantation (HCT) recipients. We sought to determine if the combination of tacrolimus and sirolimus (Tac/Sir) was more effective than tacrolimus and methotrexate (Tac/Mtx) in preventing acute GVHD and early mortality after allogeneic MRD HCT in a phase 3, multicenter trial. The primary end point of the trial was to compare 114-day grades 2-4 acute GVHD-free survival using an intention-to-treat analysis of 304 randomized subjects. There was no difference in the probability of day 114 grades 2-4 acute GVHD-free survival (67% vs 62%, P = .38). Grades 2-4 GVHD was similar in the Tac/Sir and Tac/Mtx arms (26% vs 34%, P = .48). Neutrophil and platelet engraftment were more rapid in the Tac/Sir arm (14 vs 16 days, P < .001; 16 vs 19 days, P = .03). Oropharyngeal mucositis was less severe in the Tac/Sir arm (peak Oral Mucositis Assessment Scale score 0.70 vs 0.96, P < .001), but otherwise toxicity was similar. Chronic GVHD, relapse-free survival, and overall survival at 2 years were no different between study arms (53% vs 45%, P = .06; 53% vs 54%, P = .77; and 59% vs 63%, P = .36). Based on similar long-term outcomes, more rapid engraftment, and less oropharyngeal mucositis, the combination of Tac/Sir is an acceptable alternative to Tac/Mtx after MRD HCT. This study was funded by the National Heart, Lung, and Blood Institute and the National Cancer Institute; and the trial was registered at www.clinicaltrials.gov as #NCT00406393.

2. Levy G, et al. REFINE: a ramdonimized trial comparing cyclosporine A and tacrolimus after liver transplantation for Hepatitis C. *Am J Transplant.* 2014 Mar 14(3):635-46.

Abstract
REFINE was a 12-month, prospective, open-label study in 356 patients receiving de novo liver transplantation for hepatitis C virus (HCV) cirrhosis, randomized to cyclosporine A (CsA) or tacrolimus with (i) no steroids, IL-2 receptor antibody induction and mycophenolic acid, or (ii) slow steroid tapering. The primary analysis population based on availability of liver biopsies comprised 165 patients (88 CsA, 77 tacrolimus). There was no difference in the primary endpoint, fibrosis stage ≥2 at 12 months, which occurred in 63/88 CsA-treated patients (71.6%) and 52/77 tacrolimus-treated patients (67.5%) (odds ratio [OR] 1.11; 95% CI 0.56, 2.21; p = 0.759). Similarly, no significant between-group difference occurred at month 24 (OR 1.15; 95% CI 0.47, 2.80; p = 0.767). Among steroid-free patients, fibrosis score ≥2 was significantly less frequent with CsA versus tacrolimus at month 12 (7/37 [18.9%] vs. 16/38 [42.1%]; p = 0.029). HCV viral load was similar in both the tacrolimus- and CsA-treated cohorts. Mean blood glucose was significantly higher with tacrolimus from day 15 onward. Biopsy-proven acute rejection, graft loss and death were similar. These results showed no differences in post-transplant HCV-induced liver fibrosis between patients treated with CsA or tacrolimus in steroid-containing regimens, whereas CsA in steroid-free protocols was associated with reduced severity of fibrosis progression at 1 year post-transplant.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 exp azaioprine.mp 9460
2 cyclosporine.mp or Cyclosporine/ 27272
3 everolimus.mp 3210
4 sirolimus.mp or Sirolimus/ 14682
5 mycophenolate.mp. 8571
6 immunosuppressive agents.mp or Immunosuppressive Agents/ 65117
7 tacrolimus.mp or Tacrolimus/ 16378
8 Graft Rejection/ or Lung Transplantation/ or transplantation.mp 37558
9 organ transplantation.mp or Organ Transplantation/ 14741
10 rheumatoid arthritis.mp or Arthritis, Rheumatoid/ 53500
11 inflammatory bowel disease.mp or Inflammatory Bowel Diseases/ 23618
12 ulcerative colitis.mp or Colitis, Ulcerative/ 19151
13 Graft vs. Host Disease/ or graft versus host.mp 17129
14 Crohn's disease.mp or Crohn Disease 24560
15 1 or 2 or 3 or 4 or 5 or 6 or 7 92720
16 8 or 9 or 10 or 11 or 12 or 13 or 14 164421
17 15 and 16 23834
18 limit 17 to (english language and yr="2013 -Current") and ((clinical trial, all 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) 263

After initial review for appropriate study design, study comparators, and outcomes, 45 trials remained for further review.

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Literature Scan: Topical Analgesics

Date of Review: November 2015

Date of Last Review: March 2013
Literature Search: February 2013-October 2015

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

Conclusions:
- Moderate quality evidence supports the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) as safe and effective treatment options for acute musculoskeletal pain over 1 to 2 weeks.
- Insufficient evidence exists to adequately compare efficacy or safety between most topical analgesics. However, there is low to moderate quality evidence that topical 8% capsaicin improves neuropathic pain more than lower concentrations of capsaicin topical products in post-herpetic neuralgia and neuropathic pain in HIV infected patients, though long-term evidence of safety for this product is insufficient.
- Insufficient evidence exists for the use of 5% topical lidocaine patches in the treatment of mixed peripheral neuropathic pain conditions in adults.

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

Previous Conclusions:
- Evidence does not support a difference in efficacy or safety between topical analgesics.
- Efficacy and safety not established in patients less than 18 years of age.

Previous Recommendations:
- No further review or research needed at this time. No change to the PDL recommended.

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 review assessed the efficacy and safety of topical NSAIDS in the treatment of acute musculoskeletal pain in adults.[1] Acute musculoskeletal pain was defined as pain lasting less than 3 months in duration and associated with a soft-tissue injury. Eligible studies included RCTs which compared topical NSAIDS with active treatment or similar topical placebo for adults with acute pain from recent injury such as a sprain, strain or overuse typically within previous 24-48 hours.[1] Outcomes measured included participant reported pain reduction of 50% from baseline or similar measure including a participant reported global assessment of treatment as close to 7 days as possible. Adverse events and withdrawals were assessed as secondary outcomes. The review included 61 studies and involved 5311 participants treated with a topical NSAID, 3470 with placebo, and 220 with an oral NSAID. Topical NSAID agents assessed included diclofenac, ibuprofen, ketoprofen, piroxicam, indomethacin, and benzydamine. Overall, the review was limited by heterogeneity of various trials, but all studied formulations except benzydamine demonstrated a significant higher rate of clinical success versus topical placebo.[1] An analysis of 10 studies (n=2050) with topical diclofenac versus placebo found significantly higher clinical success with diclofenac (Risk Ratio [RR] 1.6; 95% CI, 1.5 to 1.7; NNT = 4). Of 10 studies, 2 were high quality studies (RR 3.4; 95% CI, 2.7 to 5.5; NNT 2). Two moderate quality studies that compared topical ibuprofen gel versus placebo also found higher rate of clinical success with ibuprofen gel (RR 2.7; 95% CI, 1.7 to 4.2; NNT 4). Five moderate quality studies of topical ketoprofen gel found significantly more (>50%) pain reduction relative to placebo (RR 2.2; 95% CI, 1.7 to 2.8; NNT 3). Other topical NSAIDs studied had a NNT greater than 4 compared to placebo. There were insufficient data to perform a meta-analysis on differences in efficacy between topical NSAIDs and oral NSAIDs. There were insufficient data to compare different formulations of topical NSAIDs, with the exception of piroxicam versus indomethacin.[1] Topical piroxicam may have a higher clinical success rate when compared to topical indomethacin (RR 1.24; 95% CI, 1.1 to 1.4; NNT 13]. There was high quality evidence that showed no significant differences between topical NSAIDS for local adverse events, systemic adverse events, or withdrawals.[1]

A second Cochrane Review assessed the analgesic efficacy and associated adverse events of topical lidocaine formulations for mixed peripheral neuropathic pain in adults.[2] Twelve eligible studies with a total of 508 participants were included in the review. Four different formulations of lidocaine were used in the studies: 5% patch, 5% cream, 5% gel, and 8% spray.[2] Six of the studies involved participants with moderate to severe post-herpetic neuralgia, while the remaining studies included in the review enrolled a mix of various neuropathic pain conditions, including trigeminal neuralgia, post-traumatic neuralgia, phantom limb pain, and diabetic neuropathy. Outcomes measured were 30% or 50% reduction in pain or improvement on a Patient Global Impression of Change (PGIC) scale, as well as withdrawals due to lack of efficacy or adverse events. The majority of studies used a cross-over design, and two used a parallel-group design. The studies were of low quality and at high risk of bias due to small number of participants or incomplete assessment of outcomes.[2] The review found there to be insufficient evidence at this time to support use of topical lidocaine to treat mixed peripheral neuropathic pain.[2]

A third Cochrane Review investigated the efficacy and tolerability of topical (8%) capsaicin patch for chronic neuropathic pain in adults.[3] Six double-blind RCTs with a total of 2073 participants were assessed. Topical 8% capsaicin patch was compared with placebo or another active treatment. Clinical improvement was defined by a 50% pain reduction by a patient reported global impression of change (PGIC) scale at 8 and 12 weeks. PGIC scale scores were categorized as follows: none/slight pain at rest, none/slight pain on movement, pain treatment much/very much improved, or pain treatment very good/excellent. [3] Secondary

outcomes included number of patients with withdrawals due to lack of efficacy or adverse events. Four studies of participants with post-herpetic neuralgia (n=1272) showed significant benefit in PGIC scale scores (pain much/very much improved) for topical 8% capsaicin over placebo (ie, 0.04% capsaicin) control at 8 weeks [RR 1.4; 95% CI, 1.1 to 1.8; NNT 9] and 12 weeks [RR 1.6; 95% CI, 1.2 to 2.0; NNT 7]. Two studies involved participants with HIV and neuropathic pain (n=801). One of the studies (n=307) demonstrated significant pain improvement (much/very much improved) at 12 weeks [RR 2.8; 95% CI, 1.4 to 5.6; NNT 6]. Both studies reported at least 30% pain intensity reduction over weeks 2 to 12 with respect to baseline [RR 1.4; 95% CI, 1.1 to 1.7; NNT 11]. Localized skin reactions such as erythema and burning at the application site were consistently reported but self-limiting. Serious adverse events were uncommon and not statistically significant.[3]

New Guidelines:

Veterans Affairs/ Department of Defense Guidelines (VA/DoD)

The Veterans Affairs/ Department of Defense Guidelines state that topical capsaicin can be considered as first line therapy or adjunctive therapy for patients with mild to moderate pain associated with osteoarthritis of the knee [Grade C – Moderate certainty of small net benefit].[4] There was insufficient evidence to recommend for or against the use of topical capsaicin as first line or adjunctive therapy in treatment for the hip [Grade I – Insufficient evidence to assess benefit versus harm].[4]

NICE Guidance – Osteoarthritis – Care and management in adults

The National Institute for Health and Care Excellence (NICE) has maintained its recommendation for consideration of topical NSAIDS ahead of oral NSAIDS, cyclo-oxygenase 2 (COX-2) inhibitors or opioids as an option for pharmacological management of pain relief in osteoarthritis of the knee or hand.[5] Topical capsaicin was also recommended as an adjunct agent to core treatments for knee or hand osteoarthritis. [5]

NICE Guidance – Neuropathic Pain - Pharmacological management

The National Institute for Health and Care Excellence (NICE) has recommended that capsaicin cream be considered for treatment of localized neuropathic pain (except trigeminal neuralgia) in patients who wish to avoid or who cannot tolerate oral treatments. [6] NICE has also recommended against use of capsaicin patch to treat neuropathic pain when in a non-specialist setting unless instructed by a specialist.[6]

New FDA Drug Approvals:

None identified.

New Formulations/Indications:

None identified.

New FDA Safety Alerts:

No specific safety alerts for topical analgesics have been published. Due to an increase in concerns about the safety of NSAID use during pregnancy, the FDA reviewed the possible risks of miscarriage for various prescription and over-the-counter (OTC) NSAIDs.[7] It was determined that data were too limited to make

any new recommendations at this time; however, a Drug Safety Communication was released with a reminder to pregnant women to always consult with their health care professional about the risks and benefits before taking any prescription or OTC medication to treat pain or other conditions.[7]

References:

1. Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD007402. DOI: 10.1002/14651858.CD007402.pub3.

2. Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD010958. DOI: 10.1002/14651858.CD010958.pub2.

3. Derry S, Rice ASC, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD007393. DOI: 10.1002/14651858.CD007393.pub3

4. Non-Surgical Management of Hip and Knee Osteoarthritis Working Group. VA/DoD clinical practice guideline for the non-surgical management of hip and knee osteoarthritis. Washington (DC): Department of Veterans Affairs, Department of Defense; 2014. 126 p. Available at: http://www.healthquality.va.gov/guidelines/CD/OA/ . Accessed on 9 October 2015.

5. Osteoarthritis. Care and management in adults. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Feb. 36 p. (Clinical guideline; no. 177) Available at: https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations. Accessed on 9 October 2015.

6. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. London (UK): National Institute for Health and Care Excellence (NICE); Issued Nov 2013 last modified: Dec 2014. (Clinical guideline; no. 173) Available at: https://www.nice.org.uk/guidance/cg173. Accessed on 9 October 2015.

7. FDA Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy [1-9-2015] U.S. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm. Accessed 19 October 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
TOPICAL	CREAM (G)	CAPSAICIN	CAPSAICIN	Y
TOPICAL	CREAM (G)	TRIXAICIN	CAPSAICIN	Y
TOPICAL	CREAM (G)	TRIXAICIN HP	CAPSAICIN	Y
TOPICAL	KIT	QUTENZA	CAPSAICIN/SKIN CLEANSER	N
TOPICAL	GEL (GRAM)	VOLTAREN	DICLOFENAC SODIUM	N
TOPICAL	DROPS	DICLOFENAC SODIUM	DICLOFENAC SODIUM	N
TOPICAL	SOL MD PMP	PENNSAID	DICLOFENAC SODIUM	N
TRANSDERM	PATCH TD12	FLECTOR	DICLOFENAC EPOLAMINE	N
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N
TOPICAL	GEL (GRAM)	DICLOFENAC SODIUM	DICLOFENAC SODIUM	N
TOPICAL	GEL (GRAM)	SOLARAZE	DICLOFENAC SODIUM	N
TOPICAL	CREAM (G)	ZIKS	CAPSAICIN/METHYL-SALICYLATE/MENTHOL	N

Appendix 2: New Clinical Trials

A total of 92 citations were manually reviewed from the literature search. After further review, 91 trials were excluded because of wrong study design (observational), lack of comparator (placebo), outcome studied (non-clinical), or had been previously addressed by a high quality review source within the literature scan. The remaining trial is briefly described in the table below. The abstract is included in Appendix 3.

Table 1: Description of Clinical Trial

Study	Comparison	Population	Primary Outcome	Results	Quality*
Casanueva, B.; Rodero, B. et al. 2013 RCT, SC	Topical Capsaicin 0.075% versus standard medical treatment (included non-steroidal anti-inflammatory drugs, major opioids, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, or other multidisciplinary therapies)	Fibromyalgia diagnosed by a Rheumatologist, patients age 18 years or older, unresponsive to at least one standard medical treatment agent (n=130)	Improvements in myalgic score, global subjective improvement score, fatigue severity scale, pressure pain threshold, SF36 Pain Score, etc. (Twenty-nine different assessments) through 6 weeks of treatment	Capsaicin treated patients showed significant improvement in 2 of 29 areas: myalgic score (5.21 in capsaicin-treated vs 3.80 in controls, p = 0.02) and "subjective improvement" (16 cases in capsaicin-treated vs 3 cases in the control group, p = 0.001)	Poor (High risk of bias-selection, performance and detection bias, unreasonable definitions for clinical outcomes)

Abbreviations: RCT = Randomized controlled trial; SC = single-center.

*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

Appendix 3: Abstracts of Clinical Trials

Casanueva, Benigno; Rodero, Baltasar, et al. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatology International.* 2013. 33:2665–2670 doi: 10.1007/s00296-012-2490-5

ABSTRACT: The purpose of this study was to evaluate the short-term efficacy of topical capsaicin treatment in patients severely affected by fibromyalgia.
METHODS: One hundred and thirty fibromyalgia patients were randomly divided into two groups. The control group, 56 women and 4 men who continued their medical treatment, and the capsaicin group, 70 women who apart from continuing their medical treatment, also underwent topical capsaicin 0.075 % 3 times daily for 6 weeks.
RESULTS: At the beginning of the program, there were no significant differences between the two groups in any of the analyzed parameters. At the end of the treatment, there were significant improvements in the capsaicin group in the myalgic score (5.21 vs 3.8, p = 0.02) and global subjective improvement (22.8 vs 5 %, p = 0.001). Six weeks after the end of the treatment, the experimental group showed significant differences in Visual Analogue Scale of depression (5.63 vs 7.35, p = 0.02), Fibromyalgia Impact Questionnaire (67.89 vs 77.7, p = 0.02), role limitations due to emotional problems (36.17 vs 17.2, p = 0.05), Fatigue Severity Scale (6.2 vs 6.6, p = 0.04), myalgic score (3.94 vs 2.66, p = 0.02) and pressure pain threshold (79.25 vs 56.71, p = 0.004).
CONCLUSION: Patients severely affected by fibromyalgia can obtain short-term improvements following topical capsaicin 0.075 % treatment three times daily for 6 weeks.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 2 2015

1	exp Capsaicin/	6165
2	exp Diclofenac/	4732
3	exp Lidocaine/	10002
4	1 or 2 or 3	20734
5	exp Administration, Topical/	48214
6	4 and 5	1938
7	limit 6 to (english and humans and (clinical trial, all 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) and last 2 years)	92

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used appropriately for an OHP-funded condition.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed athttp://www.orpdl.org/drugs/

Note:

A complete list of PDL classes is available at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny for medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4.	**No**: Go to #5.

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
5. RPH only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less. • If not funded: Deny;not funded by the OHP.		

P&T / DUR Review: *7/15 (RC), 9/10; 9/09; 5/09*
Implementation: *8/1/15; 1/1/11, 9/16/10*

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Literature Scan: Inhaled Medications for Cystic Fibrosis

Date of Review: January 2016

Date of Last Review: May 2015
Literature Search: April 2015-December 2015

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

Conclusions:
- There is no new clinical evidence that can further inform PDL decisions for inhaled agents for Cystic Fibrosis.

Recommendations:
- No further review or research needed. Review comparative drugs costs in the executive session.

Previous Conclusions:
- There is insufficient new evidence of inhaled agents for management of Cystic Fibrosis (CF) complication that would change current PDL class management.
- There remains insufficient comparative evidence to directly compare inhaled tobramycin (TIS) to inhaled aztreonam (AZLI) for the treatment of P. aerugonisa in patients with CF and there is no evidence that continuous use is superior to the recommended 28-day cycle (on 28 days, off 28 days).
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- For the early eradication of P. aeruginosa, there is evidence that treatment with inhaled antibiotics is better than no treatment in eradication; but there is no strong evidence of a superior regimen over another. There is also moderate quality evidence that there is no significant difference between 28 days of TIS and 56 days of therapy.
- There is low quality evidence that TIS administered by the PARI LC PLUS Nebulizer is effective in improving lung function in patients with CF.

Previous Recommendations:
- Evaluate comparative costs in executive session; maintain at least one formulation of either inhaled tobramycin or aztreonam as preferred on the PDL for the treatment of chronic infection with *P. aerugonisa*.

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**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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:

Timing of hypertonic saline inhalation for cystic fibrosis [Cochrane Review]
Researchers sought to determine whether the timing of hypertonic saline inhalation (in relation to airway clearance techniques or in relation to time of day) had an impact on its clinical efficacy in patients with cystic fibrosis.[1] However, researchers were unable to identify any studies that adequately compared the timing of treatment in relation to airway clearance physiotherapy.[1]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

Reference:

1. Elkins M, Dentice R. Timing of hypertonic saline inhalation for cystic fibrosis. *Cochrane Database of Systematic Reviews*. 2012, Issue 2. Art. No.: CD008816. DOI: 10.1002/14651858.CD008816.pub2.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	VIAL-NEB	SODIUM CHLORIDE	SODIUM CHLORIDE FOR INHALATION	Y
INHALATION	VIAL-NEB	SODIUM CHLORIDE	SODIUM CHLORIDE FOR INHALATION	Y
INHALATION	VIAL-NEB	SODIUM CHLORIDE	SODIUM CHLORIDE FOR INHALATION	Y
INHALATION	VIAL-NEB	SODIUM CHLORIDE	SODIUM CHLORIDE FOR INHALATION	Y
INHALATION	SOLUTION	PULMOZYME	DORNASE ALFA	Y
INHALATION	AMPUL-NEB	TOBI	TOBRAMYCIN IN 0.225% NACL	Y
INHALATION	AMPUL-NEB	BETHKIS	TOBRAMYCIN	Y
INHALATION	CAP W/DEV	TOBI PODHALER	TOBRAMYCIN	Y
INHALATION	CAPSULE	TOBI PODHALER	TOBRAMYCIN	Y
INHALATION	AMPUL-NEB	KITABIS PAK	TOBRAMYCIN/NEBULIZER	Y
INHALATION	AMPUL-NEB	TOBRAMYCIN	TOBRAMYCIN IN 0.225% NACL	N
INHALATION	VIAL-NEB	CAYSTON	AZTREONAM LYSINE	N

Appendix 2: New Clinical Trials

A total of 6 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2015

1 exp Cystic Fibrosis/ 16588
2 dornase alfa.mp. 123
3 exp Tobramycin/ 1513
4 exp Aztreonam/ 332
5 inhal*.mp. 78918
6 2 or 3 or 4 1939
7 1 and 5 and 6 251
8 limit 7 to (english language and yr="2015 -Current") 6

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Class Update: Iron Chelators

Month/Year of Review: June 2015 **Date of Last Review:** June 2012

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

Purpose for Class Update:
Since the last update in 2012, a new formulation of deferasirox (Jadenu™) was approved by the FDA. This drug class has not been reviewed since June 2012.

Research Questions:
1. Is there any new comparative evidence regarding the efficacy of iron chelators for iron overload in patient with thalassemia syndromes?
2. Is there any new comparative evidence of harms associated with iron chelators used to treat iron overload?
3. Are there subgroups of patients based on demographics (ie, age, race, gender), comorbidities (ie, drug-disease interactions), or other medications (ie, drug-drug interactions) for which one iron chelator may be shown to be more efficacious or more harmful than another?

Conclusions:
- There is low quality evidence of no differences in mortality or hepatic fibrosis scores between iron chelators.
  Liver and Myocardial Iron Concentration
- There is low quality evidence that use of 30 mg/kg of deferasirox may result in a larger mean reduction in liver iron concentration (LIC) than deferoxamine (MD 2.50; 95% CI 0.54 to 4.62, p=0.01).
- There is also low quality evidence that LIC is reduced more in patients who take deferiprone versus deferoxamine after 12 months (ratio of geometric means 1.49; 95% CI, 1.06 to 2.09), after 24 months (1.45; 95% CI, 0.90 to 1.80), and after 30 and 34 months (0.51; 95% CI, 0.36 to 0.71).
- There is low quality evidence that combination of deferiprone and deferoxamine compared to deferoxamine monotherapy is more effective in reducing myocardial iron concentration (SMD 2.68, 95% CI 1.96 to 3.40, p<0.00001).
  Left Ventricular Ejection Fraction (LVEF)
- There is low quality evidence that combination therapy of deferiprone with deferoxamine improves LVEF to a greater extent than either agent alone (MD 5.67; 95% CI, 1.21 to 10.02, p=0.008).
- There is low quality evidence that deferiprone results in a greater percent change in LVEF from baseline compared to deferoxamine (MD 2.88; 95% CI, 1.12 to 4.64, p=0.001). Mean LVEF was higher with deferiprone and deferoxamine used in combination compared to either agent alone (78.04±8.6% vs. 67.4±9.8%; and 68.4±4.7% vs. 65.3±6%; WMD 3.37; 95% CI, 0.79 to 5.95, p=0.01).

- There is low quality evidence that patients who receive deferoxamine may have a lower risk of experiencing an adverse event compared to patients who deferiprone (RR 0.45; 95% CI, 0.24 to 0.84).

Recommendations:
- Review comparative drug pricing in the executive session to inform PDL status of Jadenu™ and other iron chelators.

Previous Conclusions and Recommendations:
- There is insufficient evidence to compare the efficacy of deferiprone with the other oral agent, deferasirox.
- Deferiprone represents the only option for patients for whom deferoxamine and deferasirox are contraindicated or prove to be inadequate in reducing iron burden.
- Recommend adding deferoxamine as a preferred agent on the PDL.
- Recommend making the oral agents deferasirox and deferiprone non-preferred and using the default non-preferred PA criteria to utilize them as second line agents.

Background:
Iron chelators are agents that bind to and reduce plasma levels of iron. In patients with iron overload, such as those with thalassemia or other conditions which require regular blood transfusions, excess iron in the blood can occur which results in damage and disruption of organ function due to iron's free-radical generating properties. Excess iron is mainly stored in the liver but can redistribute to the heart and endocrine tissues leading to sudden cardiac death, arrhythmia, heart failure, liver cirrhosis, or endocrine dysfunction. Iron chelation is used to prevent iron overload and iron's detrimental oxidizing activities on organs. Significant outcomes of interest for iron chelators are mortality, cardiac function (i.e. ejection fraction), and histological evidence of hepatic fibrosis. Unfortunately the majority of the available studies limited to less clinically relevant outcomes of measures of iron overload such as liver iron concentration, myocardial iron concentration, serum ferritin, and urinary iron excretion.[1]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls 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, Dynamed, 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 drugs, indications, and 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 systematic review of RCTs which compared deferiprone to deferoxamine, or a combination of both compared to each drug as monotherapy for reduction of iron overload in chronically transfused patients with β-thalassemia, was assessed.[1] The outcomes of mortality, reduction of end-organ damage, and measures of organ-specific iron overload in chronically transfused patients were assessed. A priori criteria were established before the conduct of review. Inclusion and

exclusion criteria were explicitly stated and agreement between two independent assessors was calculated. Disagreements were resolved by consensus. A list of included studies was provided, although a list of excluded studies could not be found. Forty-three full-text articles were assessed for eligibility after screening; 8 studies were excluded as they did not measure outcomes of interest, and 7 studies were not RCTs. Thirteen citations were merged with their primary article resulting in 13 included RCTs. Characteristics of the included studies were adequately described and quality of each study was assessed utilizing the GRADE tool. The quality of evidence for all included studies was rated as low. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Reporting bias was reported to be examined by visual inspection of funnel plots, but was not made available. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Deferiprone was found to be more efficacious than deferoxamine in improving cardiac ejection fraction, defined as change from baseline LVEF% (MD 2.88; 95% CI, 1.12 to 4.64, p=0.001) based on the results of one study. Another study of patients on deferiprone 75 mg/kg/day by mouth three times weekly or deferoxamine 30-40 mg/kg/day subcutaneously seven days a week found endocrine dysfunction, defined as bone mineral density (BMD) and pubertal status according to Tanner's stages, had progression from Tanner's stage 1 to 2 or 3 in all patients and an improvement in BMD (MD 0.09, 95% CI 0.08 to 0.10, p<0.00001). The combination therapy was found to be more efficacious than either monotherapy in improving cardiac ejection fraction (MD 5.67, 95% CI 1.21 to 10.02, p=0.008). No significant difference was found in other outcomes including mortality, hepatic fibrosis score at the end of treatment, LIC, and change from baseline serum ferritin. Myocardial iron content by cardiac MRI was reported in two studies but pooling of data was not possible. The results of the review indicate that available evidence is of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that deferoxamine is superior to deferiprone or vise-versa.[1]

A systematic review of RCTs in which the clinical effectiveness profile of iron chelators for patients with transfusion-dependent thalassemia major was assessed.[2] Outcomes assessed included ejection fraction, change in LIC, change in myocardial iron concentration, change in serum ferritin, and change in urinary iron excretion. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and phase 2 cross-over trials and studies that presented poor data or case reports were excluded. There had to be agreement between two independent assessors. A list of included studies was provided, although a list of excluded studies could not be found. Thirty-seven full-text articles were assessed for eligibility after screening. Sixteen articles were used for meta-analysis. It was not explicitly stated why 21 studies were excluded. Deferiprone, deferoxamine, and deferasirox were compared with each other as monotherapy, combinations, or when sequentially administered. Of the included studies, 1520 patients aged 5-50 years with transfusion-dependent thalassemia major in any setting worldwide made up the patient population in the review. The GRADE tool was used to rate the quality of included studies and their process was outlined. The quality of evidence for all studies included was rated as low. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. It was stated that due to a low power to detect true heterogeneity in a low number of studies, a cut-off p-value of 0.10 was used. It was stated that a bias defined as "free of selective reporting" was examined but was found to be "unclear in 70.4% of the trials with no graphical aids being offered". Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Combination therapy of deferiprone and deferoxamine versus monotherapy of either drug resulted in lower final LIC, defined as change in LIC (mcg/g dry weight) from baseline to end of treatment (p<0.0001), and increased serum ferritin levels, defined as change in ferritin levels from baseline to end of treatment. Serum ferritin as the difference between final and basal values was significantly increased in patients receiving deferasirox 5, 10, and 20 mg/kg versus deferoxamine 30, 35, and 30 mg/kg respectively (95% CI 544.71 to 1411.29, p<0.00001; 95% CI 565.98 to 1036.02, p<0.00001; and 95% CI 121.65 to 534.35, p=0.002). Ejection fraction was significantly higher in sequential deferiprone and deferoxamine groups compared to deferoxamine monotherapy in one study (78.04±4.12% vs. 69.02±6.05%; weighted mean difference (WMD) 9.02, 95% CI 6.4 to 11.64, p<0.00001). Ejection fraction was significantly higher in deferiprone and deferoxamine combination therapy groups compared to monotherapy of either agent in two trials (78.04±8.6% vs. 67.4±9.8%; and 68.4±4.7% vs. 65.3±6%; WMD 3.37, 95% CI 0.79 to 5.95, p=0.01). Urinary iron excretion (mg/kg/day) was measured in two trials and was significantly higher in patients receiving deferiprone plus deferoxamine versus patients receiving monotherapy of either agent trials (0.88±0.32 vs. 0.38±0.22; and 7.37±1.89 vs. 5.83±1.65; WMD 1.28, 95% CI 0.53 to 2.02, p=0.0008) and in patients receiving sequential deferiprone and deferoxamine compared with deferiprone alone (0.76±0.49 vs. 0.53±0.21; WMD 0.23, 95% CI 0.04 to 0.42, p=0.02).

No significant difference was found in the outcome of myocardial iron concentration at the end of intervention. In many of the other outcomes heterogeneity was not proven to be statistically significant. In all outcomes, GRADE quality of evidence was low. The authors stated that their findings did not support any specific chelation treatment. The results of the review indicate that the available evidence is limited and of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that associated and sequential deferiprone plus deferoxamine treatment can be deemed effective in clinically significant outcomes.[2]

A systematic review with meta-analysis of 16 RCTs was also conducted that compared deferiprone, deferoxamine, and deferasirox in patients with severe thalassemia.[3] The outcomes of difference in serum ferritin from baseline to intervention, difference in LIC from baseline to intervention, myocardial iron concentration, and LVEF, were assessed. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and agreement between two independent assessors was reached with differences resolved by a third reviewer. A list of included studies was provided, although a list of excluded studies could not be found. Forty-six articles were assessed for eligibility after screening; 30 studies were excluded as they did not have relevant results or were deemed to have used inappropriate comparisons between groups. Characteristics of the included studies were not adequately described although the quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration. Only three of the studies used double blinding and only four used concealed allocation. Only one of the studies presented the completed outcome data. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Reporting bias was graded as low, unclear, or high and was reported in a table but a funnel plot was not used since the study samples of each comparison were not sufficient making publication bias unclear. Trial sponsorship and conflicts of interest were not explicitly stated for either the review itself or the included studies. Eleven studies presented serum ferritin changes as an outcome. Although types of interventions, treatment duration, and number of participants of included studies were outlined, the doses used in the treatments were not explicitly stated except when indicated in the results of the outcomes. One study reported that combination therapy of deferoxamine and deferiprone reduced serum ferritin significantly compared to deferoxamine alone (standardized mean difference (SMD) 0.45, 95% CI 0.01 to 1.48, p=0.05). Another study found deferasirox decreased serum ferritin more than deferoxamine (MD 538.03, 95% CI 177.39 to 900.68, p=0.003). A subgroup analysis of the same study was performed on different doses of deferasirox and changes in serum ferritin were not observed in the 5 mg/kg or 10 mg/kg doses but were observed in the 20 mg/kg and 30 mg/kg doses. No other statistically significant differences were observed. Eights studies reported the outcome of LIC. In one study, reduction in patients taking 30 mg/kg of deferasirox had a larger mean difference in LIC at end of intervention compared to deferoxamine (MD 2.50, 95% CI 0.54 to 4.62, p=0.01). No other statistically significant differences were observed. Five studies reported myocardial iron concentration and found there to be a statistically significant difference in at the end of treatment between deferiprone and deferoxamine (SMD -0.35, 95% CI -0.63 to -0.08; p=0.01). One of the studies showed combination of deferiprone and deferoxamine compared to deferoxamine monotherapy to be more effective in changing myocardial iron concentration (SMD 2.68, 95% CI 1.96 to 3.40, p<0.00001). Five trials reported outcomes of LVEF. A significant reduction of LVEF was seen in deferiprone groups when compared to deferoxamine groups (SMD -0.35, 95% CI -0.60 to -0.10, p=0.007) and combination of deferoxamine and deferiprone compared to deferiprone monotherapy (SMD -0.70, 95% CI -1.16 to -0.23, p=0.003). The results of the review indicate that available evidence is of low quality and that more high-quality, large RCTs measuring clinically relevant outcomes are needed before it can be shown that any one iron chelator is more safe of effective than another.[3]

A systematic review of RCTs which evaluated the effectiveness and safety of oral deferasirox in people with sickle cell disease (SCD) and secondary iron overload was assessed.[4] The primary outcome assessed was mortality. Secondary outcomes included reduced end-organ damage due to iron deposition, measures of iron overload, measures of iron excretion over 24 hours, adverse events, participant satisfaction, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and cross-over studies and non-inferiority studies were excluded. One author screened all titles and abstracts of identified papers for relevance and a second author independently screened full papers and identified relevant studies for

inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. Twenty-five full-text articles were assessed for eligibility after screening. One study included in a previous review in addition to one new study were used for the analysis. Seven articles were excluded because they were a review or editorial or other form of published article. One was excluded because it included deferasirox. Fourteen were excluded due to observational data being assessed. One article was a cost-effectiveness analysis and another was excluded because it compared hydroxyurea/phlebotomy to transfusions/chelation. In both studies patients either received deferasirox or deferoxamine. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Risk of bias was stated to be high for both studies since they were classified as open-label trials. Since only two studies were used in the review, funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. There were only limited data presented on the primary outcome as only one study reported death with one occurrence in the deferasirox group (RR 1.26, 95% CI 0.05 to 30.41). No significant differences were seen in the outcomes of reduced end-organ damage due to iron absorption. Ferritin reduction was reported to be significantly greater in patients treated with deferoxamine at the end of both studies (MD of change 440.69 mcg/L, 95% CI 11.73 to 869.64). No data were available on iron excretion in urine or feces. Adverse events of any kind were stated as being reported significantly more often in the deferoxamine group although the reported statistics does not agree with this statement (RR 0.88, 95% CI 1.03 to 5.55). Serious adverse events occurred with similar frequency in both groups. Participant satisfaction with treatment, convenience, and likelihood to continue therapy were significantly higher in deferasirox patients compared to deferoxamine patients (RR 3.13, 95% CI 1.99 to 4.93; RR 3.85, 95% CI 2.28 to 6.47; and RR 6.86, 95% CI 3.38 to 13.00; respectively). Overall rate of discontinuations were lower in patients taking deferasirox (RR 0.53, 95% CI 0.31 to 0.92). No data were available on the cost of either intervention. The authors concluded that there are little data on relevant outcomes such as mortality and end-organ damage. More long-term studies on the effects of deferasirox in patients with SCD are needed in order to establish optional treatment.[4]

A systematic review of RCTs evaluated the effectiveness and safety of oral deferasirox in people with thalassemia and secondary iron overload.[5] The primary outcome assessed was mortality. Secondary outcomes included reduced end-organ damage due to iron deposition, measures of iron overload, measures of iron excretion over 24 hours, adverse events, participant satisfaction, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated and cross-over studies and non-inferiority studies were excluded. One author screened all titles and abstracts of identified papers for relevance and two authors then independently screened full papers and identified relevant studies for inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. Two-hundred eighty-nine full-text articles were assessed for eligibility after screening. Thirty-three articles were included which made up a total of four RCTs. Two open-label studies compared deferasirox to placebo or standard therapy of deferoxamine. One phase II and phase III study compared deferasirox to standard treatment with deferoxamine. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. Risk of bias was stated to be high for both studies since they were classified as open-label trials. Since only four studies were used in the review, funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. Risk of bias was determined to be “unclear” in all included studies. No deaths were observed during the two studies comparing deferasirox to placebo. Since the two studies were dose-finding studies focusing on pharmacokinetics or dynamics, efficacy was not a concentration so assessing of the end-points was not appropriate, although the studies met the inclusion criteria. For the two studies comparing deferasirox to deferoxamine, no significant difference in mortality was observed. No data on the outcomes of measures of iron excretion, reduced end-organ damage due to iron deposition, or cost were available. No significant differences were found in total adverse events. In one study, a subgroup analysis showed deferoxamine was significantly more effective than deferasirox in changing LIC and iron excretion-intake in highly iron-

overloaded patients by a mean ratio of 1.8:1. Participant satisfaction with treatment, convenience, and likelihood to continue therapy were significantly higher in deferasirox patients who had previously been treated with deferoxamine, but were not statistically significant in the small group of deferoxamine-naïve patients. Time lost from normal activities due to treatment was reported as being significantly less with deferasirox. The authors concluded that there is no evidence deeming deferasirox to be more superior to deferoxamine at the usually recommended ratio of 1 mg of deferasirox to 2 mg of deferoxamine but that similar efficacy may be achieved depending on dose and ratio. Data are limited and more long-term studies on efficacy and safety are needed.[5]

A systematic review of RCTs which evaluated the effectiveness (dose and method of administration) of desferrioxamine (also known as deferoxamine) in patients with transfusion-dependent thalasaemia was assessed.[6] The primary outcome assessed was mortality. Secondary outcomes included evidence of end-organ damage, measures of iron overload, adverse events or toxicity, participant adherence, and cost of intervention per year. A priori criteria were established before the conduct of review. Inclusion and exclusion criteria were explicitly stated. One author screened all titles and abstracts of identified papers for relevance and two authors independently screened full papers and identified relevant studies for inclusion. Disagreement was resolved via consensus or through a third party. A list of included studies was provided, although a list of excluded studies could not be found. One-hundred thirty-four full-text articles were assessed for eligibility. Eighty-three were excluded. Twenty-two studies were included in the qualitative synthesis, nine of which were listed as being relevant. Various comparisons were made, including desferrioxamine versus deferiprone or deferasirox; desferrioxamine and deferiprone versus deferiprone; or desferrioxamine monotherapy; different routes of desferrioxamine administration were also assessed. The quality of each study was assessed utilizing the Risk of Bias Tool evaluation following the recommendations from the Cochrane collaboration and the evidence was evaluated using the GRADE assessment tool. The characteristics of the patients in the original studies were fully outlined. A chi-squared test for homogeneity was utilized to assess if pooled results were sensible to combine. In general, risk of bias was stated to be unclear. Funnel plots were not used to assess publication bias. Trial sponsorship and conflicts of interest were explicitly stated for both the review itself and the included studies. One trial reported mortality as an outcome, which noted one death occurred in the deferiprone treatment group after six months of treatment but was determined not to be due to treatment. At 12 months, meta-analysis from the results of three trials showed a significant change in LVEF in favor of deferiprone (MD -1.60%, 95% CI -2.97 to -0.24), although heterogeneity was observed to be high (I^2=75%). Two trials showed a significant difference in mean change in serum ferritin from baseline at six months in patients taking desferrioxamine (MD -2108.62 ng/mL, 95% CI -3334.48 to -882.76; and 324.20 ng/mL, 95% CI -1156.81 to 1805.21), but no significant difference at 12 or 24 months. Significant differences in mean urinary iron excretion was seen in two trials favoring deferiprone in one trial and desferrioxamine in the other (MD -0.20 mg/24 hr, 95% CI -0.32 to -0.08; MD 4.10 mg/24 hr, 95% CI 0.08 to 8.12; respectively). LIC was higher in patients taking desferrioxamine versus deferiprone after 12 months according to results from three trials (ratio of geometric means 1.49, 95% CI 1.06 to 2.09), after 24 months in one trial (1.45, 95%CI 0.90 to 1.80), after 30 and 34 months in two trials with one reaching significant difference (0.51, 95%CI 0.36 to 0.71). The geometric mean value of myocardial T2 in one trial in patient receiving desferrioxamine was 10% lower than in patients receiving deferiprone after six months (0.92, 95% CI 0.85 to 0.99) and 12 months (0.90, 95% CI 0.82 to 0.98). One trial reported mean chelation efficiency as [iron excretion (mg/kg/day/chelator dose (mg/kg/day)[x [molecular weight of the respective chelator/56] x n x 100 where 56 is the molecular weight of iron and n=3 with deferiprone and n=1 with desferrioxamine. A statistically significant difference was found in favor of desferrioxamine (16.45%, 95% CI 7.05 to 25.85). One trial reported data showing patients receiving desferrioxamine have a lower risk of experiencing an adverse event compared to those taking deferiprone (RR 0.45, 95%CI 0.24 to 0.84). One trial at three years showed a significant difference in participant adherence in favor or deferiprone (MD -23.30%, 95% CI -25.08 to -21.52). Based on the results, the authors recommended desferrioxamine as first-line therapy for iron overload in patients with thalassemia major and deferiprone or deferasirox in patients whom desferrioxamine is inadequate or contraindicated. More adequately-powered, high-quality, trials comparing long-term efficacy and outcomes are needed.[6]

New Guidelines:
None identified.

New Safety Alerts:
Exjade®: In October 2013, the FDA added warnings and precautions were added regarding the post-marketing findings of Stevens-Johnson Syndrome.[7] In September 2012, a black boxed warning, contraindications, warning and precautions, and adverse reactions sections were revised in include risk for tubulointerstitial nephritis, hepatic failure, and gastrointestinal hemorrhage.[7]

New Formulations or Indications:
Jadenu™ is a tablet formulation of deferasirox approved by the FDA March 2015 for the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis in patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with nontrasfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 mg of iron per gram of liver dry weight (mg fe/g dw) and a serum ferritin greater than 300 mcg/L.[8] No specific clinical data for Jadenu™ was assessed because clinical safety and efficacy data for Exjade® (deferasirox), a tablet formulation for oral suspension, was previously reviewed by the FDA.[9]

Randomized Controlled Trials:

A total of 118 potentially relevant citations were evaluated from the literature search. After further review, most were excluded because of observational design or inappropriate control (placebo or no control). The remaining 4 randomized clinical trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Calvaruso G.[10] MC, RCT, OL	1. DFP PO 25 mg/kg TID 7 days/week 2. DFO SC 50 mg/kg/day 5 days/week	Age >13 years w/ sickle-cell-disease and serum ferritin 800-3000 ng/mL	Change from baseline value in serum ferritin levels during the 5 years (mean ± SD)	DFP: 695.00 ± 597.74 DFO: 1333.85 ± 871.74
Calvaruso G.[11] MC, RCT, OL	1. DFP PO 25 mg/kg TID 7 days/week 2. DFO SC 50 mg/kg/day 5 days/week	Age >13 years w/ thalassemia intermedia and serum ferritin 800-3000 ng/mL	Mean change in serum ferritin level over the 5-year period	No significant difference
Vichinsky E.[12] MC, RCT, OL	1. DFS PO 20 mg/kg/day 2. DFO SC 175 mg/kg/week	Age ≥2 years with sickle-cell-disease and having received ≥120 mL/kg of packed red blood cells or equivalent, or if LIC ≥7 mg Fe/g dry weight, serum ferritin levels ≥1000 ng/mL and body weight ≥10 kg	Safety during 24 weeks	Adverse events DFS: 110/125 (81.5%) DFO: 52/56 (92.9%)
Pennell D.J.[13] MC, RCT, OL	1. DFS PO 40 mg/kg/day 2. DFO SC 50-60 mg/kg/day 5-7 days/week	Age ≥10 years with β-thalassemia major, Diamond-Blackfan anemia, low/intermediate 1	Ratio of the geometric mean Gmean T2* after 1 year of treatment with DFS divided by the ratio of Gmean for DFO (95% CI)	1.055 (0.999 to 1.129) P=0.054

		myelodysplastic syndromes, or sideroblastic anemia with myocardial T2* 6 to 20 milliseconds without clinical symptoms of cardiac dysfunction		

Abbreviations: DFO = deferoxamine; DFP = deferiprone; DFS = deferasirox; Gmean = geometric mean; kg = kilograms; MC = multi-centered; mg = milligrams; mL = milliliters; ng = nanograms; OL = open label; PO = orally; RCT = randomized controlled trial; SC = subcutaneously; SD = standard deviation; TID = three times daily.

References:

1. Kuo KH and Mrkobrada M. A Systematic Review and meta-Analysis of Deferiprone monotherapy and in Combination with Deferoxamine for Reduction of Iron Overload in Chronically Transfused Patients with Beta-Thalassemia. *Hemoglobin*. 2014 38(6): 409-421.

2. Maggio A, Filosa A, Vitrano A, et al. Iron chelation therapy in thalassemia major: A systematic review with meta-analyses of 1520 patients included on randomized clinical trials. *Blood Cells, Molecules, and Diseases*. 2011; 47: 166-175.

3. Xia S, Zhang W, Huang L, Jiang H. Comparative Efficacy and Safety of Deferoxamine, Deferiprone and Deferasirox on Severe Thalassemia: A Meta-Analysis of 16 Randomized Controlled Trials. *PLOS ONE*. 2013 8(12): 1-9.

4. Meerpohl JJ, Schell LK, Rucker G, et al. Deferasirox for managing transfusional iron overload in people with sickle cell disease (Review). *The Cochrane Library*. 2014; 5: 1-41.

5. Meerpohl JJ, Antes G, Rucker G, et al. Deferasirox for managing iron overload in people with thalassaemia (Review). *The Cochrane Library.* 2012; 2: 1-51.

6. Sisher SA, Brunskill SJ, Doree C, et al. Deferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia (Review). *The Cochrane Library*. 2013; 8: 1-115.

7. FDA Center for Drug Evaluation and Research Medwatch Safety Information, October 2013. U.S. Food and Drug Administration. Available at http://www.fda.gov/safety/medwatch/safetyinformation/ucm255103.htm. Accessed September 7, 2015.

8. FDA Center for Drug Evaluation and Research Drug and Biologic Accelerated and Restricted Distribution Approvals As of June 30, 2015. U.S. Food and Drug Administration. Available at http://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/ndaandblaapprovalreports/ucm404466.pdf . Accessed September 7, 2015.

9. Jadenu™ (deferasirox) tablets [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2015. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206910s000lbl.pdf. Accessed September 13, 2015.

10. Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus Deferoxamine in Sickle Cell Disease: results from a 5-year long-term Italian multi-center randomized clinical trial. *Blood Cells, Molecules and Diseases*. 2014; 53: 265-271.

11. Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial. *American Journal of Hematology*. 2015; 90(7): 634-638.\

12. Vichinsky E, Torres M, Minniti CP, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. *Am. J. Hematology*. 2013; 88:1068-1073.

13. Pennell DJ, Porter JB, Piga A, et al. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in β-thalassemia major (CORDELIA). *Blood*. 2014; 123(10): 1447-1454.

Appendix 1: Current Status on Preferred Drug List

Form	Brand	Generic	PDL
VIAL	DEFEROXAMINE MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DESFERAL MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DEFEROXAMINE MESYLATE	DEFEROXAMINE MESYLATE	Y
VIAL	DESFERAL	DEFEROXAMINE MESYLATE	Y
TABLET	FERRIPROX	DEFERIPRONE	N
TAB DISPER	EXJADE	DEFERASIROX	N
TAB DISPER	EXJADE	DEFERASIROX	N
TAB DISPER	EXJADE	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N
TABLET	JADENU	DEFERASIROX	N

Appendix 2: Abstracts of Clinical Trials

Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus Deferoxamine in Sickle Cell Disease: Results from a 5-year long-term Italian multi-center randomized clinical trial. *Blood Cells, Molecules and Diseases*. 2014; 53: 265–271.

Blood transfusion and iron chelation currently represent a supportive therapy to manage anemia, vasculopathy and vaso-occlusion crises in Sickle-Cell-Disease. Here we describe the first 5-year long-term randomized clinical trial comparing deferiprone versus deferoxamine in patients with Sickle Cell Disease. The results of this study show that deferiprone has the same effectiveness as deferoxamine in decreasing body iron burden, measured as repeated measurements of serum ferritin concentrations on the same patient over 5 years and analyzed according to the linear mixed-effects model (LMM) (p=0.822).
Both chelators are able to decrease, significantly, serum ferritin concentrations, during 5 years, without any effect on safety (p=0.005). Moreover, although the basal serum ferritin levels were higher in transfused compared with non-transfused group (p=0.031), the changes over time in serum ferritin levels were not statistically significantly different between transfused and non-transfused cohort of patients (p=0.389).
Kaplan–Meier curve, during 5 years of study, suggests that deferiprone does not alter survival in comparison with deferoxamine (p=0.38).
In conclusion, long-term iron chelation therapy with deferiprone was associated with efficacy and safety similar to that of deferoxamine. Therefore, in patients with Sickle Cell Disease, deferiprone may represent an effective long-term treatment option.

Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial. *Am J Hematol*. 2015; 90:634-638.

In patients with thalassemia intermedia (TI), such as beta-TI, alpha-thalassemia (mainly HbH disease and mild/moderate forms of HbE/beta-thalassemia), iron overload is an important challenge in terms of diagnosis, monitoring, and treatment. Moreover, to date, the only possible chelators available are deferoxamine, deferasirox, and deferiprone. Here, we report the first 5-year long-term randomized clinical trial comparing the effectiveness of deferiprone versus deferoxamine in patients with TI. Body iron burden, which was determined by measuring serum ferritin levels in the same patient over 5 years and analyzed according to the generalized linear mixed model (GLMM), showed a linear decrease over time in the mean serum ferritin levels in both treatment groups (P=0.035). The overall period of observation was 235.2 person-years for the deferiprone patients compared with 214.3 person-years for the deferoxamine patients. The results of the log-rank test suggested that the deferiprone treatment did not affect survival compared with the deferoxamine treatment (P=0.360). The major adverse events observed included gastrointestinal symptoms and joint pain or arthralgia. Neutropenia and agranulocytosis were also detected, suggesting needing of strict hematological control. In conclusion, long-term iron chelation therapy with deferiprone is associated with an efficacy and safety similar to that of deferoxamine, suggesting that this drug is an alternative option in cases in which deferoxamine and deferasirox are contraindicated.

Vichinsky E, Torres M, Minniti CP, et al. Efficacy and safety of deferasirox compared with deferoxamine in sickle cell disease: Two-year results including pharmacokinetics and concomitant hydroxyurea. *Am J Hematol*. 2013; 88:1068-1073.

We report a prospective, randomized, Phase II study of deferasirox and deferoxamine (DFO) in sickle cell disease patients with transfusional iron overload, with all patients continuing on deferasirox after 24 weeks, for up to 2 years. The primary objective was to evaluate deferasirox safety compared with DFO; long-term efficacy and safety of deferasirox was also assessed. We also report, for the first time, the safety and pharmacokinetics of deferasirox in patients concomitantly receiving hydroxyurea. Deferasirox (n=5135) and DFO (n=568) had comparable safety profiles over 24 weeks. Adverse events (AEs) secondary to drug administration were reported in 26.7% of patients in the deferasirox cohort and 28.6% in the DFO cohort. Gastrointestinal disorders were more common with

deferasirox, including diarrhea (10.4% versus 3.6%) and nausea (5.2% versus 3.6%). The most common AE in the DFO group was injection-site pain irritation, which occurred in 7% of patients. Acute renal failure occurred in one patient on deferasirox who was continued on medication despite progressive impairment of renal function parameters. Serum ferritin levels were reduced in both treatment groups. Patients continuing on deferasirox for up to 2 years demonstrated an absolute median serum ferritin decrease of 2614 ng/mL (n=596). Increasing deferasirox dose was associated with improved response and a continued manageable safety profile. Concomitant hydroxyurea administration (n=528) did not appear to influence the efficacy, safety (including liver and kidney function), and pharmacokinetic parameters of deferasirox.

Pennell DJ, Porter JB, Piga A, et al. A 1-year randomized controlled trial of deferasirox vs deferoxamine for myocardial iron removal in b-thalassemia major (CORDELIA). *Blood*. 2014; 123:1447-1454.

Randomized comparison data on the efficacy and safety of deferasirox for myocardial iron removal in transfusion dependent patients are lacking. CORDELIA was a prospective, randomized comparison of deferasirox (target dose 40 mg/kg per day) vs subcutaneous deferoxamine (50-60 mg/kg per day for 5-7 days/week) for myocardial iron removal in 197 b-thalassemia major patients with myocardial siderosis (T2* 6-20 milliseconds) and no signs of cardiac dysfunction (mean age, 19.8 years). Primary objective was to demonstrate non-inferiority of deferasirox for myocardial iron removal, assessed by changes in myocardial T2* after 1 year using a per-protocol analysis. Geometric mean (Gmean) myocardial T2* improved with deferasirox from 11.2 milliseconds at baseline to 12.6 milliseconds at 1 year (Gmeans ratio, 1.12) and with deferoxamine (11.6 milliseconds to 12.3 milliseconds; Gmeans ratio, 1.07). The between-arm Gmeans ratio was 1.056 (95% confidence interval [CI], 0.998, 1.133). The lower 95% CI boundary was greater than the pre-specified margin of 0.9, establishing non-inferiority of deferasirox vs deferoxamine (P=0.057 for superiority of deferasirox). Left ventricular ejection fraction remained stable in both arms. Frequency of drug-related adverse events was comparable between deferasirox (35.4%) and deferoxamine (30.8%). CORDELIA demonstrated the noninferiority of deferasirox compared with deferoxamine for myocardial iron removal.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 1 2015
1 deferasirox.mp. 619
2 deferoxamine.mp. or exp Deferoxamine/ 3494
3 deferiprone.mp. 745
4 1 or 2 or 3 4193
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Class Update with New Drug Evaluation: Direct Antivirals for Hepatitis C

Date of Review: January 2016
Generic Name: daclatasvir
Generic Name: ombitasvir/paritaprevir/ritonavir

End Date of Literature Search: December 2015
Brand Name (Manufacturer): Daklinza® (BMS)
Brand Name (Manufacturer): Technivie® (Abbvie)
Dossier Received: Yes

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

Purpose for Class Update:
Since the P&T Committee last reviewed the Hepatitis C antivirals, there have been two new drug approvals, updated guidelines, new FDA indications, and a new safety alert. New comparative evidence for the class will be reviewed here.

Research Questions:
1. Are ombitasvir/paritaprevir/ritonavir (OMB/PTV-R; Technivie®) or daclatasvir (Daklinza®) added to sofosbuvir (Sovaldi ®) (DCV+SOF) more effective or efficacious than other antiviral agents for the treatment of chronic hepatitis C (CHC) in achievement of sustained virologic response (SVR) and prevention of long-term complications, including hepatocellular carcinoma (HCC), liver-related morbidity, and mortality?
2. Are OMB/PTV-R or DCV+SOF safer than other available agents for the treatment of CHC in adults?
3. What subgroups of patients will benefit most from treatment with OMB/PTV-R or DCV+SOF?

Conclusions:
- DCV+SOF was FDA approved for the treatment of genotype 3 (GT3) CHC based on 1 open-label nonrandomized phase 3 trial. OMB/PTV-R was FDA approved for the treatment of genotype 4 (GT4) CHC based on one open label phase 2b trial. In addition, updated guidelines were released for the treatment of CHC.
- There is low quality evidence from one phase 3 trial with significant methodological flaws, but a high magnitude of effect, that DCV+SOF achieved an SVR of 89% in subjects with GT3 CHC.[1] However, SVR rates were reduced in patients with cirrhosis (63%) compared to those without cirrhosis (96%). As a result, the optimal treatment duration for GT3 patients with cirrhosis is not established. Further data demonstrate that patients with cirrhosis may benefit from the addition of rivabirin (RBV) or an extended duration of 16 weeks.[2] No other treatment options have shown to be more effective in this population: SOF + ribavirin (RBV) for 24 weeks resulted in lower SVR rates (84%), and ledipasvir/sofosbuvir (LDV/SOF; Harvoni®) + RBV for 12 weeks has only proven to be effective in non-cirrhotic patients.[3,4]
- There is low quality to insufficient evidence that DCV+SOF is efficacious in GT 1 or GT2 CHC, and insufficient evidence for use in patients with cirrhosis with these genotypes.[5,6] At this time, there is more evidence to support LDV/SOF in genotype 1 (GT1) and SOF+RBV in genotype 2 (GT2) CHC.

- There is low quality evidence from one phase 2b trial (PEARL-1), with significant methodological flaws, that OMB/PTV-R +/- RBV achieved an SVR of 91-100% in GT4 CHC without cirrhosis.[7]
- There is insufficient evidence that OMB/PTV-R is efficacious in patients with cirrhosis, in patients with genotypes other than GT4, or in treatment-experienced patients with regimens other than pegylated interferon (PEG-IFN) with ribavirin.
- There is insufficient comparative evidence between direct-acting antiviral agents.
- HCV antiviral agents have insufficient evidence for long-term clinical outcomes such as liver transplantation, hepatocellular carcinoma (HCC), and mortality.
- There is low quality evidence that ombitasvir/paritaprevir/ritonavir with dasabuvir (OMB/PTV-R + DAS; Viekira Pak®) and OMB/PTV-R may cause serious liver injury, mostly in patients with underlying advanced liver disease.[8] These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

Recommendations:
- Persons with advanced liver disease (METAVIR stage F3 or F4), as well as those undergoing a liver transplantation, are at greatest risk of developing complications of liver disease or HCC and should continue to be prioritized for treatment.
- Replace LDV/SOF with DCV to current prior authorization (PA) with SOF and RBV for patients with GT3 CHC with cirrhosis. Compare cost of DCV with SOF to alternative regimens (i.e., LDV/SOF + RBV) for GT3 without cirrhosis in executive session.
- Due to extensive drug-drug interactions and safety concerns relative to LDV/SOF, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- Approve updated PA criteria in **Appendix 6** and compare costs of antiviral agents in the executive session to inform status on the Preferred Drug List (PDL).

Previous Conclusions:
- There is low quality evidence 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) results in high SVR12 rates among treatment-naïve (97-99%) and treatment-experienced (94-99%) adults with chronic hepatitis C virus (HCV) GT 1 infection. This is based on 2 poor-quality, open-label studies with a high risk of bias.
- There is low quality evidence that an 8-week regimen of LDV/SOF may have similar sustained virologic response rates as a 12-week regimen of LDV/SOF in treatment-naive adults with chronic HCV genotype 1 infection who did not have cirrhosis (94% vs. 95%; p=0.52).
- All studies remain small, with imprecise estimates of benefits and harms, particularly in patients with cirrhosis and those 65 years and older. However, there is a large magnitude of benefit seen, and LDV/SOF appears to have potential for improved value over previously approved agents, with higher SVR rates, fewer adverse events, and increased tolerability.
- There is insufficient evidence on the relapse rates associated with LDV/SOF. Larger studies with longer follow-up are needed to adequately assess relapse rates and treatment success.
- There is insufficient to low quality evidence based on one small (n=14) nonrandomized, open-label trial that patients who have viral relapse after SOF plus ribavirin can be successfully re-treated with LDV/SOF for 12 weeks.
- There is insufficient comparative evidence evaluating direct acting antivirals. There is insufficient evidence on long-term clinical outcomes such as liver transplantation, hepatocellular carcinoma, and mortality.

Previous Recommendations:
- Make LDV/SOF a preferred agent on the PDL.

- Implement prior authorization criteria consistent with the community standard to prioritize use so that patients defined by the AASLD guidelines as "highest priority" at high risk for liver-related complications and severe extrahepatic hepatitis are treated. Limit use of LDV/SOF to the following patients (highest priority based on the AASLD guidelines) at this time:
    - Stage 3 and 4 fibrosis without decompensated cirrhosis
    - Those receiving an organ transplant
    - Patients with extrahepatic manifestations, including:
        - Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)
        - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
    - Patients prescribed medication by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C.

Background:
Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. It is also the leading indication for liver transplantation in the Western world.[9] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long-term clinical trials that are large enough to provide direct evidence for these outcomes. 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 and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer.[9] However, this evidence is from observational studies only and those with cirrhosis prior to treatment have been shown to still be at risk for HCC during follow-up. The two major predictors of SVR are viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an 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. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. SVR24 has been associated with improvements in quality of life and studies have demonstrated that SVR24 is associated with a decrease in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[10] Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post-treatment.[11] In addition, genetic variation in both virus and host can affect treatment response.

Patients at greatest risk of progressing 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 hepatocellular carcinoma, or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease, and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.[12] However, a recent cost effectiveness study found that treating HCV infection at early stages of fibrosis appears to improve health outcomes and to be cost-effective but incurs substantial costs.

In the United States, GT1 infection is found in about 75% of patients with HCV and is associated with a lower response to antiviral treatment than infection with GT2 and GT3, which represent about 20% of HCV patients. [9] Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT1a and 1b

infection may differ depending on the treatment regimen. Therapies to treat HCV infection have advanced significantly over the past several years. Prior to 2011, the combination of PEG-IFN and RBV was the standard of care and approximately 55-60% of patients achieved a SVR. Severe adverse effects also limited the success of therapy. In 2011, the FDA approved the first generation direct-acting antiviral agents (DAA), boceprevir and telaprevir.[13] Several randomized controlled trials (RCTs) showed improved SVR rates (63-79%) with triple therapy compared to PEG-IFN+RBV dual therapy. However, these agents still come with several safety concerns and still depend on combination therapy with PEG-IFN+RBV which can result in serious adverse reactions. With the recent development of interferon-free regimens, these therapies have gone out of favor.

In 2013, the second-generation DAAs simeprevir (SMV) and SOF were approved.[10] SOF+RBV, studied together for 24 weeks in those ineligible to receive interferon, was the first interferon-free therapy for the treatment of genotype 1 infection (GT1). These regimens decreased the duration of therapy, decreased adverse events, and again demonstrated improved rates of SVR. In addition, recent data from show real world discontinuation rates of SOF+PEG-IFN+RBV may be up to 5-times greater than rates seen in clinical trials. In 2014, two additional interferon-free therapies were studied, including LDV/SOF and the OMB/PTV-R + DAS regimen. However, these new drugs are expensive, and a significant challenge is identifying which patients will benefit most from receiving treatment since only 5-20% of CHC patients develop cirrhosis over 20 years.[14] Technivie® is a fixed-dose combination that includes ombitasvir, a HCV NS5A inhibitor; paritaprevir, a HCV NS3/4A protease inhibitor; and ritonavir, a potent CYP3A inhibitor that is not active against HCV but boosts concentrations of paritaprevir.[15] It was approved by the FDA for use in combination with ribavirin in GT4 CHC patients without cirrhosis. Treatment options for patients with GT3 CHC remain limited and have required a longer duration of therapy (24 weeks) and the addition of ribavirin. Daclatasvir is a NS5A inhibitor approved for use in combination with sofosbuvir (DCV+SOF) for patients with GT3 CHC. Data suggests that fibrosis progression occurs most rapidly in patients with GT3 CHC and regimens have been less effective for treating this genotype.[3]

Studies that include patients with decompensated cirrhosis, renal failure, or other comorbidities, and studies that include minority racial and ethnic groups are lacking; yet these patients remain some of the most difficult to treat.[16]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 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 Guidelines:
The guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) are routinely updated to reflect rapidly changing evidence with HCV DAAs.[3] The 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 had multiple conflicts of interest.

Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation. 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. The following recommendations for initial treatment of HCV infection are provided:

1. Treatment-naive patients with GT1 infection:
    a. DCV and SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV [Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis)]
    b. LDV/SOF for 12 weeks [Class I, Level A]
    c. OMB/PTV-R + DAS with RBV (1a only) for 12 weeks (no cirrhosis or cirrhosis and 1b) or 24 weeks (cirrhosis and 1a only) [Class I, Level A]
    d. SIM and SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV (cirrhosis without the Q80K polymorphism or 1b) [Class I, Level A]

2. Treatment-naive patients with GT2 infection:
    a. DCV and SOF for 12 weeks [Class IIa, Level B]
    b. SOF and RBV for 12 weeks [Class I, Level A]
        i. Extending treatment to 16 weeks is recommended in patients with cirrhosis [Class IIb, Level C]

3. Treatment-naive patients with GT3 infection:
    a. DCV/SOF for 12 weeks (no cirrhosis) or 24 weeks with or without RBV (cirrhosis) [Class I, Level A (no cirrhosis); Class IIa, Level C (cirrhosis)]
    b. SOF and RBV plus weekly PEG-IFN for 12 weeks for IFN-eligible [Class I, Level A]
    c. SOF and RBV for 24 weeks [Class I, Level A]

4. Treatment-naive patients with GT4 infection
    a. LDV/SOF for 12 weeks [Class IIb, Level B]
    b. OMB/PTV-R with RBV for 12 weeks [Class I, Level B]
    c. SOF and RBV for 24 weeks [Class IIa, Level B]
    d. SOF and RBV plus weekly PEG-IFN for 12 weeks for IFN-eligible [Class II, Level B]

New Safety Alerts:
In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments OMB/PTV-R + DAS (Viekira Pak®) and OMB/PTV-R (Technivie®) can cause serious liver injury mostly in patients with underlying advanced liver disease.[8] As a result, drug labeling was updated to include this risk. A review of adverse events identified cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis, some of which resulted in liver transplantation or death. These events were reported mostly in patients who had evidence of advanced cirrhosis before starting treatment. These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

New Formulations or Indications:
In November, the FDA approved an expanded indication for LDV/SOF for the treatment of patients with genotypes 1, 4, 5, and 6, as well as patients co-infected with HIV.[17] It was also approved to be used in combination with RBV for 12 weeks to treat certain patients with CHC and cirrhosis. Supporting RCTs are included in Table 1.

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the literature search. After further review, 12 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical) or because of unapproved medication. Trials covered in the new drug evaluation section were also excluded. The remaining 5 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
ION-4[18]	LDV/SOF x 12 weeks *No comparator group	Adults with HCV/HIV coinfection, treatment-naïve and experienced, 20% cirrhosis; GT1 and GT4	SVR12	SVR12: 322/325 (96%) Relapse: 10/335 (3%)
SIRIUS[19]	LDV/SOF +/- RBV x 12 weeks vs. LDV/SOF x 24 weeks	Treatment-experienced with PEG+RBV and a protease inhibitor; HCV GT1 and compensated cirrhosis	SVR12	SVR12: LDV/SOF + RBV: 74/77 (96%) LDV/SOF: 75/77 (97%)
PHOTON-2[20]	SOF + RBV x 24 weeks (except 12 weeks for treatment-naïve GT2)	Adults with treatment-naïve GT 1, 2, 3 or 4 and treatment-experienced GT2 and GT3; HCV/HIV co-infection	SVR12	SVR12: GT1: 95/112 (85%) GT2: 17/19 (89%) (Treatment-naïve) GT2: 5/6 (83%) (Treatment-experienced) GT3: 52/27 (91%) (Treatment-naïve) GT3: 42/49 (86%) (Treatment-experienced) GT4: 26/31 (84%)
TURQUOISE1[21]	OMB/PTV-R + DAS + RBV x 12 weeks vs. 24 weeks	GT1; HCV/HIV co-infection; treatment-naïve or previously treated with PEG+RBV	SVR12	SVR12: 12 week: 29/31 (94%) 24 week: 29/32 (91%)
SOLAR-1[22]	LDV/SOF + RBV x 12 weeks vs. 24 weeks	GT1 or GT4; advanced liver disease	SVR12	SVR12: Non-transplant: 86-89% Transplant recipients: 96-98%

NEW DRUG EVALUATION: Daclatasvir (Daklinza®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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.

Daclatasvir is a NS5A inhibitor and sofosbuvir is a nucleotide NS5B inhibitor that was FDA approved for patients with GT3 HCV.

Clinical Efficacy:
FDA approval of DCV (with SOF) for patients with HCV GT3 was primarily based upon one Phase 3 single-arm (n=152), open-label trial (ALLY-3) conducted in the United States and Puerto Rico.[1] The ALLY-3 trial (details in evidence table) evaluated HCV GT3 patients with compensated liver disease with and without cirrhosis for treatment duration of 12 weeks. The primary efficacy endpoint was SVR12. Overall, DCV with SOF achieved an SVR12 of 89% (135/152). However, SVR12 rates were reduced in HCV GT3 patients with cirrhosis (63%, 20/32) compared to those without cirrhosis (96%, 115/120). As a result, DCV with SOF for 12 weeks may not be a reasonable regimen for those with cirrhosis. No differences in SVR12 rates were noted based upon age, gender, IL28B status, or baseline HCV RNA level. SVR12 rates were lower in patients with the Y93H polymorphism at baseline [54% (7/13); 95% CI 25% to 81%] compared to those without [92% (128/139); 95% CI 86% to 96%]. However, no commercially available assay is available to detect the presence of this polymorphism, leaving the clinical implications of this result unknown.

The ALLY-3 trial has significant methodological flaws, including an open-label design with no active comparator. It did not define a non-inferiority margin for determination of efficacy. The FDA analysis calculated it based on historical data and concluded that DCV with SOF achieved non-inferiority compared to SOF with RBV for 24 weeks (2%; 95% CI -4% to 9%).[23] Based upon these results, the FDA approved the use of DCV with SOF for 12 weeks in HCV GT3 patients with compensated liver disease with or without cirrhosis. However, the FDA stated the optimal duration for HCV GT3 patients with cirrhosis has not been established. The FDA has required a post-marketing requirement to conduct a trial to determine if a longer duration of treatment or addition of RBV improves efficacy in patients with cirrhosis. In a small, unpublished study, 21/24 (6/6 with advanced fibrosis and 15/18 with cirrhosis) patients receiving 12 weeks of DCV+SOF+RBV achieved a sustained virologic response after 4 weeks of treatment (SVR4), whereas 25/26 (8/8 with advanced fibrosis and 17/18 with cirrhosis) patients receiving 16 weeks of DCV+SOF+RBV achieved an SVR4. These data demonstrate that patients with GT3 infection and cirrhosis may benefit from extended treatment duration.[2] However, longer term and more data are needed to confirm this.

Alternative treatment options for GT3 includes LDV/SOF + RBV based on limited data from the ELECTRON 2 trial demonstrating a high rate of SVR12 (100%) in non-cirrhotics.[24]

Off-label Uses

DCV with SOF is recommended by the AASLD guidelines as a treatment option for patients with GT1, GT 2, and GT4 based on additional trials.[3]

The ALLY-2 trial is a phase 3 open-label trial that assessed DCV with SOF for 8-12 weeks for the treatment in patients with GT1, GT2, GT3 and GT4 CHC co-infected with HIV (n=203).[5] Eighty-three percent of patients had GT1 and 54% were treatment-naïve. Among previously treated patients, 94% had received PEG-IFN therapy. Treatment-naïve patients were randomized to receive either 12 weeks or 8 weeks of DCV with SOF and previously treated subjects received

the regimen for 12 weeks. Ninety-two (46%) patients had a fibrosis score of at least F3 and only 14% had cirrhosis. The SVR12 rate was 96% (95% CI 89.8 to 99.2%) in treatment-naïve patients with GT1 who received 12 weeks of therapy and was 75.6% (95% CI 59.7 to 87.6%) among previously untreated patients who received 8 weeks of treatment. However, only 9 of these patients had cirrhosis. The SVR12 rate in treatment-experienced patients was 97.7% (95% CI 88 to 99.9%). The SVR24 rates were 92% in the two 12-week groups and 72% in the 8-week group; the authors noted this difference due to missing data. Rates of virologic breakthrough was greater in patients treated for 8 weeks versus 12 weeks, which suggests 12 weeks of therapy should be considered for patients with HIV and HCV co-infection. In patients with GT2, GT3, and GT4, SVR12 was 100% (26/26) when treated for 12 weeks and 78% (7/9) when treated for 8 weeks.

A similar open-label phase 2 trial evaluated DCV with SOF in HCV patients with GT1, GT2, or GT3 without cirrhosis at baseline.[6] This trial included a lead-in period with SOF to determine whether it would decrease the emergence of DCV-resistant variants. Forty-four patients were infected with HCV GT2 or GT3 and 167 with GT1. Patients were randomized to receive SOF for 1 week, then DCV with SOF for 23 weeks; DCV with SOF for 24 weeks; or DCV with SOF and RBV for 24 weeks. The majority of patients had moderate fibrosis (F2 or F3). In patients with GT2 or GT3, SVR12 was 91% (40/44) and with GT1, SVR12 was 98% in previously untreated subjects and 95% in previously treated.

Overall, patients with cirrhosis were not adequately represented in these studies and the optimal duration of treatment for patients with cirrhosis remains unclear.

Other treatment options for GT1 have more supporting data, include LDV/SOF (SVR12 94-99% in non-cirrhosis and 94-100% in cirrhosis) and OMB/PTV-R + DAS (SVR12 96-100% in non-cirrhosis and 89-100% in cirrhosis).[4]

Current treatment options for GT2 include SOF + RBV for 12 weeks or 16 weeks with cirrhosis. At this time there is more evidence to support this regimen.[3]

Clinical Safety:
Overall, the limited short-term data for DCV does not show cause for any serious safety concerns and because DCV was the third NS5A inhibitor the FDA Advisory committee was not required to meet prior to approval of DCV. Overall, approximately 1900 patients with HCV infection have been treated with DCV in combination with other HCV agents in clinical trials. The safety assessment described in the prescribing information was primarily based on the Phase 3 clinical trial (ALLY-3) in patients with GT3 CHC with compensated liver disease with and without cirrhosis.[25]

The most common adverse reactions in the ALLY-3 trial were headache, nausea and fatigue. All adverse reactions were mild to moderate in severity. One subject experienced a serious adverse event that was considered unrelated to DCV and no subjects discontinued therapy for adverse events. Adverse events that occurred in at least 5% of patients are included below[25]:

Adverse Reaction	**n (%)** **n=152**
Headache	21 (14%)
Fatigue	21 (14%)
Nausea	12 (8%)
Diarrhea	7 (5%)

Further review has identified a potential drug-drug interaction with use of amiodarone co-administered with SOF in combination with another DAA, including DCV that can result in potential severe bradycardia. The FDA has updated labeling to include a warning to avoid the combination of amiodarone with DCV and SOF.

Pharmacology and Pharmacokinetic Properties of Daclatasvir[25]:

Parameter	
Mechanism of Action	Inhibitor of HCV nonstructural protein 5A (NS5A).
Oral Bioavailability	67%
Distribution and Protein Binding	Vd: 47 L; Protein binding ~99%
Elimination	Feces (88%, 53% unchanged); urine (6.6%, primarily unchanged)
Half-Life	12 to 15 hours
Metabolism	Substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism.

Abbreviations: HCV = hepatitis C virus; L = liters; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:
1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

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. ALLY-3[1] OL phase 3 study	1. DCV 60 mg + SOF 400 mg once daily x 12 weeks	Demographics: 59% male Median age 55 90% white 21% cirrhotics 66% treatment naïve 61% with non –CC IL28B GT Key Inclusion Criteria: Adults ≥ 18 y/o, treatment naïve or treatment experienced, chronic genotype 3 infection, HCV-RNA levels ≥ 10,000 IU/ml Key Exclusion Criteria: Treatment experienced with a NS5A inhibitor, previous intolerance to SOF, coinfection with HIV or HBV, HCC, decompensation	ITT 152	SVR12 (Total): 1. 135/152 (89%); 95% CI 83-93% Without Cirrhosis: 115/120 (96%); 95% CI 91-99% With Cirrhosis: 20/32 (63%); 95% CI 44-79% SVR12 (Treatment-naive): 1. 91/101 (90%); 95% CI 83-95%) Without Cirrhosis: 80/82 (98%; 95% CI 91-100%) With Cirrhosis: 11/19 (58%); 95% CI 34-80% SVR12 (Treatment-experienced): 44/51 (86%); 95% CI 74-94% Without Cirrhosis: 35/38 (92%); 95% CI 74-94% With Cirrhosis: 9/13 (69%); 95% CI 39-91% p=0.52	NA	Discontinuations due to Adverse Events: 0 Serious AE: 1 (1%) Relapse: 1) 11 (5.1%) 2) 9 (4.2%) 3) 3 (1.4%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: high; nonrandomized; no comparator group Performance Bias: high; open-label; no comparator group Detection Bias: high; open label Attrition Bias: low; overall low attrition Reporting Bias: unclear **Applicability**: Patient: Almost all white patients; included patients with more moderate disease severity with a low percentage of cirrhotics and overall higher baseline HCV RNA level Intervention: Appropriate intervention Comparator: No comparator and the study did not define a noninferiority margin for determination of efficacy. Unable to assess safety based on trial design. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: Monitoring and follow-up difficult to mirror in clinical practice in the hepatitis C patient population.
ALLY-2[5] OL phase 3 study	Treatment-naïve 1. DCV 60 mg + SOF 400 mg once daily x 12 weeks 2. DCV 60 mg + SOF 400 mg once daily x 8 weeks	Demographics: 87% male 34% black 14% cirrhosis 46% ≥ F3 83% GT1 Key Inclusion Criteria:	ITT 1. 101 2. 50	SVR12: *Treatment-naïve:* 1. 98 (97%; 95% CI 91.6-99.4% 2. 38 (76%; 95% CI 61.8-86.9% *Treatment experienced:* 51 (98.1%; 95% CI 89.7-100%)	N/A	Discontinuations due to Adverse Events: 0 Serious AE: *Treatment-naïve:* 1. 1 (1%) 2. 0 (0%)	N/A NS	**Risk of Bias (low/high/unclear)**: Selection Bias: high; only treatment-naïve patients randomized. Performance Bias: high; open-label; Detection Bias: high; open label Attrition Bias: low; overall low attrition ; ITT used Reporting Bias: unclear

	Treatment-experienced 1. DCV 60 mg + SOF 400 mg once daily x 12 weeks	Adults ≥ 18 y/o, HIV coinfection, HCV-RNA levels ≥ 10,000 IU/ml Key Exclusion Criteria: Treatment experienced with a NS5A inhibitor; decompensated cirrhosis, pregnancy, h/o cancer, HCC, uncontrolled diabetes (HgA1C > 8.5%), active substance abuse, active severe psychiatric disorders, abnormal laboratory values (ALT, albumin, platelets, Hg), CrCl < 50 ml/min	1. 52			*Treatment-experienced:* 3 (6%)		**Applicability**: Patient: Majority of patients GT1; less than 10% with cirrhosis in previously untreated patients. Significant exclusion criteria limit generalizability to patient population (renal dysfunction, significant diabetes, etc.) Intervention: Appropriate intervention Comparator: No active comparator group to assess efficacy and safety of medication Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: Monitoring and follow-up difficult to mirror in clinical practice in the hepatitis C patient population.
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DCV = daclatasvir; GT = genotype; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; OMB = ombitasvir; PTV = paritaprevir; R = ritonavir; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virtologic response at 12 weeks after treatment; TN = Treatment naïve; TE = treatment experienced							

NEW DRUG EVALUATION: ombitasvir/paritaprevir/ritonavir (OMB/PTV-R) (Technivie®)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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:

OMB/PTV-R was approved for GT4 CHC without cirrhosis based on one randomized, open-label phase 2b study.[7] Treatment-naïve patients were randomly assigned to receive treatment with or without RBV for 12 weeks, while treatment-experienced patients only received the treatment regimen with ribavirin for 12 weeks after investigators realized the addition of RBV to the regimen was superior in this population. Treatment-experienced patients were limited to those who had failed treatment with PEG-IFN with ribavirin. All genotype 1b-infected patients without cirrhosis were enrolled and completed treatment before enrolment of GT4 treatment-naïve patients to allow for a sequential evaluation of the 2 DAA regimens in these populations. Patients with cirrhosis were excluded from the study. There was no significant difference in SVRxx rates in treatment-naïve patients between those who received RBV and those who did not

(100% vs. 91%; Mean difference −9.16%; 95% CI, -19.61 to 1.29%; P=0.086). All treatment-experienced patients who received ribavirin achieved SVRxx. Three treatment-naïve patients without RBV had virological failure and no patients who received RBV had virological failure. Overall, the patient population studied had more mild disease, with 77% fibrosis F0-F2 and no cirrhotics. Most patients were European, limiting the generalizability of the results to clinical practice.

Clinical Safety:
Overall, treatment was well tolerated but safety data are based on short-term studies composed of few patients. The most commonly reported adverse reactions with an incidence greater than 10% in clinical trials were headache, asthenia, fatigue, nausea and insomnia.[26] No patients reported any serious adverse events related to study drug or adverse events resulting in discontinuation of therapy. The following table displays adverse reactions that occurred in greater than 5% of subjects. [26]

	PEARL-1[7,26]	
Adverse Reaction	Ombitasvir, paritaprevir, ritonavir + RBV 12 weeks 12 weeks N=91 %	Ombitasvir, paritaprevir, ritonavir 12 weeks N=44 %
Astehnia	29	25
Fatigue	15	7
Nausea	14	9
Insomnia	13	5
Pruritus	7	5
Skin reactions	7	5

Elevated liver enzymes to greater than 5-times the upper limit of normal occurred in approximately 1% of subjects which were typically asymptomatic. The long-term effects of OMB/PTV-R on liver function are unknown.

Pharmacology and Pharmacokinetic Properties[26]:

Parameter	
Mechanism of Action	Ombitasvir inhibits HCV NS5A and interferes with viral RNA replication and virion assembly. Paritaprevir inhibits HCV NS3/4A protease and interferes with HCV coded polyprotein cleavage necessary for viral replication. Ritonavir is not active against HCV but is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (ie, AUC).
Oral Bioavailability	Ombitasvir: ~48%; Paritaprevir: ~53%; Ritonavir: Not evaluated
Distribution and Protein Binding	Ombitasvir: Vd: 173 L; Paritaprevir: Vd: 103 L; Ritonavir: Vd: Not evaluated
Elimination	Ombitasvir: Feces (~90%, mainly as unchanged drug); urine (<2%, mainly as unchanged drug) Paritaprevir: Feces (~88%, mainly as metabolites); urine (~9%, mainly as metabolites) Ritonavir: Feces (~86%); urine (~11%)

Half-Life	Ombitasvir: 21 to 25 hours; Paritaprevir: 5.5 hours; Ritonavir: 4 hours
Metabolism	Ombitasvir: Metabolized by amide hydrolysis and oxidative metabolism Paritaprevir: Metabolized by CYP3A4 and to a lesser extent CYP3A5 Ritonavir: Metabolized by CYP3A and to a lesser extent CYP2D6

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:
1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

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. PEARL-1[7] phase 2b, randomized, OL	Treatment-naïve 1. OMB/PTV-R x 12 weeks 2. OMB/PTV-R + RBV x 12 weeks Treatment-experienced 1. OMB/PTV-R + RBV x 12 weeks	Demographics: 86% from Europe Age 48 years Key Inclusion Criteria: Adults ≥18 y/o, treatment-naïve or treatment-experienced, chronic genotype 4 infection, HCV-RNA levels ≥ 10,000 IU/mL Key Exclusion Criteria: Cirrhosis, HBV, HIV, other causes of liver disease	mITT TN 1. 44 2. 42 TE 1. 49	SVR12: *Treatment-naïve* 1. 91% (95% CI 78.3-97.5%) 2. 100% (95% CI 91.6-100%) Mean difference −9·16%; 95% CI −19·61 to 1·29%, P=0·086 *Treatment-experienced* 1. 100% (95% CI 92.7-100%)	NA	Discontinuations due to Adverse Events: 0 Serious AE: 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: high; only treatment naïve subjects were randomized to receive therapy with ribavirin or no ribavirin using a computer generated randomization list. Treatment experienced subjects were not randomized. More patients in the group w/o RBV had F0-F1 fibrosis score (86% vs. 79%) Performance Bias: high; open-label Detection Bias: high; open label Attrition Bias: low; overall low attrition and ITT performed Reporting Bias: unclear **Applicability**: Patient: Almost all white patients; included patients with more mild disease severity (77% F0-F2) with a low percentage of cirrhotics and overall higher baseline HCV RNA level; majority of patients from Europe (86%). Treatment experienced patients were limited to those who have failed treatment with PEG/RBV. Intervention: Appropriate intervention Comparator: No active comparator group besides addition of RBV to truly assess efficacy of OMB/PTV-R

								Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: Multicenter sites in Europe and US

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open label; OMB = ombitasvir; PTV = paritaprevir; R = ritonavir; RBV = ribavirin; SVR12 = sustained virtologic response at 12 weeks after treatment; TN = Treatment-naïve; TE = treatment-experienced

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	Y
SUB-Q	KIT	PEGINTRON	PEGINTERFERON ALFA-2B	Y
SUB-Q	PEN IJ KIT	PEGINTRON REDIPEN	PEGINTERFERON ALFA-2B	Y
SUB-Q	PEN INJCTR	PEGASYS PROCLICK	PEGINTERFERON ALFA-2A	Y
SUB-Q	SYRINGE	PEGASYS	PEGINTERFERON ALFA-2A	Y
SUB-Q	VIAL	PEGASYS	PEGINTERFERON ALFA-2A	Y
ORAL	CAPSULE	REBETOL	RIBAVIRIN	Y
ORAL	CAPSULE	RIBASPHERE	RIBAVIRIN	Y
ORAL	CAPSULE	RIBAVIRIN	RIBAVIRIN	Y
ORAL	TABLET	COPEGUS	RIBAVIRIN	Y
ORAL	TABLET	MODERIBA	RIBAVIRIN	Y
ORAL	TABLET	RIBASPHERE	RIBAVIRIN	Y
ORAL	TABLET	RIBAVIRIN	RIBAVIRIN	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N
ORAL	SOLUTION	REBETOL	RIBAVIRIN	N
ORAL	TAB DS PK	MODERIBA	RIBAVIRIN	N
ORAL	TAB DS PK	RIBASPHERE RIBAPAK	RIBAVIRIN	N

Appendix 2: Abstracts of Clinical Trials

Naggie, et al. Ledipasvir and Sofosbuvir for HCV in patients Coinfected with HIV-1. *N Engl J Med* 2015; 373:705-13.

BACKGROUND: Effective treatment for hepatitis C virus (HCV) in patients coinfected with human immunodeficiency virus type 1 (HIV-1) remains an unmet medical need.
METHODS: We conducted a multicenter, single-group, open-label study involving patients coinfected with HIV-1 and genotype 1 or 4 HCV receiving an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine, or raltegravir. All patients received ledipasvir, an NS5A inhibitor, and sofosbuvir, a nucleotide polymerase inhibitor, as a single fixed-dose combination for 12 weeks. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.
RESULTS: Of the 335 patients enrolled, 34% were black, 55% had been previously treated for HCV, and 20% had cirrhosis. Overall, 322 patients (96%) had a sustained virologic response at 12 weeks after the end of therapy (95% confidence interval [CI], 93 to 98), including rates of 96% (95% CI, 93 to 98) in patients with HCV genotype 1a, 96% (95% CI, 89 to 99) in those with HCV genotype 1b, and 100% (95% CI, 63 to 100) in those with HCV genotype 4. Rates of sustained virologic response were similar regardless of previous treatment or the presence of cirrhosis. Of the 13 patients who did not have a sustained virologic response, 10 had a relapse after the end of treatment. No patient had confirmed HIV-1 virologic rebound. The most common adverse events were headache (25%), fatigue (21%), and diarrhea (11%). No patient discontinued treatment because of adverse events.
CONCLUSIONS: Ledipasvir and sofosbuvir for 12 weeks provided high rates of sustained virologic response in patients coinfected with HIV-1 and HCV genotype 1 or 4. (Funded by Gilead Sciences; ION-4 ClinicalTrials.gov number, NCT02073656.).

Bourliere, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS) *Lancet Infect Dis* 2015; 15:397-404.

BACKGROUND: Patients with cirrhosis resulting from chronic hepatitis C virus (HCV) infection are at risk of life-threatening complications, but consistently achieve lower sustained virological response (SVR) than patients without cirrhosis, especially if treatment has previously failed. We assessed the efficacy and safety of the NS5A inhibitor ledipasvir and the nucleotide polymerase inhibitor sofosbuvir, with and without ribavirin.

METHODS: In this multicentre, double-blind trial, between Oct 21, 2013, and Oct 30, 2014, we enrolled patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens at 20 sites in France. With a computer-generated randomisation sequence, patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg sofosbuvir plus weight-based ribavirin for 12 weeks, or ledipasvir-sofosbuvir plus placebo once daily for 24 weeks. The primary endpoint was SVR 12 weeks after the end of treatment (SVR12), for which 95% CIs were calculated with the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, number NCT01965535.

FINDINGS: Of 172 patients screened, 155 entered randomisation, 77 were assigned to receive ledipasvir-sofosbuvir plus ribavirin and 78 ledipasvir-sofosbuvir. 114 (74%) were men, 151 (97%), were white, 98 (63%) had HCV genotype 1a, and 145 (94%) had non-CC IL28B alleles. SVR12 rates were 96% (95% CI 89-99) for patients in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91-100) in the ledipasvir-sofosbuvir group. One patient discontinued treatment because of adverse events while receiving only placebo. The most frequent adverse events were asthenia and headache, pruritus, and fatigue.
INTERPRETATION: Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible

Molina, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study *Lancet* 2015; 385:1098-106.

BACKGROUND: Although interferon-free regimens are approved for patients co-infected with HIV and genotype-2 or genotype-3 hepatitis C virus (HCV), interferon-based regimens are still an option for those co-infected with HIV and HCV genotypes 1 or 4. These regimens are limited by clinically significant toxic effects and drug interactions with antiretroviral therapy. We aimed to assess the efficacy and safety of an interferon-free, all-oral regimen of sofosbuvir plus ribavirin in patients with HIV and HCV co-infection.
METHODS: We did this open-label, non-randomised, uncontrolled, phase 3 study at 45 sites in seven European countries and Australia. We enrolled patients (aged ≥18 years) co-infected with stable HIV and chronic HCV genotypes 1-4, including those with compensated cirrhosis. Once-daily sofosbuvir (400 mg) plus twice-daily ribavirin (1000 mg in patients with bodyweights <75 kg and 1200 mg in those with weights ≥75 kg) was given for 24 weeks to all patients except treatment-naive patients with genotype-2 HCV, who received a 12-week regimen. The primary efficacy endpoint was sustained virological response 12 weeks after treatment. We did analysis by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT01783678.
FINDINGS: Between Feb 7, 2013, and July 29, 2013, we enrolled 275 eligible patients, of whom 262 (95%) completed treatment; 274 patients were included in the final analysis. Overall rates of sustained virological response 12 weeks after treatment were 85% (95% CI 77-91) in patients with genotype-1 HCV, 88% (69-98) in patients with genotype-2 HCV, 89% (81-94) in patients with genotype-3 HCV, and 84% (66-95) in patients with genotype-4 HCV. Response rates in treatment-naive patients with HCV genotypes 2 or 3 (89% [95% CI 67-99] and 91% [81-97], respectively) were similar to those in treatment-experienced patients infected with those genotypes (83% [36-100] and 86% [73-94], respectively). There was no emergence of sofosbuvir-resistance mutations in patients with HCV viral relapse. Six (2%) patients discontinued treatment because of adverse events. The most common adverse events were fatigue, insomnia, asthenia, and headache. Four (1%) patients had serious adverse events regarded as related to study treatment. Additionally, four (1%) patients receiving antiretroviral treatment had a transient HIV viral breakthrough; however, none required changes in antiretroviral regimen.
INTERPRETATION: Sofosbuvir and ribavirin provided high rates of sustained virological response after 12 weeks of treatment in treatment-naive and treatment-experienced patients co-infected with HIV and HCV genotypes 1-4. The characteristics of this interferon-free combination regimen make sofosbuvir plus ribavirin a useful treatment option for this patient population.

Sulkowski, et al. *JAMA* 2015 Mar 24-31;313(12):1223-31. doi: 10.1001/jama.2015.1328.

IMPORTANCE: Patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are at high risk for liver disease progression. However, interferon-based treatments for HCV infection have significant toxicities, limiting treatment uptake.
OBJECTIVE: To assess the all-oral 3 direct-acting antiviral (3D) regimen of ombitasvir, paritaprevir (co-dosed with ritonavir [paritaprevir/r]), dasabuvir, and ribavirin in HCV genotype 1-infected adults with HIV-1 co-infection, including patients with cirrhosis.
DESIGN, SETTING, AND PARTICIPANTS: TURQUOISE-I is a randomized, open-label study. Part 1a of this pilot study was conducted at 17 sites in the United States and Puerto Rico between September 2013 and August 2014 and included 63 patients with HCV genotype 1 and HIV-1 co-infection who were HCV treatment-naive or had history of prior treatment failure with peginterferon plus ribavirin therapy. The study allowed enrollment of patients, including those with cirrhosis, with a CD4+ count of 200/mm3 or greater or CD4+ percentage of 14% or more and plasma HIV-1 RNA suppressed while taking a stable atazanavir- or raltegravir-inclusive antiretroviral regimen.
INTERVENTIONS: Ombitasvir/paritaprevir/r, dasabuvir, and ribavirin for 12 or 24 weeks of treatment as randomized.
MAIN OUTCOMES AND MEASURES: The primary assessment was the proportion of patients with sustained virologic response (HCV RNA <25 IU/mL) at posttreatment week 12 (SVR12).
RESULTS: Among patients receiving 12 or 24 weeks of 3D and ribavirin, SVR12 was achieved by 29 of 31 (94%; 95% CI, 79%-98%) and 29 of 32 patients (91%; 95% CI, 76%-97%), respectively. Of the 5 patients who did not achieve SVR, 1 withdrew consent, 2 had confirmed virologic relapse or breakthrough, and 2 patients had clinical history and phylogenetic evidence consistent with HCV reinfection. The most common treatment-emergent adverse events were fatigue (48%), insomnia (19%), nausea (18%), and headache (16%). Adverse events were generally mild, with none reported as serious or leading to discontinuation. No patient had a confirmed HIV-1 breakthrough of 200 copies/mL or greater during treatment.
CONCLUSIONS AND RELEVANCE: In this open-label, randomized uncontrolled study, treatment with the all-oral, interferon-free 3D-plus-ribavirin regimen resulted in high SVR rates among patients co-infected with HCV genotype 1 and HIV-1 whether treated for 12 or 24 weeks. Further phase 3 studies of this regimen are warranted in patients with co-infection.

Charlton, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease*Gastroenterology* 2015; 149:649-59.

BACKGROUND & AIMS: There are no effective and safe treatments for chronic hepatitis C virus (HCV) infection of patients who have advanced liver disease.

METHODS: In this phase 2, open-label study, we assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were assigned randomly (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12).

RESULTS: We enrolled 337 patients, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection. In cohort A (nontransplant), SVR12 was achieved by 86%-89% of patients. In cohort B (transplant recipients), SVR12 was achieved by 96%-98% of patients without cirrhosis or with compensated cirrhosis, by 85%-88% of patients with moderate hepatic impairment, by 60%-75% of patients with severe hepatic impairment, and by all 6 patients with fibrosing cholestatic hepatitis. Response rates in the 12- and 24-week groups were similar. Thirteen patients (4%) discontinued the ledipasvir and sofosbuvir combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation.
CONCLUSION: The combination of ledipasvir, sofosbuvir, and ribavirin for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation. ClinTrials.gov: NCT01938430.

Appendix 3: Highlights of Prescribing Information (Daclatasvir)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DAKLINZA™ (daclatasvir) tablets, for oral use
Initial U.S. Approval: 2015

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

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection. (1)

Limitations of Use:

- Sustained virologic response (SVR) rates are reduced in patients with cirrhosis. (14)

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

- 60 mg taken orally once daily with or without food in combination with sofosbuvir. (2.1)
- Recommended treatment duration: 12 weeks. (2.1)
- Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers. (2.2)

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

- Tablet: 60 mg and 30 mg (3)

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

- Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort. (4)

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

- Bradycardia When Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.3)

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

Most common adverse reactions (≥10%) observed with DAKLINZA in combination with sofosbuvir were headache and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Drug Interactions: Coadministration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions. (2.2, 4, 5.1, 7, 12.3)

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

Revised: 7/2015

Appendix 4: Highlights of Prescribing Information (Ombitasvir, paritaprevir and ritonavir)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TECHNIVIE (ombitasvir, paritaprevir and ritonavir) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage, Removed-Limitations of Use (1)	10/2015
Dosage and Administration, Testing Prior to Initiation of TECHNIVIE (2.1)	10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2)	10/2015
Dosage and Administration, Dosage in Patients with Hepatic Impairment (2.3)	10/2015
Contraindications (4)	10/2015
Warnings and Precautions (5.1)	10/2015

INDICATIONS AND USAGE

TECHNIVIE is a fixed-dose combination of ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor and is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection without cirrhosis. (1)

DOSAGE AND ADMINISTRATION

- Testing Prior to Initiation: Assess baseline hepatic laboratory and clinical parameters. (2.1)
- Recommended dosage: Two tablets taken orally once daily (in the morning) with a meal without regard to fat or calorie content. TECHNIVIE is recommended to be used in combination with ribavirin. (2.2)

Patient Population	Treatment	Duration
Genotype 4 without cirrhosis	TECHNIVIE + ribavirin*	12 weeks
*TECHNIVIE administered without ribavirin for 12 weeks may be considered for treatment-naïve patients who cannot take or tolerate ribavirin *[see Microbiology (12.4) and Clinical Studies (14)]*.		

DOSAGE FORMS AND STRENGTHS

Tablets: 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir. (3)

CONTRAINDICATIONS

- The contraindications to ribavirin also apply to this combination regimen. (4)
- Patients with moderate to severe hepatic impairment. (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate and strong inducers of CYP3A. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Discontinue treatment in patients who develop evidence of hepatic decompensation. (5.1)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting TECHNIVIE (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on TECHNIVIE, monitor closely and follow recommendations in full prescribing information. (5.2)
- Risks Associated With Ribavirin Combination Treatment: The warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- Drug Interactions: The concomitant use of TECHNIVIE and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of TECHNIVIE. (5.4)

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence greater than 10% of subjects, all grades) observed with treatment with ombitasvir, paritaprevir and ritonavir with ribavirin for 12 weeks were asthenia, fatigue, nausea and insomnia. (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

Co-administration of TECHNIVIE can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of TECHNIVIE. The potential for drug-drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

Appendix 5: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 Hepatitis C/ or hepatitis c virus.mp. or Hepatitis C, Chronic 43,112
2 Antiviral Agents/ or direct acting antivirals.mp 49116
3 sofosbuvir.mp 283
4 ledipasvir.mp 74
5 ombitasvir.mp. 33
6 daclatasvir.mp. 129
7 dasabuvir.mp. 27
8 1 or 2 44131
9 3 or 4 or 5 or 6 or 7 or 8 49149
10 9 and 10 12809
11 limit 11 to (english language and humans and yr="2015 -Current" and (clinical trial, phase ii or clinical trial, phase iii or controlled clinical trial or meta analysis or systematic reviews)) 20
12 from 12 keep 2, 11, 17-18, 20-24, 27-28, 31... 8

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Prioritize populations in greatest need of treatment who will benefit the most from therapy.
- Provide consistent patient evaluations across all hepatitis C treatments.

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 Hepatitis C?	**Yes:** Go to #3	**No:** Pass to RPh; deny for appropriateness.
3. Has the patient failed treatment with any HCV NS5A inhibitor (including daclatasvir plus sofosubvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir)? Note: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (See table below)	**Yes:** Pass to RPh; deny for appropriateness. Note: If patient needs urgent retreatment, resistance testing must be done to indicate susceptibility to prescribed regimen for retreatment	**No:** Go to #4
4. What regimen is requested?	Document and go to #5	

Approval Criteria		
5. Is the regimen prescribed by, or in consultation with, a hepatologist or gastroenterologist with experience in treatment of Hepatitis C?	**Yes:** Go to #6	**No:** Pass to RPh; deny for appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.
6. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate advanced fibrosis (METAVIR F3), compensated cirrhosis (METAVIR F4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score of 8 through 11), with an expected survival from non-HCV-associated morbidities greater than 5 years?	**Yes:** Go to #9	**No:** Go to #7 <u>Note:</u> Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director.
7. 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) and have an expected survival from non-HCV-associated morbidities greater than 5 years? a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis) b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis	**Yes:** Go to #9	**No:** Go to #8

Approval Criteria		
8. Does the patient have Hepatitis C in the transplant setting, including the following scenarios: a) Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b) Post-transplant patients with Stage 4 fibrosis c) Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection **And** expected survival from non-HCV-associated morbidities greater than 5 years?	**Yes:** Go to #9	**No:** Pass to RPh; deny for medical appropriateness. Note: Other scenarios not included can be brought to the OHP Medical Director on a case-by-case basis.
9. Has the patient been abstinent from illicit drug and marijuana use AND alcohol abuse for 6 months or longer? If the patient has a history of alcohol abuse, has the patient been abstinent from all alcohol for 6 months or longer?	**Yes:** Go to #10	**No:** Pass to RPh; deny for appropriateness.
10. Does the patient have significant renal impairment (CrCl ≤30 mL/min) or end-stage renal disease?	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #11
11. Does the patient have a baseline HCV RNA level?	**Yes:** Record value and go to #12	**No:** Pass to RPh. Request provider obtains baseline lab value.
12. What is the Hepatitis C genotype of the patient?	Record genotype and go to #13	
13. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-16 weeks based on Table 1.	**No:** Pass to RPh; deny for appropriateness.

Table 1: Recommended Regimens for Chronic Hepatitis C.

Genotype	Cirrhosis Status	Approved Regimen^	Duration of Treatment
Genotype 1			
Treatment-naïve	**NO**	• LDV/SOF	12 weeks *Note: If HCV RNA < 6 million IU/mL, limit treatment to 8 weeks*
	YES	• LDV/SOF	12 weeks
Treatment-experienced	**NO**	• LDV/SOF	12 weeks
	YES	• LDV/SOF + RBV	12 weeks
Genotype 2			
Naïve or Experienced	**YES/NO**	• SOF + RBV	12 weeks**
Genotype 3			
Naïve or Experienced	**NO**	• DCV + SOF • LDV/SOF + RBV	12 weeks
Naïve or Experienced	**YES**	• DCV + SOF + RBV	12 weeks
Genotype 4 or 6			
Naïve or Experienced	**YES/NO**	• LDV/SOF	12 weeks

*Addition of RBV indicated for genotype 1a
**Previous non-responders to PEG/RBV with cirrhosis may benefit by extension of therapy to 16 weeks

Abbreviations: DCV = daclatasvir (Daklinza®); LDV/SOF = ledipasvir and sofosbuvir (Harvoni®); OMB/PTV-R = ombitasvir, paritaprevir and ritonavir (Technivie™); OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir (Viekira Pak®); RBV = ribavirin; SOF = sofosbuvir (Sovaldi®)

^Approved regimens are:

- DCV: 1 tablet once daily
- LDS/SOFL: 1 tablet once daily;
- OMB/PTV-R: 2 tablets each morning;
- OMB/PTV-R + DAS: 1 tablet OMB/PTV-R twice daily and 1 tablet DAS twice daily;
- RBV: twice daily weight-based dosing;
- SOF: 1 tablet once daily

P&T/DUR Review: *1/16 (MH); 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 10/15; 4/15,1/15; 9/14; 7/14; 3/14*

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

New Drug Evaluation: Ferric Citrate tablets, oral

Date of Review: December 2015
Generic Name: ferric citrate
PDL Class: Phosphate Binders

End Date of Literature Search: October 2015
Brand Name (Manufacturer): Auryxia™ (Keryx Biopharmaceuticals)
Dossier Received: not available via AMCP

Research Questions:

- Is ferric citrate superior in efficacy to other phosphate binders (calcium acetate, lanthanum carbonate, sevelamer hydrochloride, sevelamer carbonate, and ferric oxyhydroxide) in lowering serum phosphorus in patients who have chronic kidney disease (CKD), are on dialysis, and have hyperphosphatemia?
- Is ferric citrate effective in improving mortality or morbidity associated with hyperphosphatemia, and is ferric citrate effective in lowering serum phosphorus levels in patients with CKD on dialysis?
- Is ferric citrate superior in safety, tolerance, and compliance to other phosphate binders in CKD dialysis patients with hyperphosphatemia?

Conclusions:

- There is no evidence ferric citrate is superior to other phosphate binders or improves mortality or morbidity associated with hyperphosphatemia in CKD patients on dialysis. However, there is low quality evidence ferric citrate is effective in lowering serum phosphorus. The efficacy of ferric citrate is supported by two phase 3 open-label, randomized trials: Trial 304 and Trial 305. Trial 304 was a sequential, three-phase study with a 2-week washout period, followed by a 52-week active-controlled safety period, followed by a 4-week placebo-controlled efficacy period. Patients who completed the 52-week safety period were re-randomized to ferric citrate (n=91) or placebo (n=91) for the efficacy period. The efficacy period showed that the adjusted mean difference in serum phosphorus levels for subjects on ferric citrate vs subjects on placebo was -2.2 mg/dL. Trial 305 was a 4-week non-controlled dose-ranging and efficacy study comparing the mean change in serum phosphorus for subjects on fixed-dose 1-g, 6-g, and 8-g ferric citrate daily. The mean reduction in serum phosphorus from baseline to week 4 was 0.1 mg/dL, 1.9 mg/dL, and 2.1 mg/dL for the 1-g, 6-g, and 8-g arms, respectively, with a statistically significant difference in the 8-g vs 1-g and 6-g vs 1-g arms in pairwise comparison.

  Among several validity concerns were the following: (1) Both trials used an open-label design, which was mitigated by the objective nature of the outcome; however, it was unclear whether laboratory personnel were blinded; (2) Both trials excluded patients intolerant to phosphate binders, which limits determining the drug's effectiveness in a general population of CKD patients on dialysis who have hyperphosphatemia; (3) The efficacy assessment periods of both trials were short in comparison to the chronic nature of the condition; (4) Only patients completing the 52-week safety period of Trial 305 were randomized to the efficacy period, which resulted in exclusion of 39% of subjects between the start of the safety phase and the start of the efficacy phase.

- Two primary safety concerns exist with all phosphate binders: (1) drug-drug interactions resulting in the reduced bioavailability of concomitant medications and (2) gastrointestinal (GI) adverse events. Two major safety concerns specific to iron-based phosphate binders are the masking of GI bleeding and iron

overload, particularly in patients with genetic predisposition (i.e., hemochromatosis). No empirical data are available on drug interactions between ferric citrate and most oral drugs often taken concomitantly by patients with CKD. During the 52-week safety period of Trial 304, 21% of patients on ferric citrate discontinued treatment because of an adverse event versus 14% patients on active control (calcium acetate or sevelamer carbonate or both). However, the study excluded patients intolerant to any of the active control treatments. At 14% (vs 4% for active control), GI adverse reactions were the most common reason for discontinuation. Researchers observed elevated serum ferritin and transferrin saturation (TSAT) levels in clinical trials. Although, in Trial 304, 19% of patients treated with ferric citrate vs 9% of patients treated with active control had a ferritin level >1500 ng/mL, no elevated risk of iron overload was detected when reviewing adverse events indicative of iron overload. However, the ability to detect complications due to iron overload may have been limited by study size and duration. Ferric citrate is associated with dark stools, which can visually mask GI bleeding. However, laboratory tests for occult bleeding are unaffected by this dark staining of feces, because the tests detect heme rather than non-heme iron.

- There is no evidence ferric citrate is superior to other phosphate binders, and evidence supporting its effectiveness is of low quality. Additionally, GI adverse events indicate patients may be less tolerant to ferric citrate in comparison with calcium acetate and sevelamer carbonate, and safety questions with regard to iron overload have not yet been resolved.

Recommendations:

- Designiate ferric citrate as non-prefered at this time and incorporate into current prior authorization (see Appendix 4 of phosphate binders literature scan).

Background:

Auryxia (ferric citrate) is a phosphate binder indicated for the control of serum phosphorus levels in patients with CKD on dialysis. Ferric citrate is approved as Riona in Japan and as Fexeric in the European Union (EU). However, clinical trials in Japanese subjects used a ferric citrate formulation different from the main clinical trials used to form the basis of approval for Auryxia and Fexeric (JTT-751 for Japanese vs KRX-0502).[1, 2]

Derangement of phosphate homeostasis in CKD results in hyperphosphatemia, which is associated with increased mortality. The two main consequences of hyperphosphatemia of CKD are bone disease and ectopic calcification in the soft tissue and blood vessels, which is thought to contribute to the high cardiovascular risk and increased cardiovascular mortality seen in patients with end-stage kidney disease.[3] Observational studies have shown hemodialysis patients have a 10- to 100-fold higher cardiovascular mortality and total mortality than age-matched controls.[4]

Placebo-controlled randomized trials showing decreased morbidity or mortality from the use of phosphate binders in hyperphosphatemia of CKD are lacking.[5] However, prospective cohort studies have shown an association between the use of phosphate binders in dialysis patients and significantly lower mortality.[6, 7]

The FDA has approved six types of phosphate binders: calcium acetate, lanthanum carbonate, sevelamer hydrochloride, sevelamer carbonate, and ferric oxyhydroxide. Generally, intolerability (e.g., GI intolerability or hypercalcemia) and noncompliance (e.g., pill burden) limit phosphate binder use. Aluminum hydroxide, magnesium hydroxide or carbonate, and calcium carbonate also have been used off-label to treat hyperphosphatemia; however, their use is limited by toxicities.[1]

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) 2010 guidelines recommend treating hyperphosphatemic CKD dialysis patients with phosphate binders, in addition to management of diet and dialysis frequency, and suggest reducing serum phosphorus levels to the reference range. The guidelines state one phosphate binder has not been proven to be superior over another. Therefore, binders may be chosen based on effectiveness and adverse effect profiles, and binders may be combined to minimize adverse effects that may result from using high doses of one agent.[5]

National Institute for Health and Clinical Excellence (NICE) guidelines on the management of hyperphosphatemia in CKD (2013) recommend, for children and adults, a calcium-based phosphate binder as the first-line therapy, in addition to dietary management; however, the guidelines also recommend taking into account patient preference, ease of administration, and clinical circumstances. For children and young people, the guidelines further recommend considering combining a calcium-based binder with sevelamer hydrochloride if serum calcium measurements show a trend toward the age-adjusted upper limit of normal (ULN) or if hyperphosphatemia remains and serum calcium rises above the age-adjusted ULN. In the latter case, switching to sevelamer hydrochloride may also be considered. For adults with stage 5 CKD on dialysis who remain hyperphosphatemic despite adhering to the maximum recommended or tolerated dose of calcium-based binder, combining the calcium-based binder with or switching to a non-calcium-based binder may be considered. For adults who have serum phosphate levels controlled by diet and a calcium-based binder but also have serum calcium levels elevated above the ULN or low serum parathyroid hormone levels, either combining the calcium-based binder with, or switching to, sevelamer hydrochloride or lanthanum carbonate may be considered.[3]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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 primarily based its approval of ferric citrate for the treatment of hyperphosphatemic CKD dialysis patients on two phase 3 trials: KRX-0502-304 (Trial 304) and KRX-0502-305 (Trial 305).[1]

Trial 304
Lewis, et al. (2014) performed a sequential three-period, 58-week, open-label, randomized-controlled trial to determine the efficacy and safety of ferric citrate as a phosphate binder, as well as to evaluate ferric citrate's ability to supplement iron stores and reduce the use of intravenous (IV) iron and erythropoiesis-stimulating agents (ESA). The study included adult patients with end stage renal disease (ESRD) who were on hemodialysis or peritoneal dialysis 3-times weekly for at least 3 months before screening, were prescribed 3 to 18 doses of phosphate binder daily, and had serum ferritin <1000 ng/mL, TSAT <50%, and phosphorus ≥2.5 and ≤8 mg/dL at screening. The study excluded patients who absolutely required oral iron or vitamin C or were intolerant to calcium acetate and sevelamer. The study allowed vitamin D therapy, cinacalcet, calcium supplementation, erythropoietin-stimulating agents (EMA), and IV iron as concomitant therapies.[8]

The trial included an up to 2-week washout period, a 52-week active-controlled safety period, and a 4-week placebo-controlled efficacy assessment period. Subjects who had a serum phosphorus level between 6 and 10 mg/dL during the 2-week phosphate-binder wash-out period were randomized 2:1 into the ferric citrate group (n=292) or the active-control (calcium citrate or sevelamer carbonate or both) group (n=149) for the safety period. Following the safety period, subjects in the ferric citrate group and subjects in the active control group who had been switched to ferric citrate were eligible to be re-randomized 1:1 into the efficacy period if they had completed the final visit of the safety period on the study drug. The eligible subjects (n=193 from ferric citrate group; n=2 from active control group) either continued on the ferric citrate doses they were on at the end of the efficacy assessment visit or switched to placebo. During the safety and efficacy periods, the ferric citrate dose was titrated based on serum phosphate level, with the goal of maintaining the level between 3.5 and 5.5 mg/dL. The mean baseline serum phosphorus levels of subjects entering the efficacy period were 5.12 for the ferric citrate arm and 5.44 for the placebo arm.[1, 8]

The primary endpoint as specified in the final statistical analysis plan in the placebo-controlled efficacy period was change in serum phosphorus from baseline (Visit 21, Week 52) to end of the 4-week efficacy period. Efficacy analysis was performed using the population of subjects who took at least one dose of study medication, had baseline assessments, and had at least one post-baseline efficacy assessment.[1] The efficacy period's final sample size provided at least a 95% power at a two-sided significance level of 5% to detect a mean difference in phosphorus level between ferric citrate and placebo groups of 1.2 mg/dL, assuming the two groups had a common SD of 2 mg/dL. The primary analysis was performed using last observation carried forward (LOCF) analysis of covariance (ANCOVA), controlling for baseline phosphorus, and was repeated in a sensitivity analysis adjusted for sex, ferritin, and hemoglobin, which were imbalanced between the treatment groups at baseline.[8]

For the efficacy period, both analyses found a mean difference in phosphorus levels between the ferric citrate group (n=91) and placebo group (n=91) of -2.2±0.2 mg/dL (mean±SEM) ($p<0.001$). Treatment failures with a serum phosphorus level ≥9 mg/dL included 21 subjects on placebo and 1 subject on ferric citrate. During the safety period, the mean serum phosphorus level was not significantly different between the ferric citrate and active control groups at the end of 52 weeks: 5.4±1.6 mg/dL (mean±SD) for the ferric citrate group vs 5.4±1.7 and 5.3±1.4 mg/dL for the sevelamer carbonate group ($p=0.94$) and the calcium acetate group ($p=0.84$), respectively.[8]

Trial 305

Dwyer et al. (2013) performed phase 3, randomized, uncontrolled, open-label, dose-ranging and efficacy study in adult patients with ESRD on thrice-weekly hemodialysis. Additional eligibility criteria included taking 3 to 15 doses daily of calcium acetate 667 mg or sevelamer as hydrochloride or carbonate 800 mg daily and having a serum ferritin level <1,000 mcg/L, TSAT ≤50%, and phosphorus level ≥3.5 to ≤8 mg/dL at the screening visit. Major exclusion criteria included active GI bleeding or inflammatory bowel disease (IBD), severe hyperphosphatemia (≥10 mg/dL) within 3 months of screening, malignancy within 5 years of screening, or an absolute requirement for oral iron therapy, vitamin C, or calcium-, magnesium-, or aluminum-containing drugs. Permitted concomitant therapies included cinacalcet, calcium, vitamin D therapy, IV iron therapy, and ESA.[9]

Following a 1- to 2-week washout period, 151 patients with serum phosphorus levels ≥6 mg/dL were randomly assigned 1:1:1 to a fixed dose of ferric citrate 1, 6, or 8 g daily. The researchers determined patient sample sizes to provide at least 90% power to detect a treatment difference in serum phosphorus level of at least 1.4 mg/dL, assuming a common SD of 2 mg/dL. Patients who had both baseline and post-baseline assessments comprised the ITT population. Patients considered treatment failures were those who discontinued study drug due to a serum phosphorus level ≤2.5 mg/dL at day 7 or ≤2.5 or ≥9 mg/dL at day 14 or day 21. The primary analysis of change in serum phosphorus level from baseline to the end of the 28-day treatment period was performed using a regression model with dose effect, while the secondary efficacy assessment employed a LOCF ANCOVA for a pairwise comparison of dose, using treatment as the fixed class effect and baseline phosphorus level as the covariate.[9]

About 79% of patients completed the study, and 10% discontinued treatment but completed all study assessments. Following the initiation of treatment, serum phosphorus levels decreased in a dose-dependent manner, with mean changes of −0.1 ± 1.3, −1.9 ± 1.7, and −2.1 ± 2 mg/dL in the 1-g daily, 6-g daily, and in 8-g daily groups, respectively. The pairwise comparison revealed significant mean differences in change from baseline values between the 1-g daily and the 6- and 8-g daily groups ($p<0.001$), but not between the 6- and 8-g daily groups. About 15% (n=22) of patients were considered treatment failures by the end of treatment, with 73% of the 15 treatment failures with phosphorus levels ≥9 mg/dL coming from the 1-g daily group and all seven of the treatment failures with phosphorus levels ≤2.5 mg/dL split between the 6-g and 8-g daily groups.[9]

Trials 304 and 305 had several limitations. The internal validity concerns included the following: (1) Both trials used an open-label design, which was mitigated by the objective nature of the outcome; however, it was unclear whether laboratory personnel were blinded; (2) The number of subjects in both trials was small; (3) Both studies used last observation carried forward and had high rates of attrition despite limiting the study to patients tolerant to phosphate binders; (4) Trial 304 had an imbalance in sex, ferritin, and hemoglobin between the study arms, but a sensitivity analysis was performed, which showed the mean treatment difference persisted; (5) The statistical plan for Trial 304 was finalized after the trial finished; however the FDA determined this did not affect the study's findings;[1] and (6) The method of randomization for Trial 305 was unclear ("randomization list provided by the statistician").

The external validity concerns included the following: (1) Both studies used serum phosphorus level as a surrogate outcome; however, it is an accepted one; (2) Both trials excluded patients intolerant to phosphate binders, which limits determining the drug's effectiveness in a general population of CKD patients on dialysis who have hyperphosphatemia; (3) The efficacy assessment periods of both trials was short in comparison to the chronic nature of the condition; (4) Only patients completing the 52-week safety period of Trial 305 were randomized to the efficacy period, which resulted in exclusion of 39% of subjects between the start of the safety phase and the start of the efficacy phase; and (5) Trial 305 did not have a comparator.

Clinical Safety:

Two primary safety concerns exist with all phosphate binders: (1) drug-drug interactions resulting in the reduced bioavailability of concomitant mediations, including drug binding by phosphate binders and (2) GI adverse events, including diarrhea, constipation, and obstruction. Two major safety concerns specific to iron-based phosphate binders are the masking of GI bleeding and iron overload, particularly in patients with genetic predisposition (i.e., hemochromatosis).[1]

Researchers observed elevated serum ferritin and TSAT levels in clinical trials. In Trial 304, 55 (19%) of patients treated with ferric citrate vs 13 (9%) of patients treated with active control had a ferritin level >1500 ng/mL. Therefore, prescribing information contraindicates ferric citrate in patients with iron overload syndromes (e.g., hemochromatosis) and recommends assessing iron parameters before initiating ferric citrate and during therapy and reducing the dose or discontinuing of IV iron therapy when required.[10]

The pooled safety data set for ferric citrate comes from active control Trial 304 and 3 short-term trials (uncontrolled Trial 305, pharmaceutical grade ferric citrate trial PBB00101, and uncontrolled phase 2 Trial 201). Across the 4 trials, 557 unique patients received ferric citrate, ranging from up to 28 days for short-term trials and up to 52 weeks for Trial 304 with dosage regimens ranging from 210 mg to 2,520 mg of ferric iron daily (equivalent to 1 to 12 ferric citrate tablets). Similar adverse events were reported for ferric citrate versus active control groups.[1, 10]

Adverse events reported in greater than 5% of patients treated with ferric citrate included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%). During the 52-week, active-control period of Trial 304, 21% of patients on ferric citrate (n=60) discontinued treatment because of an adverse event versus 14% patients (n=21) on active control. However, the study excluded patients intolerant to any of the active control treatments. At 14% (vs 4% for active control), GI adverse reactions were the most common reason for discontinuation.[10]

No empirical data are available on drug interactions between ferric citrate and most oral drugs often taken concomitantly by patients with CKD. Therefore, the prescribing information recommends (1) considering separating the timing of the administration of oral medications where reduced bioavailability of that medication would significant affect its safety or efficacy and (2) monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.[10]

Ferric citrate is associated with dark stools, which can visually mask GI bleeding. However, laboratory tests for occult bleeding are unaffected by this dark staining of feces because the tests detect heme rather than non-heme iron.[10]

Unanswered safety questions:

- How safe is ferric citrate in pediatric patients? The safety and efficacy of ferric acid have not been established in pediatric patients.
- How safe is ferric citrate in patients with GI disorders? Clinical trials excluded patients with IBD or active, symptomatic GI bleeding. Therefore safety has not been established in these populations.
- Which adverse events are associated with ferric citrate versus CKD and its morbidities? Data comparing ferric acid with placebo are limited. Some adverse events described in clinical trials may be disease-related, rather than treatment-related.
- What is the safety profile of ferric citrate compared with other phosphate binders? The study excluded patients intolerant to any of the active control treatments, making it difficult to compare adverse event rates between ferric citrate and the active controls.
- What is the true risk for iron overload? The ability to detect complications due to iron overload may have been limited by study size and duration.[1]

Look-alike / Sound-alike Error Risk Potential: Oracea, Oracit, Oraqix, various ferric and ferrous iron dietary supplements and prescription drugs

Pharmacology and Pharmacokinetic Properties: [10]

Parameter	
Mechanism of Action	Ferric citrate reacts with dietary phosphate in the GI tract to form ferric phosphate, an insoluble precipitate that is excreted in the feces. Decreasing phosphate absorption lowers serum phosphate concentration.
Oral Bioavailability	No data*
Distribution and Protein Binding	No data*
Elimination	No data*
Half-Life	No data*
Metabolism	No data*

*No formal pharmacokinetic studies have been performed. However, serum iron parameters show systemic absorption of iron from ferric citrate.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Improved mortality
2) Improved morbidity, e.g., cardiovascular outcomes
3) Improved serum phosphorus levels
4) Safety: Iron overload
5) Tolerability: GI adverse events

Primary Study Endpoint:
1) For Trial 304, change in serum phosphorus from baseline (visit 21, week 52) to end of the 4-week efficacy period (compared with placebo)

2) For Trial 305, change in serum phosphorus from baseline to the end of the 28-day treatment period.

Comparative Evidence Table [1, 8, 9, 11]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Lewis 2014; Umanath 2013; and FDA Medical Review 2014 December 2010 to November 2012 60 sites in US and Israel Phase 3, sequential three-period, randomized, open-label, efficacy and safety trial	Efficacy 1. FC (6 to 12 caplets daily; median 8-g daily) 2. PLA Duration: 4 weeks Safety 1. FC 2. AC Duration: 52 weeks	Demographics: (FC, PLA) · Age (yr), median 54, 56 · Men (%) 73, 49 · Race (%) Black 65, 53 White 31, 43 · Heart disease (%): CHF 34, 33 MI/CAD 38, 30 · ESA (%) 60, 66 · IV iron (%) 16, 22 · vit D/analogs (%) 85, 81 · Phos (mg/dl) median 5.1, 5.3 · Calcium (mg/dl) median 9.23, 9.20 · Ferritin (mg/dl) median 858, 932 · TSAT (%) median 36, 34 · Hemoglobin (g/dl) median 11.4, 10.9 Key Inclusion Criteria: · adults w/ ESRD · 3x-week HD or PD for ≥3 months · 3–18 doses phosphate binder daily · ferritin <1000 ng/mL · TSAT <50% · phosphorus ≥2.5 and ≤8 mg/dl Key Exclusion Criteria: · active GI bleed/IBD · parathyroidectomy <6 months prior · severe hyperphos · intolerance to calcium acetate and sevelamer	Efficacy period ITT: 1. 95 2. 95 mITT: 1. 91 2. 91 Efficacy period attrition: 1. FC: 5/95 (5%) 2. PC: 25/95 (26%) Safety population: 1. FC: 289 2. AC: 149 Safety period attrition: 1. FC: 96 (33%) 2. AC: 38 (26%)	Mean change from baseline in serum phosphorus (mg/dL): 1. FC: -0.26 2. AC: +1.77 Adjusted mean difference FC vs PLA: -2.18 (CI: -2.59 to -1.77), p<0.001	NA	TEAE (safety period): Infections and infestations: 1. FC: 12.8% 2. AC: 20.1% GI disorders: 1. FC: 6.9% 2. AC: 12.1% Respiratory, thoracic, mediastinal disorders: 1. FC: 6.9% 2. AC: 10.1% Nervous system disorders: 1. FC: 4.8% 2. AC: 4% Hepatobiliary disorders: 1. FC: 0.7% 2. AC: 1.3% D/C due to TEAE (safety period): 1. FC: 20.8% 2. AC: 14.1% All SAEs any time after drug initiation: 1. FC: 41.9% 2. AC 51% D/C due to AE during efficacy period: 1. FC: 2% 2. PC: 3%	-7.3/-14 -5.2/-19 -3.2/-31 -0.8/2 -0.6/2 6.4/16 -9.1/-11 -1/-100	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Sex, ferritin, and hemoglobin were imbalanced between the study arms, but sensitivity analysis was performed and showed the mean treatment difference persisted. Performance Bias: Low. The study was open-label, but the study outcomes were objectively defined. Detection Bias: Unclear. The study was unclear as to whether outcome assessors were blinded. The FDA Medical Review makes a statement that laboratory staff were blinded but the published study and design do not. Attrition Bias: High. The study used LOCF. During the efficacy period there was greater attrition in the PLA arm, while the FC and PLA arms both had the same withdrawal rates for AE and consent. Reporting Bias: High. The statistical plan was finalized after the trial finished. **Applicability**: Patient: The 52-week safety period resulted in the exclusion of 39% of subjects entering the efficacy phase, with 13% and 8% excluded for AE and "other," respectively. Patients intolerant to phosphate binders were excluded. Intervention: The 4-week efficacy period was short in duration, but the overall treatment period was 56 weeks. Comparator: The efficacy period comparator was placebo. Outcomes: Serum phosphorus level is a surrogate outcome, but it is an accepted one. Setting: The effectiveness of FC in a general population of CKD dialysis patients with hyperphosphatemia is unclear because only subjects tolerant to phosphate binders were included in the study.

2. Dwyer 2013 15 sites in US Phase 3, randomized, uncontrolled, open-label, dose-ranging and efficacy trial	1. FC 1-g 2. FC 6-g 3. FC 8-g Duration: 4 weeks	Demographics: (FC 1-g, 6-g, 8-g) · Age (y) 56, 57, 53 · Male (%) 64, 59, 58 · Race (%) Black 50, 61, 60 White 42, 33, 29 · Serum phosphorus (mg/dL) 7.3, 7.6, 7.5 · Calcium (mg/dL) 9, 8.9, 8.9 · Ca x P (mg^2/dL^2) 66, 67, 66 · Ferritin (mg/dL) 558, 515, 527 · TSAT (%) 32, 34, 30 Key Inclusion Criteria: · adults with ESRD · 3x-week HD/PD for ≥3 months · 3–15 doses phosphate binder daily · ferritin <1000 ng/mL · TSAT <50% · phosphorus ≥3.5 and ≤8 mg/dL Key Exclusion Criteria: Same as above	ITT: 1. 51 2. 52 3. 48 Attrition: 1. 23% 2. 10% 3. 24%	Mean change in serum phosphorus (mg/dL±SD): 1. -0.1 ± 1.3 2. -1.9 ± 1.7 3. -2.1 ± 2 Pairwise comparison: 6-g vs 1-g: 1.3 (CI: 0.69 to 1.9), p<0.001 1-g vs 8-g: 1.5 (CI: 0.86 to 2.1), p<0.001 6-g vs 8-g: 0.21 (CI: -0.39 to 0.81), p=0.5	NA	GI AE: 1. 43.1% 2. 42.3% 3. 52.1% All SAEs: 1. 11.8% 2. 13.5% 3. 18.8% D/C due to AE: 1. 3.9% 2. 5.8% 3. 16.7%	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. The method of randomization was unclear. Performance Bias: Low. The study was open-label, but the study outcomes were objectively defined. Detection Bias: Unclear. The study was unclear as to whether outcome assessors were blinded. Attrition Bias: High. The study used LOCF. The attrition rates were high, driven by treatment failure for the 1-g arm and AE in 8-g arm. Reporting Bias: Low. No reporting bias apparent **Applicability**: Patient: Patients intolerant to phosphate binders were excluded. Intervention: The study was only 4 weeks in duration. Comparator: No comparator was used. Outcomes: Serum phosphorus level is a surrogate outcome, but it is an accepted one. Setting: The effectiveness of FC in a general population of CKD dialysis patients with hyperphosphatemia is unclear because only subjects tolerant to phosphate binders were included in the study.

Abbreviations [alphabetical order]: AC = active control (median 7.7 tabs daily calcium acetate 667-mg capsules; median 9 tabs daily sevelamer carbonate 800-mg tablets; or both titrated according to prescribing information); AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; D/C = discontinuations; FC = ferric citrate (1-g tablets contained 210 mg ferric iron); GI = gastrointestinal; HD = hemodialysis; IBD = inflammatory bowel disease; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PD = peritoneal dialysis; PLA = placebo; PP = per protocol; TEAE = treatment emergent adverse events.

References:

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AURYXIA (ferric citrate) tablets , for oral use
Initial U.S. Approval: 2014

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

Auryxia™ is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis (1)

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

- Starting dose is 2 tablets orally 3 times per day with meals (2)
- Adjust dose by 1 to 2 tablets as needed to maintain serum phosphorus at target levels, up to a maximum of 12 tablets daily. Dose can be titrated at 1-week or longer intervals. (2)

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

- Tablets: 210 mg ferric iron, equivalent to 1 g ferric citrate (3)

---------- **CONTRAINDICATIONS** ----------

- Iron overload syndromes (e.g., hemochromatosis) (4)

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

- Iron overload: Monitor ferritin and TSAT. Patients may require a reduction in dose or discontinuation of IV iron. (5.1)
- Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately. (5.2)
- Patients with gastrointestinal bleeding or inflammation: Safety has not been established. (5.3)

---------- **ADVERSE REACTIONS** ----------

- In clinical trials, likely adverse reactions occurring with Auryxia included diarrhea, discolored feces, constipation, nausea, and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Keryx Biopharmaceuticals at 1-844-445-3799 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- **DRUG INTERACTIONS**----------

- When clinically significant drug interactions are expected, consider separation of the timing of administration. Consider monitoring clinical responses or blood levels of the concomitant medication (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07\2015

From Lewis 2014: [8]

Appendix 4. Adverse events during the 52-week active-control period.

Type of AE	Patients with Treatment Emergent Adverse Events Within 12 Weeks of Randomization[1]		Patients with Treatment Emergent Adverse Events[2]		Patients with Adverse Events Recorded Anytime After Drug Initiation[3]	
	Ferric Citrate	Active Control	Ferric Citrate	Active Control	Ferric Citrate	Active Control
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All SAEs	46 (15.9%)	26 (17.4%)	113 (39.1%)	73 (49.0%)	121 (41.9%)	76 (51.0%)
All AEs	214 (74.0%)	108 (72.5%)	261 (90.3%)	133 (89.3%)	266 (92.0%)	138 (92.6%)
GI Serious AEs	6 (2.1%)	4 (2.7%)	20 (6.9%)	19 (12.8%)	24 (8.3%)	19 (12.8%)
GI Non-serious AEs[4]	121 (41.8%)	32 (21.5%)	143 (49.5%)	52 (34.9%)	141 (48.8%)	55 (36.9%)
Infection Serious AEs	13 (4.5%)	9 (6.0%)	36 (12.5%)	27 (18.1%)	42 (14.5%)	29 (19.5%)
Infection Non-serious AEs[3]	35 (12.1%)	21 (14.1%)	73 (25.3%)	35 (23.5%)	79 (27.3%)	36 (24.2%)
Cardiac Serious AEs	7 (2.4%)	4 (2.7%)	21 (7.3%)	18 (12.1%)	27 (9.3%)	20 (13.4%)
Cardiac Non-serious AEs[3]	11 (3.8%)	5 (3.3%)	30 (10.4%)	14 (9.4%)	33 (11.4%)	14 (9.4%)

[1] Counts of subjects with treatment emergent adverse events in the indicated categories. Counts for nonserious adverse events include non-serious adverse events occurring after study drug initiation and prior to 12 weeks after randomization or

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Literature Scan: Phosphate Binders

Date of Review: January 2016

Date of Last Review: May 2014
Literature Search: April 2014 to December 2015

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

Conclusions:
- New evidence for phosphate binders is limited to one new systematic review for use in children with chronic kidney disease (CKD) and one new guideline for use in adults with CKD. Both publications found insufficient evidence of differences between phosphate binders in clinically relevant outcomes (bone fractures, bone deformities, bone pain, and reduced growth rates) or phosphate and PTH levels in children or adults. There is low strength evidence calcium-based phosphate binders may result in higher serum calcium levels in some patients compared to non-calcium-based phosphate binders.
- One new drug approval was identified. Auryxia™ (ferric citrate) was approved in September 2014 to control serum phosphorous levels in patients with CKD on dialysis. It is reviewed separately as a new drug evaluation.
- One new formulation was also identified. Fosrenol® (lanthanum carbonate oral powder) was approved in September 2014 based on pharmacokinetic studies that compared the powder formulation to the chewable tablet formulation already on the market.

Recommendations:
- Continue to prefer at least one calcium-based phosphate binder and one non-calcium-based phosphate binder on the Preferred Drug List (PDL).
- No changes to the current Prior Authorization (PA) are recommended (see **Appendix 4**).
- Evaluate comparative costs in the executive session.

Previous Conclusions and Recommendations:
- Phosphate binders should be selected based on each patient's specific clinical needs.
- Consider adding a non-calcium-based phosphate binder to the preferred class, based on cost. There is no evidence that shows that one agent is more effective or safer than an alternative, however there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide.
- 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**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality

(AHRQ), 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:

Cochrane Review of Interventions for Metabolic Bone Disease in Children with Chronic Kidney Disease

Cochrane reviewers updated a 2010 systematic review on interventions for metabolic bone disease in children with CKD.[1] Adverse outcomes such as bone fractures, bone deformities, bone pain, and reduced growth rates can occur in children with CKD.[1] Randomized controlled trials that compared different interventions to prevent or treat bone disease in children with CKD were eligible for inclusion in this review.[1] The review included 18 trials (n=576 children) but only 5 studies evaluated phosphate binders.[1] In 2 studies (n=29), calcium carbonate and aluminum hydroxide were used as phosphate binders and compared as interventions in pre-dialysis children with CKD.[1] There was no significant difference between the 2 interventions when mean final height, rates of hypercalcemia, or differences in serum parathyroid hormone (PTH) and phosphorous levels were assessed.[1] In 3 studies, sevelamer was compared with calcium-containing phosphate binders (calcium acetate or calcium carbonate) in patients with Stages 2 to 4 CKD.[1] There were no significant differences in the final calcium (mean difference (MD) -0.40 mg/dL, 95% CI -1.16 to 0.36; I^2=59%), phosphorus (MD 0.17 mg/dL, 95% CI 0.37 to 0.71; I^2=0%) or PTH levels (MD 51.92 pg/mL, 95% CI -77.53 to 181.36; I^2=34%) between phosphate binders.[1] However, incidence of hypercalcemia was higher with calcium-containing binders.[1] Bone histology reports also did not differ between the groups.[1] According to the reviewers, there is insufficient evidence on the effect of phosphate binders on clinically relevant outcomes (bone fractures, bone deformities, bone pain, and reduced growth rates) in children with CKD.[1]

New Guidelines:

VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care

The Department of Veterans Affairs (VA) and the Department of Defense (DoD) Evidence-based Practice Working Group updated their 2008 guideline for the management of CKD in 2015.[2] In CKD, hyperphosphatemia can occur in patients with CKD (eg, when glomerular filtration rate (GFR) is reduced to less than 30-35 mL/min/1.73m^2).[2] The initial approach to manage hyperphosphatemia is dietary restriction of phosphorus-containing foods.[2] However, phosphate binders are approved by the U.S. Food and Drug Administration (FDA) to control serum phosphate levels in patients with CKD.[2] Oral phosphate binders are categorized as calcium-based (eg, calcium acetate) or non-calcium-based (e.g., sevelamer, lanthanum salts, iron-based binders).[2]

Use of these phosphate binders in patients with CKD has been evaluated in placebo-controlled and comparator clinical studies.[2] Outcomes consistently studied included changes in serum calcium, phosphate and PTH levels.[2] Some studies reported calcitriol levels and few studies reported bone mineral density or vascular calcification.[2] The Guideline Working Group found the evidence for phosphate binders in patients with CKD to have conflicting and inconsistent results.[2] There were conflicting results in regard to change in serum PTH or serum phosphate levels with use of lanthanum carbonate in patients with normal baseline serum phosphorous (mean <3.5 mg/dL).[2] Use of sevelamer did not result in significant changes in serum phosphorous, PTH, calcitriol or calcidiol or bone mineral

density after 40 weeks in patients with CKD with normal baseline phosphorous levels.[2] In patients with CKD and hyperphosphatemia, however, use of calcium acetate resulted in a 50% reduction in serum PTH levels and a significant decline in serum phosphate levels, but at the expense of significant incidence of hypercalcemia.[2] In a study that randomized patients with CKD 1:1:1 using calcium acetate, sevelamer and lanthanum versus placebo, there were not significant changes found in serum PTH levels with active therapy but there was a 21% increase in PTH levels of patients who received placebo.[2] Serum phosphate was significantly lower in patients who received lanthanum.[2] The calcium acetate group showed significant improvement in annualized bone density.[2] Patients on an active phosphate binder were more likely to have progression of coronary calcification compared to patients on placebo (38% vs. 17%; p=0.03).[2] Another study confirmed the beneficial effects of calcium acetate and sevelamer on serum phosphorus levels in CKD patients with hyperphosphatemia but both groups had a significant increase in serum PTH levels after only 8 weeks.[2]

The guideline does not recommend use of phosphate binders in patients with normal serum phosphorous levels based on insufficient evidence and possible increased risk of vascular calcification (weak recommendation against use).[2] However, oral phosphate binders may be considered in patients with CKD and hyperphosphatemia that do not respond to dietary interventions alone.[2]

New FDA Drug Approvals:
Auryxia® (ferric citrate) was approved September 2014 as a phosphate binder to control serum phosphorous levels in patients with CKD on dialysis.[3] The drug is evaluated separately in a new drug evaluation.

New Formulations/Indications:
Fosrenol® (lanthanum carbonate) oral powder for oral use was approved by the FDA in September 2014 based on pharmacokinetic studies.[4] The new formulation of lanthanum carbonate joins the chewable tablet formulation already marketed. Both formulations are indicated as phosphate binders to reduce serum phosphate in patients with CKD.[4]

New FDA Safety Alerts:
None identified.

References:

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2. The Management of Chronic Kidney Disease Working Group, Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care. Version 3.0; 2014. Available at http://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG.pdf. Accessed December 3, 2015.
3. Auryxia (ferric citrate) tablets [Prescribing Information]. New York, NY: Keryx Biopharmaceuticals, Inc., July 2015.
4. Fosrenol (lanthanum carbonate) oral powder [Prescribing Information]. Wayne, PA: Shire US Inc., September 2014.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	CALCIUM ACETATE	CALCIUM ACETATE	Y
ORAL	CAPSULE	PHOSLO	CALCIUM ACETATE	Y
ORAL	TABLET	CALCIUM ACETATE	CALCIUM ACETATE	Y
ORAL	TABLET	CALPHRON	CALCIUM ACETATE	Y
ORAL	TABLET	ELIPHOS	CALCIUM ACETATE	Y
ORAL	TABLET	RENAGEL	SEVELAMER HCL	Y
ORAL	POWD PACK	FOSRENOL	LANTHANUM CARBONATE	N
ORAL	POWD PACK	RENVELA	SEVELAMER CARBONATE	N
ORAL	SOLUTION	PHOSLYRA	CALCIUM ACETATE	N
ORAL	TAB CHEW	FOSRENOL	LANTHANUM CARBONATE	N
ORAL	TAB CHEW	VELPHORO	SUCROFERRIC OXYHYDROXIDE	N
ORAL	TABLET	AURYXIA	FERRIC CITRATE	N
ORAL	TABLET	MAGNEBIND 300	CALCIUM CARBONATE/MAG CARB	N
ORAL	TABLET	MAGNEBIND 400 RX	CALCIUM CARBONATE/MAG CARB/FA	N
ORAL	TABLET	RENVELA	SEVELAMER CARBONATE	N

Appendix 2: New Clinical Trials

A total of 44 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2015

1 calcium acetate.mp. 293
2 sevelamer.mp. 698
3 lanthanum carbonate.mp. 348
4 sucroferric oxyhydroxide.mp. 6
5 ferric citrate.mp. 653
6 1 or 2 or 3 or 4 or 5 1762
7 limit 6 to (english language and yr="2014 -Current" and (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 practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 44

Phosphate Binders

Goal(s):

- Promote use of preferred drugs.
- Reserve non-calcium-based phosphate binders for second-line therapy.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred phosphate binders
- Preferred non-calcium-based phosphate binders

Covered Alternatives:

- Preferred alternatives 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:** Go to #5
3. Has the patient tried or contraindicated to calcium acetate?	**Yes:** Document trial dates and/or intolerance and go to #4.	**No:** Pass to RPh. Deny for medical appropriateness. Recommend trial of preferred calcium acetate product.
4. Will the prescriber consider a change to a preferred non-calcium-based phosphate binder?	**Yes:** Approve for 1 year and inform presriber of preferred alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis. • If funded and clinic provides supporting literature, approve for up to 12 months. • If non-funded, deny (not funded by the OHP).		

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Drug Effectiveness Review Project Summary Report – ADHD

Date of Review: January 2016 **Date of Last Review:** January 2015

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

Research Questions:

1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness outcomes (ie, functional capacity as it relates to social, academic and occupational productivity; or quality of life for patients, family members, caregivers or teachers) or efficacy outcomes (symptom response assessing specific magnitude of improvement in scores on ADHD rating scales)?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (ie, tolerability, serious and long-term adverse events, and 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 (eg, tics, anxiety, substance use disorders, disruptive behavior disorders)?

Conclusions:

- 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). However, there is no difference in the proportion of patients with clinical improvement (Relative Risk [RR] 1.15; 95% CI, 0.93 to 1.43).
- 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 stimulant adverse effects are appetite loss, abdominal pain, headaches and sleep disturbance; there is only low quality evidence to suggest any differences in harms between the agents.
- 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.

Recommendations:

- No new evidence in the DERP report, or from the approval of a new chewable tablet formulation of extended-release methylphenidate (QuilliChew ER™), suggests changes should be made to the PDL based on clinical differences between agents. Review comparative drug costs in the executive session to inform PDL status of both stimulants and non-stimulants for ADHD.
- Streamline safety edits for ADHD agents by updating the current safety edit (**Appendix 2**). Remove modafinil and armodafinil from the safety edit since these drugs go through a separate prior authorization (PA) process (**Appendix 2**).

Previous Conclusions:

- New clinical evidence suggests no changes to the PDL are needed.

Previous Recommendations:

- No changes to the PDL made. No further review or research needed.

Methods:

The July 2015 Drug Class Review on Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for the ADHD drug class.

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

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

In addition, new approvals and safety alerts from the U.S. Food and Drug Administration (FDA) since the DERP report was published were identified.

Summary Findings:

A total of 1,022 citations were identified. The ADHD drugs eligible to be included in the DERP drug review are listed in Table 1. After excluding sources that did not meet criteria for inclusion, 15 publications, including 8 head-to-head trials in 12 publications and 3 observational studies, were included in the DERP drug review.

Table 1. Drugs for ADHD Included in DERP Review.

Generic Name	Trade Name	Formulation
Mixed amphetamine salts*	Adderall XR®	Extended-release oral capsule
Atomoxetine	Straterra®	Oral capsule
Clonidine	Catapres®, Catapres TTS®	Oral tablet
	Kapvay™	Extended-release oral tablet
Dexmethylphenidate HCl	Focalin®	Oral tablet
	Focalin XR®	Extended-release oral capsule
Dextroamphetamine sulfate	Dexedrine®	Oral tablet
	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine HCl	Intuniv®	Extended-release oral tablet
	Tenex™	Oral tablet
Lisdexamfetamine dimesylate	Vyvanse®	Oral capsule
Methamphetamine HCl	Desoxyn®	Oral tablet
Methylphenidate	Daytrana®	Extended-release transdermal film
Methylphenidate HCl	Concerta®	Extended-release oral tablet
	Metadate CD®	Extended-release oral capsule
	Metadate ER®	Extended-release oral tablet
	Methylin®	Oral chewable tablet and solution
	Quillivant™ XR	Extended-release oral suspension
	Ritalin®	Oral tablet
	Ritalin LA®	Extended-release oral capsule
	Ritalin-SR®	Extended-release oral tablet
Modafinil	Provigil®	Oral tablet
Armodafinil	Nuvigil®	Oral tablet

* Active ingredients = amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate

EFFICACY/EFFECTIVENESS AND SAFETY OF ADHD DRUGS

Young children (preschool age; 3-5 years)

- Comparative evidence was not found; placebo-controlled evidence had mixed efficacy outcomes.
- Adverse events occurred significantly more often with methylphenidate than with placebo. Over long-term treatment, some adverse events resolved but others did not.

Children (elementary school age; 6-12 years)

Stimulants

- Immediate-release vs. Extended-release Formulations
    - There was conflicting evidence that compared methylphenidate IR and methylphenidate ER OROS formulation. Two double-blind trials were unable to identify differences between the IR and OROS formulations and 2 open-label studies found the OROS formulation was associated with greater improvements in some, but not all, assessments.
    - Limited evidence was available to adequately compare IR and ER methylphenidate formulations. Overall, the studies were unable to identify differences between methylphenidate sustained-release (SR) and IR methylphenidate; and methylphenidate CD was non-inferior to IR methylphenidate.
    - Response to treatment was 18% higher in children who took lisdexamfetamine compared to children who took methylphenidate OROS. A greater improvement in the ADHD-RS scores at 7 weeks was also found with lisdexamfetamine, with a difference of 5.6 points. Parent rating scores were also better for lisdexamfetamine. Overall, adverse event rates did not differ between lisdexamfetamine and methylphenidate OROS: more children had anorexia, decreased appetite, decreased weight, insomnia and nausea with lisdexamfetamine; headaches and nasopharyngitis were more common with methylphenidate OROS.
- Sustained-release vs. Sustained-release Formulations
    - Limited evidence from 2 small crossover studies suggested that methylphenidate long-acting (LA) was superior to methylphenidate OROS on some, but not all efficacy outcomes.
    - Methylphenidate CD was superior to methylphenidate OROS in the morning, but inferior in the evening; both formulations were similarly effective in the afternoon. Methylphenidate OROS had statistically higher rates of insomnia and decreased appetite than methylphenidate CD.
    - Limited evidence indicates dexmethylphenidate extended-release (ER) resulted in a better response from 0.5 to up to 6 hours post-dose compared to methylphenidate OROS; however, methylphenidate OROS resulted in better scores later in the day, from 10 to 12 hours post-dose.
    - Limited evidence of no difference in response rates or symptom improvement was found between dexmethylphenidate ER and mixed amphetamine salts extended-release (XR) after 8 weeks.
    - Differences were not found between lisdexamfetamine and mixed amphetamine salts XR using the Swanson, Kotkin, Agler, M-Flynn, and Perlham Deportment Scale (SKAMP-DS) scores in a simulated classroom setting , or using the Clinical Global Impressions – Improvement (CGI-I) response rates after 1 week.
- Immediate-release vs. Immediate-release Formulations
    - Evidence clearly indicates no difference in efficacy between dextroamphetamine IR and methylphenidate IR, though weight loss may be greater with dextroamphetamine IR than with methylphenidate IR.
    - Mixed amphetamine salts IR were superior to methylphenidate IR on a few efficacy outcomes evaluated in 2 trials, but clear evidence of superiority is lacking.

    - No differences were found between modafinil and methylphenidate IR over 6 weeks.
    - Limited evidence suggests dextroamphetamine IR is superior to dextroamphetamine SR in the morning, and dextroamphetamine SR is superior to amphetamine salts in the afternoon. Transient weight loss was greater with mixed amphetamine salts and dextroamphetamine SR than with dextroamphetamine IR.
- Transdermal Methylphenidate vs. Methylphenidate OROS or Methylphenidate IR
    - Methylphenidate transdermal system has similar efficacy to methylphenidate OROS (over 7 weeks starting 4 hours after administration) and methylphenidate IR (over 12 hours in a simulated classroom setting, starting 30 minutes after dosing). No differences in adverse events were observed.

Nonstimulants

Atomoxetine

- Atomoxetine vs. Methylphenidate IR
    - Evidence from 2 trials suggests atomoxetine and methylphenidate IR result in similar efficacy.
- Atomoxetine vs. Methylphenidate OROS
    - Methylphenidate OROS had higher response rates; 56% methylphenidate OROS and 45% atomoxetine (p=0.02) and greater reduction in ADHD-RS scale scores after 4 to 6 weeks.
- Atomoxetine vs. Lisdexamfetamine
    - Lisdexamfetamine resulted in clinical improvement 9 days earlier and more patients had achieved clinical response (82% vs. 64%) than atomoxetine; similarly, lisdexamfetamine had greater change in the ADHD-RS score (difference -6.5) at 9 weeks than atomoxetine.
- Atomoxetine vs. Mixed Amphetamine Salts
    - Mixed amphetamine salts XR was found to be superior to atomoxetine on most measures of efficacy in a simulated classroom study.
- Atomoxetine was associated with significantly higher rates of vomiting, somnolence, nausea, and anorexia than stimulants, depending on the specific drug comparison. Incidence of vomiting (12-13%) was about 3-times greater than methylphenidate IR or mixed amphetamine salts XR. Incidence of somnolence (6-26%) was 3- to 4-times greater than methylphenidate OROS and mixed amphetamine salts XR. However, methylphenidate OROS and mixed amphetamine salts XR caused higher rates of insomnia than atomoxetine in 2 trials (7% atomoxetine, 13% methylphenidate OROS, 28% mixed amphetamine salts XR).

Clonidine

- Current evidence does not clearly identify a difference in improvement of ADHD symptoms between clonidine IR and methylphenidate IR (both with and without comorbid Tourette's disorder); however, these results should be interpreted with caution due to inconsistency in some outcomes.
- Clonidine IR resulted in higher rates of sedation (42%) than methylphenidate IR (14%), with 28% reporting the sedation to be moderate or severe.
- No head-to-head evidence is available on clonidine ER.

Guanfacine

- No head-to-head evidence was available on guanfacine IR.
- Guanfacine ER had superior reduction in ADHD-RS scores at 6 weeks compared with atomoxetine (difference of 5.1), but no difference in the proportion of patients who clinically improved (RR 1.15; 95% CI, 0.93 to 1.43) based on a single study. Adverse event rates did not differ.

Adolescents

- Methylphenidate OROS resulted in better simulated driving scores only in the late evening or nighttime than methylphenidate IR and mixed amphetamine salts.

Adults

- Four small short-term trials provide low-strength evidence of similar effects on ADHD symptoms after 2 to 6 weeks for the comparisons between dextroamphetamine IR and either modafinil or guanfacine, between continuing with methylphenidate IR or switching to methylphenidate OROS, or between IR and ER mixed amphetamine salts. Those same 4 trials provided low-strength evidence of no difference in harms, except for the comparison of IR and ER mixed amphetamine salts, for which there was insufficient evidence to draw conclusions on harms.

Long-term Safety

- Cardiovascular Deaths and Events
    - Two retrospective cohort studies in children provide low-strength evidence that there is no difference between methylphenidate or amphetamine products in the rate of emergency department visits for cardiac reasons or between methylphenidate, amphetamines or atomoxetine in sudden death or ventricular arrhythmia.
    - Two retrospective cohort studies in adults provide low-strength evidence of similar risk of stroke or transient ischemic attack (TIA) for atomoxetine compared with stimulants; similarly, one retrospective cohort provided low-strength evidence of similar risk of sudden cardiac death for atomoxetine compared with stimulants.
- Growth
    - There is moderate-strength evidence that dextroamphetamine IR was associated with more suppression of height and weight compared to methylphenidate IR within the first few years, but the differences resolved in later years. There is moderate-strength evidence that methylphenidate IR and mixed amphetamine salts had similar effects on height and weight at 3 years.
- Only low-strength evidence is available on difference between ADHD drugs on long-term insomnia, appetite suppression and headaches. No comparative evidence is available on long-term outcomes such as tics, seizures, cardiovascular events, injury frequency and hepatotoxicity.

ABUSE/MISUSE/DIVERSION

- 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.

SUBGROUPS

- No head-to-head evidence was found for demographic, socioeconomic, or co-intervention subgroups.
- In children with Tourette's disorder, methylphenidate IR and clonidine IR had similar effects on ADHD symptoms.

New Safety Alerts:
None identified.

New Formulations or Indications:
The U.S. Food and Drug Administration (FDA) approved a chewable tablet formulation of extended-release methylphenidate (QuilliChew ER™) for ADHD in children aged 6 years and older in December 2015. QuilliChew ER, at an optimized dose specific for each child, significantly improved attention and behavior compared to placebo in a blinded, controlled laboratory classroom study that involved 90 children aged 6 to 12 years who had a diagnosis of ADHD. At the end of the double-blind treatment period, raters and teachers evaluated the attention and behavior of the students throughout the day using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The SKAMP scale measures behaviors of ADHD using observations of the student's impairment in the classroom. SKAMP combined score is comprised of 13 items (including subscales: attention with items 1-4, deportment with items 5-8, quality of work with items 9-11 and compliance with items 12-13). The SKAMP composite score was obtained by summing up each item score where each item is rated on a 7-point impairment scale (0=normal to 6=maximal impairment) for a total possible combined score of 0 to 78; where higher score signified worst impairment. The combined SKAMP score, which was measured at 7 time points on the last day of the pre-determined treatment period, was used to assess the primary and secondary efficacy endpoints. The primary efficacy endpoint was the average treatment effect across all time points on the last day of the treatment period. QuilliChew ER was statistically significantly superior to placebo with respect to the primary endpoint by a difference of -7.0 points (95% CI, -10.9 to -3.1).
[Ref: Quillichew ER™ (methylphenidate hydrochloride extended-release) [product information]. Monmouth Junction, NJ: Tris Pharma, Inc., December 2015]

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	TRADE NAME	GENERIC NAME	PDL
ORAL	TABLET	EVEKEO	AMPHETAMINE SULFATE	Y
ORAL	CAPSULE	STRATTERA	ATOMOXETINE HCL	Y
ORAL	TABLET	FOCALIN	DEXMETHYLPHENIDATE HCL	Y
ORAL	CPBP 50-50	FOCALIN XR	DEXMETHYLPHENIDATE HCL	Y
ORAL	CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	DEXMETHYLPHENIDATE HCL	Y
ORAL	TABLET	ADDERALL	DEXTROAMPHETAMINE/AMPHETAMINE	Y
ORAL	TABLET	AMPHETAMINE SALT COMBO	DEXTROAMPHETAMINE/AMPHETAMINE	Y
ORAL	CAPSULE	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	Y
ORAL	CPBP 30-70	METADATE CD	METHYLPHENIDATE HCL	Y
ORAL	TABLET	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	Y
ORAL	TABLET	RITALIN	METHYLPHENIDATE HCL	Y
TRANSDERM	PATCH TD24	DAYTRANA	METHYLPHENIDATE	Y

ORAL	TABLET	NUVIGIL	ARMODAFINIL	**V**
ORAL	TAB ER 12H	CLONIDINE HCL ER	CLONIDINE HCL	**V**
ORAL	TAB ER 12H	KAPVAY	CLONIDINE HCL	**V**
ORAL	TAB ER 24H	GUANFACINE HCL ER	GUANFACINE HCL	**V**
ORAL	TAB ER 24H	INTUNIV	GUANFACINE HCL	**V**
ORAL	TABLET	MODAFINIL	MODAFINIL	**V**
ORAL	TABLET	PROVIGIL	MODAFINIL	**V**
ORAL	TABLET	EVEKEO	AMPHETAMINE SULFATE	N
ORAL	CAPSULE ER	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
ORAL	CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	DEXTROAMPHETAMINE SULFATE	N
ORAL	TABLET	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
ORAL	SOLUTION	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
ORAL	SOLUTION	PROCENTRA	DEXTROAMPHETAMINE SULFATE	N
ORAL	TABLET	ZENZEDI	DEXTROAMPHETAMINE SULFATE	N
ORAL	CAP ER 24H	ADDERALL XR	DEXTROAMPHETAMINE/AMPHETAMINE	N
ORAL	CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	DEXTROAMPHETAMINE/AMPHETAMINE	N
ORAL	TABLET	DEXMETHYLPHENIDATE HCL	DEXMETHYLPHENIDATE HCL	N
ORAL	TABLET	METHAMPHETAMINE HCL	METHAMPHETAMINE HCL	N
ORAL	TABLET	DESOXYN	METHAMPHETAMINE HCL	N
ORAL	CPBP 30-70	METHYLPHENIDATE HCL CD	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	METHYLPHENIDATE LA	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	N
ORAL	SOLUTION	METHYLIN	METHYLPHENIDATE HCL	N
ORAL	SOLUTION	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
ORAL	SU ER RC24	QUILLIVANT XR	METHYLPHENIDATE HCL	N
ORAL	TAB CHEW	METHYLIN	METHYLPHENIDATE HCL	N
ORAL	TAB CHEW	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
ORAL	TAB ER 24	CONCERTA	METHYLPHENIDATE HCL	N
ORAL	TAB ER 24	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	TABLET ER	METADATE ER	METHYLPHENIDATE HCL	N
ORAL	TABLET ER	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	

Appendix 2: Prior Authorization Criteria

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)
- Excludes modafinil and armodafinil products, which require separate prior authorization (see PA for modafinil / armodafinil.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

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

	STIMULANTS		NON-STIMULANTS		
Indication	**Methylphenidate and derivatives**	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years~~, except methyphenidate IR approved for age ≥4 years~~	Age ≥36 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
~~**Drug-Induced Sedation**~~	~~Age ≥6 years~~	~~Age ≥6 years~~	~~Not approved~~	~~Not approved~~	~~Not approved~~
~~**Obstructive Sleep Apnea**~~	~~Not approved~~	~~Not approved~~	~~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		60 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		30 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg ~~or 2 mg/kg/day if age <18 yrs~~
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine~~Dextroamphetamine~~ IR	6		40 mg ~~or 0.5 mg/kg/ day if age <18 yrs~~
CNS Stimulant	dextroamphetamine LA	6		60 mg
~~CNS Stimulant~~	~~dextroamphetamine/amphetamine~~	~~6~~		~~60 mg or 0.5 mg/kg/ day if age <18 yrs~~
CNS Stimulant	lisdexamfetamine	6		70 mg ~~or 0.5 mg/kg/ day if age <18 yrs~~
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate ~~immediate release~~IR	4		~~90~~60 mg ~~or 2 mg/kg/ day if age <18 yrs~~
CNS Stimulant	methylphenidate ~~sustained release~~LA	6		~~90~~72 mg ~~or 2 mg/kg/ day if age <18 yrs~~
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine~~Clonidine~~ LA	6	17	0.4 mg
Non-Stimulant	guanfacine~~Guanfacine~~ LA	6	17	4 mg
~~Non-Traditional Stimulant~~	~~armodafinil~~	~~18~~		~~250 mg~~
~~Non-Traditional Stimulant~~	~~modafinil~~	~~18~~		~~200 mg~~

Key: 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 (ER or IR) + Guanfacine ER 1 -CNS Stimulant Formulation (ER or IR) + Clonidine ER
Age ≥18 years**	Combination therapy not recommended

* 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.

Approval Criteria		
3. Is the requested drug preferred on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs do not require co-pay and 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:** ~~Pass to RPh. Deny for medical appropriateness.~~ ~~May approve continuation of existing therapy once up to 90 days to allow time to appeal.~~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 adjunctive combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9

Approval Criteria		
~~7.~~9. ~~Is the request from a psychiatrist or w~~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~~Go to #7~~	**No:** Pass to RPh. Deny for 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.~~**No:** Go To #8~~
~~8. Are all CNS stimulants that the client is to be on prescribed by or in consultation with the same psychiatrist or specialist?~~	~~**Yes:** Approve 12 months~~	~~**No:** Pass to RPH. Confirm that the requesting specialist approves of the full regimen or deny for medical appropriateness.~~
~~9. Are the age and the dose within the limits in Table 2? Note: For children under 18, the maximum dose for some medications may require a recent weight.~~	~~**Yes:** Go To #9~~	~~**No:** Pass to RPH. Deny for medical appropriateness. Doses exceeding defined limits are only approved when prescribed by a psychiatrist or in consultation with a psychiatrist. May approve continuation of existing therapy once up to 90 days to allow time to schedule appointment with a psychiatrist.~~
~~10. Is the requested agent the only ADHD treatment that has been filled within the last 30 days?~~	~~**Yes:** Approve 12 months~~	~~**No:** Go To #10~~

Approval Criteria		
~~11. Have all other recent ADHD medications been discontinued or are they in the process of being discontinued / tapered?~~	~~**Yes:** Approve 12 months~~	~~**No:** Go To #11~~
~~12. Is the request for a single short acting CNS stimulant and a single long acting CNS stimulant?~~	~~**Yes:** Approve 12 months~~	~~**No:** Pass to RPH. Deny for medical appropriateness.~~ ~~Non-standard polypharmacy regimens are only approved when prescribed by a psychiatrist or in consultation with a psychiatrist.~~ ~~May approve continuation of existing therapy once up to 90 days to allow time to schedule appointment with a psychiatrist.~~

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

Modafinil / Armodafinil

Goal(s):

- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit OR doses above those in Table 2.

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD10 G47411; G47419; G4730; G4731; G4733; G4739)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)
Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
Depression augmentation (unipolar or bipolar)	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Cancer-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Drug-related fatigue	Not FDA approved; insufficient evidence	Not FDA approved;
Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome)	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

ADHD	Not FDA approved; Insufficient evidence	Not FDA approved; insufficient evidence
Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum Daily Dose
armodafinil	18 years	250 mg
modafinil	18 years	200 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a funded diagnosis? Non-funded diagnoses: - Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) - Unspecified hypersomnia (ICD10 G4710)	Yes: Go to #3	No: Pass to RPh; Deny, not funded by OHP
3. Will prescriber consider a preferred alternative?	Yes: Inform prescriber of options (eg, preferred methylphenidate)	No: Go to #4
4. Is the request for continuation of current therapy?	Yes: Pass to RPh; Go to #12	No: Go to #5
5. Is the prescribed daily dose higher than recommended in Table 2?	Yes: Pass to RPh; Deny for medical appropriateness.	No: Go to #6
6. Is diagnosis narcolepsy or obstructive sleep apnea (ICD10 G47411; G47419; G4730; G4731; G4733; G4739) AND is the drug prescribed by, or in consultation with, a sleep specialist or neurologist?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #7

Approval Criteria		
7. Is the request for armodafinil?	Yes: Pass to RPh; Deny for medical appropriateness. There is insufficient evidence for any off-label use.	No: Go to #8
8. Is the diagnosis unipolar or bipolar depression?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #9
9. Is the diagnosis MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	Yes: Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #10
10. Is the diagnosis ADHD?	Yes: Pass to RPh; Deny for medical appropriateness. There is insufficient evidence for benefit for ADHD. See available options at www.orpdl.org/drugs/	No: Go to #11
11. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness or fatigue as a result of other conditions is currently insufficient and should be denied for "medical appropriateness". • Evidence to support cognition enhancement is insufficient and should be denied for "medical appropriateness". If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Approval Criteria

12. Continuation of therapy requires submission of documented evidence of clinical benefit and tolerability (faxed copy or equivalent). The same clinical measure (eg, Epworth score, Brief Fatigue Inventory, or other validated measure) used to diagnose fatigue or depression is recommended to document clinical benefit.

    - Approve up to 12 months with chart documentation of positive response.
    - Deny for “medical appropriateness” in absence of documented benefit.

P&T / DUR Review: *01/16; 09/15 (kk)*
Implementation: *10/15*

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Class Update: Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors

Date of Review: January 2016 **Date of Last Review:** September 2015

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

Purpose for Class Update:
The sodium-glucose cotransporter 2 (SGLT2) inhibitor class was updated in September as part of the non-insulin antidiabetic agent class review. However, new evidence on the cardiovascular (CV) effects of the SGLT2 inhibitor empagliflozin has become available. The goal of this review is to evaluate updated evidence for SGLT2 inhibitors and determine if changes related to current prior authorization (PA) criteria the Oregon Health Plan (OHP) Preferred Drug List (PDL) are needed.

Research Questions:
1. Is there any new comparative evidence for SGLT2 inhibitors pertaining to CV benefits or other clinically relevant outcomes (e.g. microvascular, macrovascular and mortality outcomes)?
2. Is there any new evidence of comparative harms between SGLT2 inhibitors and other non-insulin antidiabetic treatments?
3. Are there subgroups of patients with type 2 diabetes (T2DM) in which SGLT2 inhibitors may be more effective or associated with less harm?

Conclusions:
- One randomized controlled trial and two Food and Drug Administration (FDA) safety updates have been published since the last review. There are no new systematic reviews or guidelines.[1,2]
- In patients with a history of CV disease, there was moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) decreased the primary composite CV endpoint of 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; P<0.001 for noninferiority; P=0.04 for superiority).[1] Reduction in the primary endpoint was driven by a statistically significant reduction in CV death.[1] There were no statistically significant differences between empagliflozin and placebo in incidence of non-fatal MI or non-fatal stroke.[1]
- Statistically significant reductions due to death from any cause favored empagliflozin over placebo (8.3% vs. 5.7%) (HR 0.68; 95% CI, 0.57 to 0.82; P<0.001).[1]
- Empagliflozin reduced death related to CV causes compared to placebo (5.9% vs. 3.7% [HR 0.62; 95% CI, 0.49 to 0.77]; P<0.001).[1]
- The CV benefit may be from the diuretic effect of empagliflozin. This theory is supported by the reduction in hospitalizations related to heart failure found in the empagliflozin group compared to placebo (4.1% vs. 2.7% [HR 0.65; 95% CI, 0.50 to 0.85]; P=0.002).[1]
- No dose-response with empagliflozin was found; therefore, the 10 mg dose is recommended for most patients. Seventy-eight percent of patients were on additional antidiabetic therapy, the most common drugs being metformin (74%), insulin (48%) and sulfonylureas (43%).[1]

- Empagliflozin is the first diabetes drug to demonstrate reduction in CV events in an adequately powered randomized controlled trail (RCT); however, it is unknown if the risk reduction would also be seen in T2DM patients *without* preexisting CV disease. A systematic review and meta-analysis of dapagliflozin and canagliflozin studies demonstrated inconclusive findings on the effect of SGLT2 inhibitors on CV outcomes (OR 0.89; 95% CI, 0.70 to 1.14).[4] Results from ongoing studies with canagliflozin and dapagliflozin will help to determine if the benefits seen with empagliflozin is a class effect of SGLT2 inhibitors or if it is unique to empagliflozin.[5,6]
- There was a nonsignificant increase in the rate of nonfatal strokes in empagliflozin-treated patients, which warrants further investigation.[1] An FDA analysis reported higher incidence of nonfatal stroke with canagliflozin, another SGLT2 inhibitor, compared to controls (HR 1.46; 95% CI 0.83 to 2.58).[4] Canagliflozin has also been associated with increased rates of bone fractures. The long-term effect of SGLT2 inhibitors on bone density is still unknown.[2]
- There is high strength evidence that genital mycotic infections are more common with SGLT2 inhibitors in both females and males, which was again seen in the latest empagliflozin trial with an incidence of 6.4% compared to 1.8% for placebo ($p<0.001$).[1,4]
- SGLT2 inhibitors are considered one of many reasonable second-line treatment options for T2DM by the American Diabetes Association (ADA).[7] The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommends them as an option for patients presenting with all levels of A1C.[8,9] However, these recommendations are largely guided by opinions of the guideline writers. The National Institute for Health and Care Excellence (NICE), which also factors in cost-effectiveness, recommends empagliflozin or canagliflozin as a third-line option in patients already taking metformin and a SU, unless a sulfonylurea (SU) is contraindicated.[10,11]

Recommendations:

- Modify current PA criteria to allow use of SGLT2 inhibitors as a third-line option with metformin and sulfonylureas (Appendix 4).
- No changes to the PDL are recommended until results of post-marketing trials of canagliflozin and dapagliflozin are available.

Previous Conclusions:

- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for type 2 diabetes mellitus (T2DM).[12] Evidence-based recommendations in new clinical practice guidelines from the American Diabetes Association (ADA), Institute for Clinical Systems Improvement (ICIS), and the National Institute for Health and Care Excellence (NICE), American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) and a systematic review draft report from the Agency for Healthcare Research and Quality (AHRQ), support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL).[12]
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a dipeptidyl peptidase-4 (DPP-4) inhibitor, or metformin plus a SGLT-2 inhibitor have similar rates of all-cause mortality, based on one systematic review.[12]
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of A1C based on one systematic review.[12]
- 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).[12]
- 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.[12] Data from the EXAMINE and TECOS found these drugs to be non-inferior to placebo when a composite of CV outcomes were evaluated.[12]

- Moderate quality evidence from two meta-analyses showed a statistically significant increase in HF outcomes with DPP-4 inhibitors compared to placebo or active treatment.[12] Studies included in the meta-analyses were of short duration and the majority of included outcomes were limited to 2 trials only [SAVORTIMI53 (saxagliptin) and EXAMINE (alogliptin)].[12]
- High quality evidence suggest hypoglycemia rates are higher with SU than comparative T2DM therapy based on two systematic reviews.[12]
- 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).[12]
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease based on one systematic review. Evidence from this review suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m2) without increased risk of lactic acidosis, based on evidence from primarily non-clinical trial data. The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.[12]
- In December of 2014 liraglutide injection (Saxenda) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity. Treatments for weight loss are not funded by the OHP.[12]

Previous Recommendations:
- Make exenatide (Byetta®) a preferred agent but subject to current prior authorization (PA) for GLP1 receptor antagonists.
- Make empagliflozin/linagliptin (Glyxambi®) non-preferred drug subject to current PA for SGLT-2 inhibitors.
- Reorganize PDL classes for non-insulin antidiabetic agents to the following:
    - DPP-4 Inhibitors
    - GLP-1 Receptor Antagonists
    - Miscellaneous Antidiabetic Agents (metformin, pramlintide, meglitinides, others).
    - SGLT-2 Inhibitors
    - Sulfonylureas
    - Thiazolidinediones
- Remove clinical PA for pramlintide due to low overall utilization and current FDA-mandated Risk Evaluation Mitigation Strategy (REMS) already in place to promote safe use through education.
- Modify SGLT-2 inhibitor clinical PA to require monitoring renal function every 6 months.
- Continue clinical PA criteria for all DPP-4 inhibitors and all GLP-1 RAs.

Background:
SGLT2 inhibitors are the newest class of antidiabetic agents for patients with T2DM. SGLT2 inhibitors increase urinary glucose excretion by decreasing renal absorption of glucose.[13] Because of their mechanism of action, SGLT2 inhibitors pose low risk for hypoglycemia but increase the likelihood of urinary tract and genital infections. Additional benefits of SGLT2 inhibitors are weight loss and reduced blood pressure, likely through their diuretic effect. SGLT2 inhibitors are associated with modest A1C lowering of approximately 0.5% in placebo-controlled comparisons.[14] There are currently three SGLT2 inhibitors available, offered as monotherapy or in combination formulations with metformin: canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance).

Cardiovascular disease is the primary complication in patients with diabetes mellitus (DM).[15] It is well documented that lowering A1C is associated with reduced microvascular outcomes, however the evidence for macrovascular benefits are uncertain. Additionally, some antidiabetic therapies have been associated with additional CV risk, prompting the FDA to require studies to evaluate the impact of new antidiabetic therapies on CV outcomes. Evidence suggests metformin is likely to reduce the incidence of CVD based on data from the United Kingdom Prospective Diabetes Study (UKPDS).[7] The TECOS trial (DPP-4 inhibitors) and ELIXA study (GLP-1 agonists) have shown a neutral impact on CV markers.[16,17] This review will focus on the recent evidence on the benefits of empagliflozin on CV outcomes. Two additional trials are underway with canagliflozin (CANVAS) and dapagliflozin (DECLARE) to determine the CV impact of these therapies.[5,6] These studies will provide valuable evidence on how to best manage the increased risk of CV disease seen in patients with T2DM.

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.

New Systematic Reviews:
No new systematic reviews identified.

New Guidelines:
No new guidelines identified.

New Safety Alerts:
In September 2015, the Food and Drug Administration (FDA) released a warning of an increased risk of bone fractures and decreased bone mineral density associated with the use of canagliflozin, also a SGLT2 inhibitor.[2] It is unknown if this is a class effect and the FDA is continuing to evaluate if other SGLT2 inhibitors convey this same risk.

The FDA released a drug safety communication in December 2015 on labeling changes for the SGLT2 inhibitor class for the risk of ketoacidosis and serious urinary tract infections, potentially leading to hospitalizations. Postmarketing studies are being required from the manufacturers of the SGLT2 inhibitors to gain additional clarity on the risk.[3]

New Formulations or Indications:
No new formulations.

Randomized Controlled Trials:
Twenty-three citations were manually reviewed from the literature search. After further review, 22 trials were excluded because of wrong study design (observational), comparator (placebo), outcome studied (non-clinical) or outside the search dates. The remaining trial is described below. The full abstract is included in **Appendix 2**.

The CV effects and mortality associated with empagliflozin treatment was studied in double-blind, randomized, placebo controlled trial.[1] Adult patients (n=7020) with T2DM were randomized to receive a daily dose of empagliflozin 10 mg, empagliflozin 25 mg or placebo and were followed for a median 3.1 years. The median treatment duration was 2.6 years. Patients were a mean age of 63 years old, predominately male (71%), white (72%) and had a prior history of CV disease. The most common CV risk factor was coronary artery disease (CAD) (75%) followed by multi-vessel CAD (47%) and history of MI (47%). Baseline A1C levels were 8.07%. Background antidiabetic therapies were allowed.[1] Metformin, insulin and sulfonylureas were most commonly used with similar rates across all treatment groups. Angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARBs) were used by 81% of patients. Twenty-six percent of patients had moderate renal insufficiency (<60 mL/min/1.73m^2).[1] The primary composite outcome was death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome plus hospitalization for unstable angina was a key secondary outcome.

Patients were analyzed using a modified intention-to-treat analysis of pooled empagliflozin data versus placebo.[1] The noninferiority threshold for the primary outcome comparison between empagliflozin and placebo was set at a margin of 1.3 for the hazard ratio. A two-sided P value of 0.0498, or less, was used for statistical significance and the confidence interval (CI) was calculated at 95.02% for the primary outcome.

Empagliflozin (pooled data from both doses) was found to significantly lower the incidence of the composite primary outcome compared to placebo (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99; p<0.001 for noninferiority and p=0.04 for superiority).[1] Empagliflozin was noninferior, but not statistically superior, to placebo for the key secondary composite outcome, which was the primary composite outcome plus hospitalizations for unstable angina (12.8% vs 14.4%, respectively (HR 0.89; 95% CI, 0.78 to 1.01; p<0.001 for noninferiority and p=0.08 for superiority)). When individual endpoints were analyzed, patients on empagliflozin had statistically significant lower incidence of death from CV causes, all-cause mortality, and hospitalizations for heart failure (Table 1). Rates of MI and fatal or nonfatal stroke were similar between both groups.[1]

Fatal or nonfatal stroke rates were higher with empagliflozin compared to placebo (HR 1.18; 95% CI, 0.89 to 1.56; p=0.26). Empagliflozin was also associated with an increased risk of nonfatal stroke (HR 1.24; 95% CI, 0.92 to 1.67; p=0.16) There was no significant difference in CV outcomes between the empagliflozin 10 mg and empagliflozin 25 mg doses. Differences is A1C reduction between the 10 mg and 25 mg doses and placebo were also similar (-0.54% [95% CI, -0.58 to -0.49] in the 10 mg group and -0.60% [95% CI, -0.64 to -0.55] in the 25 mg group).[1] However, by week 206 the difference had decreased to -0.24% for empagliflozin 10 mg and -0.36% for empagliflozin 25 mg, compared to placebo. Changes in CV risk factors with empagliflozin compared to placebo include reductions in the following; small changes in weight, waist circumference, uric acid levels, and systolic and diastolic blood pressure. Small increases in LDL and HDL cholesterol were seen with empagliflozin in comparison to placebo.[1] There was no substantial difference in A1C lowering between empagliflozin 10 mg and empagliflozin 25 mg, suggesting treatment with the 10 mg dose to be adequate for most patients.

Adverse events leading to discontinuation were lower in the pooled empagliflozin group compared to placebo, 17.3% and 19.4%, respectively.[1] Genital infections were the most common adverse effect associated with empagliflozin treatment, which occurred at a significantly higher rate than placebo (6.4% vs, 1.8%,

respectively (p<0.001). Hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, symptoms of volume depletion and electrolyte changes were similar between empagliflozin and placebo.[1]

Table 1. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	N	Outcomes	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Zinman, et al (EMPA-REG OUTCOME)[1] RCT, DB, DD, PG, Phase 3	1. Empagliflozin 10 mg (E10) 2. Empagliflozin 25 mg (E25) 3. Placebo (P) Study duration: 3.1 years	Demographics (mean): Age: 63 years Male: 71% White: 72% Diabetes diagnosis >10 years: 57% A1C: 8.1% Key Inclusion Criteria: ● T2DM ● ≥ 18 years of age • Body max index of ≤45 • eGFR ≥30 ml/min/1.73m^2 • Established CVD • A1C 7-9% on no glucose lowering therapy or A1C of 7-10% on 12 weeks of a stable dose of glucose-lowering therapy* Key Exclusion Criteria:	ITT: 1. 2345 2. 2342 3. 2333 PP: 1. 1790 2. 1800 3. 1650 Attrition: 1. 555 (24%) 2. 542 (23%) 3. 683 (29%)	Primary Outcome: **Composite of CV death, non-fatal MI, or non-fatal stroke):** E*: 490 (10.5%) vs. P: 282 (12.1%); HR 0.86 (95.04% CI, 0.74 to 0.99; P<0.001 for noninferiority and p=0.04 for superiority) Secondary Outcomes: **Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization from unstable angina):** E*: 599 (12.8%) vs. P: 333 (14.3%); HR 0.89 (95.04% CI, 0.78 to 1.01; P<0.001 for noninferiority and p=0.08 for superiority) **Hospital admission for HF:** E*: 126 (2.7%) vs. P: 95 (4.1%); HR 0.65 (95% CI, 0.50 to 0.85; P=0.002) **CV mortality:** E*: 172 (3.7%) vs. P: 137 (5.9%); HR 0.62 (95% CI, 0.49 to 0.77; P<0.001) **All-cause mortality:**	6/63 NS 1.4/71 2.2/45	**D/C due to AE:** E*: 813 (17.3%) vs. P: 453 (19.4%); P<0.01 **Any hypoglycemia:** E*: 1303 (27.8%) vs. P: 650 (27.9%); P-value not given **Genital infections:** E*: 301 (6.4%) vs. P: 42 (1.8%); P<0.001	2/48 NA 5/20	**Risk of Bias (low/high/unclear)**: Selection bias (low): Randomization was done via a computer-generated random-sequence and interactive voice- and Web- response system. Performance bias (low): Trial was double-blind design with medication concealment using double-dummy design. Detection bias (low): Outcome assessors were blinded to randomization treatment assignments. Outcomes were adjudicated by clinical-events committees. Attrition bias (low): Overall attrition was 25%. mITT analysis with LOCF was used for all data. Reporting bias (low): Study protocol was followed and outcomes were reported as specified. **Applicability**: Patients: Patients were well matched. Ninety-nine percent of patients had a history of cardiovascular disease. Intervention: Pooled doses of empagliflozin 10 mg and empagliflozin 25 mg was appropriate due to the low incidence of expected events for the primary outcome. Comparator: Matched placebo is an appropriate comparator. Outcomes: 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

		• eGFR < 30 ml/min/1.73 m^2 • Liver disease • Surgery • Cancer * Glucose lowering treatment at baseline: - metformin (73.8%) - Insulin (48.0%) - sulfonylureas (43.0%)		E*: 269 (5.7%) vs. P: 194 (8.3%); HR 0.68 (95% CI, 0.57 to 0.82; P<0.001) **Fatal or nonfatal stroke:** E*: 164 (3.5%) vs. P: 69 (3.0%); HR 1.18 (95% CI, 0.89 to 1.56; P=0.26) **Nonfatal stroke:** E*: 150 (3.2%) vs. P: 60 (2.6%); HR 1.24 (95% CI, 0.92 to 1.67; P=0.16) **Fatal or nonfatal MI:** E*: 223 (4.8%) vs. P: 126 (5.4%); HR 0.87 (95% CI, 0.70 to 1.09; P=0.23) E*= Pooled data for 10 mg and 25 mg doses.	2.6/39 NS NS NS			risk. In this study, empagliflozin was shown to reduce cardiovascular outcomes including death and all-cause mortality. Setting: Forty-two countries and 590 outpatient centers.
Abbreviations [alphabetical order]: A1C = hemoglobin A1C; ACE = angiotensin converting enzyme; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DB = double-blind; D/C = discontinuations; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; PP = per protocol								

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Appendix 1: Current Status on Preferred Drug List

Diabetes, Sodium-Glucose Co-Transporter Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	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

Appendix 2: Abstracts of Clinical Trial

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Sep 17. [Epub ahead of print].

The effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known. Methods We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina. Results A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events. Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to October Week 4 2015

Search Strategy:

#	Searches	Results
1	sodium glucose cotransporter-2 inhibitor.mp.	58
2	limit 1 to (english language and humans and yr="2015 -Current")	5
3	dapagliflozin.mp.	174
4	canagliflozin.mp.	148
5	empagliflozin.mp.	95
6	2 or 3 or 4 or 5	359
7	limit 6 to (english language and yr="2015 -Current")	43
8	limit 7 to (clinical trial, all or clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	23

Appendix 4: Prior Authorization Criteria

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

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

Length of Authorization:
- Up to 12 months

Requires PA:
- All 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, have contraindications to these treatments or is requesting a SGLT-2 inhibitor to be used with metformin and a sulfonylurea? (document contraindication, if any)	Yes: Go to #5	No: Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

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

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: *1/16 ;9/15; 1/15; 9/14; 9/13*
Implementation: *TBD; 2/15*

Abbreviated Drug Review

Drug Product		
Cholbam® (cholic acid) capsule (oral)	Claims: 0	Wholesale Acquisition Cost: $49,650/month for 20 kg patient [based on 50 mg (#90): $24,825]

Indications

- **Bile acid synthesis disorders**: Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs)
- **Peroxisomal disorders**: Adjunctive treatment of peroxisomal disorders (PDs), including Zellweger spectrum disorders, in patients who exhibit manifestations of hepatic disease, steatorrhea, or complications from decreased fat soluble vitamin absorption.

Dosage

- 10-15 mg/kg/day in 1 or 2 divided doses
- Children 3 weeks of age or older and adults

Background

- Bile acid synthesis is complex requiring at least 17 enzymes.
- Cholic acid is an endogenous bile acid synthesized in the liver facilitates fat absorption, absorption of fat-soluble vitamins, and enhances bile flows.
- Disorders of bile acid synthesis are rare and clinical severity is variable. These disorders can be primary or secondary:
  - SEDs are primary enzyme defects involved in the synthesis of cholic acid and other primary bile acids.
  - PDs are secondary metabolic defects that impact primary bile acid synthesis.
- Impaired bile acid synthesis is associated with insufficient bile acid secretion from the hepatocyte, which results in accumulation of intermediate hepatotoxic bile acids. Accumulation may lead to cholestasis, bile acid plugs, giant cell hepatitis and cirrhosis, or death.

Efficacy

- The primary study is an unpublished, non-randomized, open-label, non-controlled, compassionate-use study (average duration 145 weeks).
- Supplemental data are from a post-hoc subgroup analysis of responders, an extension study, and case series reports.
- Data were evaluated for 50 patients with bile acid synthesis disorders and 29 patients with peroxisomal disorders.
- Blood and urine samples were monitored every 3-6 months; liver biopsy was performed in some patients every 6 months.
- A patient was consider a "Responder" to treatment if they were alive at last follow-up, and
  - **a)** met ≥2 lab criteria; or **b)** met ≥1 lab criterion and had increased body weight by 10% or stable at >50th percentile
- SED: 62% responders; 22% non-responders; 16% data not available
- PD: 0% responders; 76% non-responders; 24% data not available
  - (modified "Responder" criteria that removed lab criteria showed 2/29 patients responded)

Laboratory Criteria

- ALT/AST reduced to <50 U/L, or baseline level reduced by 80%
- Total bilirubin reduced to ≤1 mg/dL
- No evidence of cholestasis on liver biopsy

Safety

- Gastrointestinal: exacerbation of cholestasis (≤14%)
- Hepatic: increased serum bilirubin (≤14%); increased serum transaminases (≤14%)

Evidence Gaps/Limitations

The safety and effectiveness of cholic acid on *extrahepatic manifestations* of bile acid synthesis disorders due to SEDs or PDs, including Zellweger spectrum disorders, have not been established.

Recommendation

Refer claims to DMAP Medical Director through Prior Authorization.

References

- Center for Drug Evaluation and Research. Medical Review: Application number 205750Orig1s000 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed May 23, 2015.
- Cholbam (cholic acid) [prescribing information]. Baltimore, MD: Asklepion Pharmaceuticals; March 2015.

Abbreviated Drug Review

Drug Product

Viberzi® (**eluxadoline**) tablet (oral)	Indication not funded

Indications

- **Irritable Bowel Syndrome with diarrhea (IBS-D)**

Dosage

• Adults: 100 mg orally twice daily with food	• Dose Adjustment: 75 mg twice daily in patients without a gallbladder, are unable to tolerate 100 mg dose, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment

Background

- IBS associated with recurrent painful abdominal distress with constipation, diarrhea, or both.
- Management typically consists of lifestyle and dietary modifications with or without adjunctive pharmacotherapy.
- Mu-opioid receptor agonism/delta-receptor antagonism thought to treat IBS-D with limited effects on constipation

Efficacy

- Two phase 3 double-blind, RCTs in IBS-D patients
- Both Studies demonstrated statistically significant difference in percent reduction of the composite endpoint compared to placebo at 12 weeks:
  - Study 1: **8%** (95% CI, 2.6 to 13.5; p<0.01; n=1280)
  - Study 2: **13%** (95% CI, 7.5 to 19.2; p<0.001; n=1145)

Composite Primary Endpoint:

- ≥30% improvement of worst abdominal pain score in past 24 hrs compared to the baseline weekly average
- Reduction in the Bristol Stool Score (BSS) to <5
  or the absence of a bowel movement if accompanied with ≥30% improvement as detailed above

Safety

Common adverse reactions: • Constipation and nausea (8% each); abdominal pain (7%). • Nine cases of pancreatitis observed, which resolved with discontinuation.	**Contraindication**: History of biliary duct obstruction or sphincter of Oddi disease. **Avoid use:** History of pancreatitis, severe liver impairment, severe constipation, or in patients who drink >3 alcoholic beverages per day.

Evidence Gaps/Limitations

No additional studies found to support evidence for use in the treatment of other Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Viberzi (eluxadoline) [Prescribing Information]. Cincinnati, OH; Patheon Pharmaceuticals, Inc. May 2015.
2. FDA Center for Drug Evaluation and Research Summary Review. Available at:http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206940Orig1s000SumR.pdf. Accessed November 24, 2015.

Abbreviated Drug Review

Drug Product	
Addyi® (**flibanserin**) tablet (oral)	Indication not funded

Indication

- **Hypoactive Sexual Desire Disorder** (HSDD)**:** to be used in premenopausal women with low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance.

Dosage

- 100 mg orally taken daily at bedtime

Background

Flibanserin is thought to balance neurotransmission and enhance sexual excitement through activating dopamine and norepinephrine receptors and mixed effect on serotonin receptor activity (5-HT_{1A}agonism/5-HT_{2A}antagonism).

Efficacy

- Three 24-week, randomized, double-blind, placebo controlled trials (n=2375)
- Subjects were pre-menopausal women with HSDD for ≥6 months
- First 2 trials failed to show statistically significant difference in co-primary sexual desire endpoint
- First two trials met secondary endpoint goals for female sexual desire and distress related to desire
- Third trial used FSFI desire domain as the pre-specified co-primary endpoint which showed statistically significant improvement over placebo: Treatment difference = 0.3 (95% CI, 0.2-0.4; p<0.001)

Two co-primary endpoints assessed over a 28-day period:

- Number of satisfying sexual events days
- Changes in sexual desire score as recorded on a patient daily diary
  - Scale 0 (no desire) to 3 (strong desire); range 0-84

Other endpoints assessed:

- Sexual desire as measured through a female sexual function index (FSFI) score*
  - Scale 1 (almost never/never) to 5 (almost always/always); range 1.2-6.0
- Female Sexual Distress Scale-Revised (FSDS-R) score Question 13
  - Scale 0 (never) to 4 (always); range 0-4

*=secondary endpoint in first 2 trials; co-primary endpoint in third trial

Safety

- Black-box warning: avoid concomitant use of flibanserin and alcohol for increased the risk of severe hypotension and syncope.
- Contraindicated for use with strong or moderate CYP3A4 inhibitors and with hepatic impairment.
- Common Adverse Events (>10%): somnolence, dizziness, and nausea.
- Flibanserin distribution is limited through a Risk Evaluation and Mitigation Strategy (REMS) program.

Evidence Gaps/Limitations

No additional studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Addyi (flibanserin) [Prescribing Information]. Raleigh, NC; Sprout Pharmaceuticals, Inc., September 2015.
2. FDA Center for Drug Evaluation and Research. Summary Review. Application Number: 022526Orig1s000. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022526Orig1s000SumRedt.pdf

Abbreviated Drug Review

Drug Product	
Saxenda® (**liraglutide**) inj solution (subcutaneous)	Indication not funded

Indications

- **Chronic Weight Management:** to be used as an adjunct to reduced-calorie diet and increased physical activity for chronic wt. management in adults with initial body mass index (BMI) of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity.

Dosage

- 0.6 mg subcutaneously once daily for 1 week, then increased by 0.6 mg/day weekly until target dose 3 mg once daily.

Background

- Glucagon-like peptide-1 (GLP-1) is an incretin hormone that amplifies nutrient-induced insulin secretion, inhibits glucagon release, and slows gastric motility.
- Liraglutide is a GLP-1 receptor agonist designed to promote weight loss primarily through appetite suppression.
- Victoza® = identical strength/formulation of liralglutide but is approved by FDA for Type 2 diabetes mellitus (T2DM) at target daily dose of 1.8 mg.

Efficacy

- **Trial 1839**: (n=3731): obese or overweight subjects with weight-related comorbidity
  - % weight change:-5.4% (95% CI, -5.8 to -4.95; p<0.0001)
  - 5% weight loss: OR 4.80 (95% CI, 4.12 to 5.60; p<0.0001)
  - 10% body weight: OR 4.34 (95% CI, 3.54 to 5.32; p<0.0001)
- **Trial 1922** (n=846): Obese or overweight subjects with T2DM
  - % weight change: -4.0% (95% CI, -4.8 to -3.1; p<0.0001)
  - 5% weight loss: OR 6.8 (95% CI, 4.3 to 10.7; p<0.0001)
  - 10% weight loss: OR 7.1 (95% CI, 3.5 to 14.5; p<0.0001)
- **Trial 1923** (n=422): obese or overweight subjects with ≥1 weight-related comorbidity
  - % weight change: -6.1% (95% CI, -7.5 to -4.6; p<0.0001)
  - 5% weight loss: OR 3.9 (95% CI, 2.4 to 6.1; p<0.0001)
  - Maintained 5% BW loss: OR 4.8 (95% CI, 3.0 to 7.7; p<0.0001)

- Three Phase 3 RCTs studied liraglutide 3 mg daily versus placebo in approximately 4800 patients over 56 weeks.
- **Primary endpoints :**
  - **% change from baseline body weight (BW)**
  - **proportion subjects losing at least 5% baseline BW**
  - **proportion subjects losing at least 10% baseline BW***
  - **maintenance of weight loss (minimum 5%) achieved after a 4-12 week run-in using a low calorie diet****

*** = trial 1839 and 1922 only**

Safety

Back Box Warning: Thyroid C-cell tumors in rats and mice. **Contraindications:** History of medullary thyroid carcinoma; Multiple Endocrine Neoplasia syndrome type 2; pregnancy.	**Caution** in patients with thyroid C-cell tumors; acute pancreatitis; acute gallbladder disease; serious hypoglycemia; renal impairment; suicidal behavior/ideation. **Common AEs:** Nausea 40%, vomiting 15%; 6.4% req'd discontinuation of therapy due to GI issues

Evidence Gaps/Limitations

As with most weight loss drugs, there are no long-term cardiovascular and mortality outcomes. The drug should impact A1C outcomes related to T2DM by nature of the drug's mechanism of action; however, the Victoza® formulation has FDA approval for that indication.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization. Use Victoza® for management of T2DM.

References

1. Saxenda (liraglutide) [Prescribing Information]. Plainsboro, NJ;Novo Nordisk Inc., January 2015.
2. FDA Center for Drug Evaluation and Research Summary Review. Available at:http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206321Orig1s000SumR.pdf. Accessed November 24, 2015.