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, November 19, 2015 1:00 - 5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

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. Approval of Agenda and Minutes	B. Origer (Chair)
D. 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. "Treating UTIs with the Tried and True"
b. "Hypertension Guidelines: Do Blood Pressure Goals Change with Age?"
c. "Is Long-term Proton Pump Inhibitor Treatment for GERD Worth the Risk?"

III. DUR OLD BUSINESS

A. Intranasal Allergy Drug Policy — T. Williams (OSU)
1. Prior Authorization for Preferred Intranasal Drugs
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

B. LABA/ICS Drug Policy — K. Sentena (OSU)
1. Prior Authorization for LABA/ICS for COPD
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. LABA/LAMA Drug Policy — K. Sentena (OSU)
1. Prior Authorization for LABA/LAMA for COPD
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

IV. DUR NEW BUSINESS

A. DURM Methods — M. Herink (OSU)
1. Methods for DURM Evidence Summary Reviews
2. Methods for DURM Abbreviated Drug Reviews
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

B. Botulinum Toxins Drug Policy — T. Williams (OSU)
1. Updated Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. Ivabradine (Corlanor®) New Drug Evaluation — M. Herink (OSU)
1. New Drug Evaluation/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

V. PREFERRED DRUG LIST NEW BUSINESS

A. Ivacaftor/Lumacaftor (Orkambi™) New Drug Evaluation — M. Herink (OSU)
1. New Drug Evaluation/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

B. Cross-sex Hormone Class Review — K. Sentena (OSU)
1. Class Review/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. PCSK9 Inhibitor Class Review — M. Herink (OSU)
1. DERP Summary/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

D. Long-acting Insulin Class Update — M. Herink (OSU)
1. DERP Summary/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

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

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

G. Iron Chelator Drug Class Update — D. Engen (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

H. Drug Class Literature Scans — M. Herink/D. Engen (OSU)

1. Immunosuppressants
2. Topical Analgesics
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. 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	Philomath	December 2018
Vacant	Physician			December 2016

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 24, 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; Tracy Klein, PhD., FNP; William Origer, MD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD;

Members Present by Phone:

Staff Present: Kathy Ketchum, RPh, MPA:HA; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Andrew Gibler, PharmD; Dee Weston; David Engen, PharmD; Kim Wentz, MD

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Don Stecher (Novartis), Mary Fitzpatrick (Biogen)*, Jeannie Kenyon (AstraZeneca), Dr. Doug Gelowitz (AstraZeneca)*, Bridget Martin (Boehringer Ingelheim), Jenny Morrison (Boehringer Ingelheim), Diann Matthews (Biogen), Kim Copper (AstraZeneca), Kristi Benson (AstraZeneca), Steven Hall (Boehringer Ingelheim)*, Karen Dienko (Boehringer Ingelheim), Kelsey Bnick, Megan Carroll, Lisa Ashton (J&J); Margaret Olman (AbbVie), Camille Kerr (Amgen), Dr. McCale (Baxacta), Barry Benson (Merck), Stephanie Lattig (Novo Nordisk), Merrie Kay Alzola (Novo Nordisk), Sally Zweber (Novo Nordisk), Michael Estos (Pfizer)*, Venus Holder (Lilly), Jeana Colabianchi (Sunovion), Nik Seifter (GlaxoSmith Kline)*, Bruce Smith (GlaxoSmith Kline), Becky Gonzales (ViiV Healthcare), David Putelo (Viiv Healthcare), Stella McCaughey (Novartis), Mary Kemhus (Novartis)*, Jon Ward (Novartis), Paul Bonham (Novo Nordisk), Mark Pledger (Novartis),

(*) 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 4 - 9)

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

d. Department updates for OHA.

II. DUR OLD BUSINESS

a. Initial Pediatric SSRI High Dose Prior Authorization Criteria (pages 10 - 11)
Dr. Williams presented the revised criteria.

ACTION: Motion, 2nd. Approved.

b. Codeine Prior Authorization Criteria update (page 12)
Dr. Gibler presented the updated criteria.

ACTION: Motion, 2nd. Approved.

III. PREFERRED DRUG LIST NEW BUSINESS

a. Asthma and COPD Class Updates (pages 13 - 41)
Dr. Sentena presented the following class update:

1. Maintain tiotropium/olodaterol, fluticasone furoate and fluticasone furoate/vilanterol drug products non-preferred.
2. Create new PDL class for long-acting muscarinic antagonist/long-acting beta-agonist (LAMA/LABA) fixed-dose combination inhaler products.
3. Re-organize and modify clinical PA criteria to promote step-therapy that is consistent with Oregon Asthma Guidelines and with medical evidence for COPD:
   - All non-preferred LABA inhalers must go through the LABA PA criteria for appropriate step therapy.
   - All non-preferred inhaled corticosteroids (ICS) must go through the ICS PA criteria for appropriate step therapy.
   - Updated LABA/ICS combination inhalers PA proposed criteria were rejected. Bring back to P&T Committee in November and clarify COPD severity stages in criteria.
   - Proposed new PA criteria for LAMA/LABA products were rejected. Bring back to P&T Committee and clarify evidence for ICS monotherapy prior to LABA/LAMA use and COPD severity stages in criteria.
   - Remove existing clinical PA for “asthma controllers” and indacterol. Drugs under these PAs will be incorporated into the ICS or LABA PA criteria.
   - Remove clinical PA for leukotriene inhibitors. Non-preferred leukotriene inhibitors will go through the generic non-preferred PDL PA.
   - Clerical changes to the roflumilast clinical PA criteria.
4. Evaluate cost in executive session for PDL decision making.

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

5. No changes to PMPDP.

Public Comment:
Nik Seifter from GSK gave public comment.

b. Diabetic Class Updates (pages 42 - 66)

Dr. Sentena presented the following class update:

1. Include at least one GLP-1 RA on the PDL as a preferred third-line option for T2DM after metformin and a SU.
2. Maintain GLYXAMBI® (empagliflozin and linagliptin) as non-preferred subject to current clinical PA for SGLT-2 inhibitors.
3. 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
4. No longer require clinical PA for pramlintide.
5. Continue current clinical PAs for DPP-4 inhibitors, SGLT-2 inhibitors, and non-preferred GLP-1 Receptor antagonists.
6. Evaluate cost in executive session for PDL decision making.
7. SGLT-2 inhibitor clinical PA: change duration PA approval to 6 months under #5 so renal function can be re-evaluated. Develop renewal criteria that require re-analysis of renal function in last 6 months for re-approval.
8. ALL GLP-1 receptor antagonists subject to clinical PA.

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

9. *Make Byetta® PDL = Y.

Public Comment:
Bob Snediker from J&J gave public comment.
Dr. Doug Gelowitz from AstraZeneca gave public comment.
Steve Hall from Boehringer Ingelheim gave public comment.

ACTION: Motion, 2nd. Approved.

c. Drug Class Literature Scans

1. Oral Multiple Sclerosis Drugs (pages 67 – 78)\
   Dr. Gibler presented the updated scan.

   a. No further research or review needed at this time.
   b. Evaluate comparative costs in executive session.
   c. #2 in clinical PA, for No: “not funded under the OHP” and refer to guideline.

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

Public Comment:
Mary Fitzpatrick from Biogen gave public comment.
Mary Kemhus from Novartis gave public comment.

2. Growth Hormones (pages 79 – 85)
   Dr. Gibler presented the updated scan.

   a. No further research or review needed at this time.
   b. Evaluate comparative costs in executive session.

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

c. *#2 in clinical PA: Leave definition of adult as “older than 18 years of age”.

Public Comment:
Micheal Estos from Pfizer gave public comment.

3. Inflammatory Bowel Agents (pages 86 – 92)
   Dr. Gibler presented the updated scan.

   a. At least one oral corticosteroid formulation should be available on the PDL for adjunctive management of mild Crohn’s disease.
   b. Budesonide rectal foam should not be a prefered agent at this time due to limited short-term evidence.
   c. No further research or review needed at this time.
   d. Evaluate comparative costs in the executive session.

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

4. Alzheimer’s Agents (pages 93 – 100)
   Dr. Gibler presented the updated scan.

   1. No further research or review needed at this time.
   2. Evaluate comparative costs in executive session.

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

d. Sacubitril/Valsartan New Drug Evaluation (pages 101 - 114)
   Dr. Gibler presented the following new drug evaluation:

   1. Restrict use of sacubitril/valsartan to populations where it has demonstrated efficacy.
   2. Approve proposed prior authorization.
   3. #1 clinical PA: “Is this a request for renewal of a prior approved PA”?

ACTION: Motion, 2nd. Approved.

Public Comment:
Mary Kemhus from Novartis gave public comment.

e. Ivabradine New Drug Evaluation (pages 115 - 128)
   Dr. Gibler presented the following new drug evaluation:

   Evaluation was deferred to the November meeting.

f. Influenza Class Update (pages 129 – 142)
   Dr. Gibler presented the following class update:

   The class update was deferred to the November meeting.

IV. DUR NEW BUSINESS

a. Modafinil/Armodafinil Drug Use Evaluation (pages 143 – 167)
   Ms. Ketchum presented the following review and evaluation:

1. Implement proposed prior authorization criteria for patients initiated on modafinil or armodainil (no claims evidence within 102 days) and without previous claims evidence of narcolepsy or obstructive sleep apnea.
2. Grandfather current modafinil/armodafinil users for one year.
3. Clerical amendments: Remove “or other CNS stimulants” from Yes under #3, Remove “Pass to RPH” from Yes under #4.

ACTION: Motion, 2nd. Approved.

b. Tetracyclines Drug Use Evaluation (pages 168 – 177)
Dr. Williams presented the following drug use evaluation:

1. Restrict use of all tetracycline antibiotics to a 14-day supply every 6 months.
2. Make tetracycline antibiotic therapy exceeding 14 days every 6 months subject to prior authorization to verify the presence of an OHP funded condition.

ACTION: Motion, 2nd. Approved.

c. Low Dose Quetiapine Policy Evaluation (pages 178 – 189)
Ms. Ketchum presented the following drug evaluation:

1. Automatically approve for:
   - Patients with a claim for a second generation antipsychotic in the past six months.
   - Patients with prior medical claims evidence of schizophrenia or bipolar disorder.
   - Prescriptions identified as being written by a mental health provider when the claims system has the capability.

ACTION: Motion, 2nd. Approved.

d. Clinical Review of Existing Prior Authorization Criteria
1. Tesamorelin for injection (pages 190 – 191)
Dr. Gibler presented the following clinical review for the existing PA.

a. No further research or review needed at this time.
b. No changes to the current PA criteria.

ACTION: Motion, 2nd. Approved.

2. Becaplermin topical gel (pages 192 – 193)
Dr. Gibler presented the following clinical review for the existing PA.

a. No further research or review needed at this time.
b. No changes to the current PA criteria.

ACTION: Motion, 2nd. Approved.

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

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Pharmacy Utilization Summary Report: April 2014 - March 2015

Eligibility	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Total Members (FFS & Encounter)	933,189	961,855	969,341	981,835	997,487	1,008,231	1,021,045	977,740	998,873	1,027,655	1,043,479	1,059,499	998,352
FFS Members	137,326	138,745	136,943	132,379	140,158	134,462	132,913	140,236	139,950	157,174	140,889	134,463	138,803
OHP Basic with Medicare	27,903	28,145	28,393	28,468	28,659	28,804	29,015	29,111	29,136	29,283	29,328	29,255	28,792
OHP Basic without Medicare	24,179	24,696	24,989	24,836	24,911	24,494	23,833	21,350	18,720	18,429	17,581	16,680	22,058
ACA	82,228	82,479	80,139	79,075	86,588	81,164	80,065	89,775	92,094	109,462	93,980	88,528	87,131
Encounter Members	795,863	823,110	832,398	849,456	857,329	873,769	888,132	837,504	858,923	870,481	902,590	925,036	859,549
OHP Basic with Medicare	38,134	38,244	38,302	38,419	38,620	38,770	38,810	38,812	38,946	39,105	39,244	39,267	38,723
OHP Basic without Medicare	226,830	224,805	222,503	220,955	219,511	215,256	205,287	164,063	131,637	120,645	116,957	116,321	182,064
ACA	524,688	552,052	562,718	590,082	599,198	619,743	644,035	634,629	688,340	710,731	746,389	769,448	636,838

Gross Cost Figures for Drugs	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	YTD Sum
Total Amount Paid (FFS & Encounter)	$43,117,443	$47,202,933	$49,946,699	$53,132,675	$50,738,874	$54,183,983	$56,958,136	$49,846,206	$58,946,093	$58,947,288	$55,255,189	$62,942,638	$641,218,156
Mental Health Carve-Out Drugs	$9,878,456	$10,180,980	$10,281,236	$10,921,674	$10,588,025	$11,072,974	$11,558,114	$10,236,122	$11,028,779	$10,882,866	$10,381,758	$11,644,323	$128,655,308
OHP Basic with Medicare	$10,812	$13,664	$9,967	$4,573	$5,442	$2,452	$5,630	$6,949	$10,422	$10,229	$10,140	$10,995	$101,275
OHP Basic without Medicare	$6,222,199	$6,157,090	$6,158,408	$6,348,075	$6,058,902	$6,191,009	$6,281,657	$5,362,128	$5,468,698	$5,357,983	$5,004,213	$5,538,569	$70,148,930
ACA	$3,623,617	$3,945,852	$4,026,349	$4,470,302	$4,438,711	$4,785,138	$5,188,930	$4,801,929	$5,505,669	$5,482,203	$5,336,388	$6,063,677	$57,668,765
FFS Physical Health Drugs	$3,327,528	$3,275,037	$3,348,501	$3,394,260	$3,222,584	$3,477,819	$3,449,164	$3,306,505	$3,792,580	$3,868,726	$3,258,529	$3,110,955	$40,832,191
OHP Basic with Medicare	$265,906	$278,862	$269,577	$270,866	$240,008	$244,614	$246,416	$228,081	$251,397	$249,591	$226,909	$239,355	$3,011,581
OHP Basic without Medicare	$1,450,688	$1,430,593	$1,419,716	$1,360,975	$1,254,951	$1,444,294	$1,375,246	$1,212,628	$1,292,974	$1,298,051	$1,154,986	$1,168,342	$15,863,445
ACA	$1,525,057	$1,478,133	$1,571,387	$1,665,913	$1,640,058	$1,706,537	$1,744,438	$1,792,657	$2,168,255	$2,249,265	$1,801,528	$1,633,185	$20,976,413
FFS Physician Administered Drugs	$1,498,879	$1,442,472	$1,580,677	$1,379,064	$1,525,864	$1,848,586	$1,669,336	$1,356,975	$1,384,121	$1,780,120	$1,464,184	$1,717,687	$18,647,965
OHP Basic with Medicare	$185,345	$132,200	$220,708	$182,939	$154,986	$155,504	$177,379	$134,520	$178,784	$235,517	$232,397	$199,813	$2,190,093
OHP Basic without Medicare	$646,491	$442,913	$562,692	$425,879	$443,656	$531,028	$423,735	$500,987	$282,212	$366,624	$294,086	$342,268	$5,262,571
ACA	$448,192	$647,791	$600,722	$561,857	$676,180	$940,237	$869,638	$556,360	$752,134	$935,211	$795,529	$989,083	$8,772,934
Encounter Physical Health Drugs	$22,806,704	$26,308,077	$28,738,858	$30,274,471	$29,412,182	$31,254,252	$32,951,469	$28,975,978	$35,588,090	$35,470,655	$33,794,337	$38,781,764	$374,356,836
OHP Basic with Medicare	$156,053	$177,887	$196,505	$193,686	$195,549	$201,593	$199,118	$196,335	$196,602	$247,742	$233,504	$246,611	$2,441,185
OHP Basic without Medicare	$11,269,475	$12,485,630	$13,205,678	$13,846,045	$12,792,727	$13,269,767	$13,430,639	$10,864,216	$12,333,488	$11,794,302	$10,829,052	$12,129,637	$148,250,657
ACA	$11,202,852	$13,319,740	$14,986,265	$15,901,806	$16,121,818	$17,480,482	$19,038,154	$17,643,983	$22,871,059	$23,212,631	$22,584,682	$26,237,157	$220,600,630
Encounter Physician Administered Drugs	$5,605,876	$5,996,367	$5,997,427	$7,163,205	$5,990,217	$6,530,351	$7,330,054	$5,970,626	$7,152,523	$6,944,920	$6,356,380	$7,687,909	$78,725,856
OHP Basic with Medicare	$174,757	$188,679	$184,374	$202,856	$175,051	$154,676	$191,303	$146,010	$143,961	$222,323	$183,672	$162,445	$2,130,107
OHP Basic without Medicare	$2,387,668	$2,532,198	$2,529,826	$3,429,246	$2,440,759	$2,441,705	$2,600,487	$2,120,459	$2,270,033	$2,232,660	$1,994,585	$2,459,426	$29,439,050
ACA	$2,626,395	$2,925,843	$3,053,679	$3,308,490	$3,165,076	$3,680,274	$4,277,813	$3,540,664	$4,555,709	$4,336,727	$4,053,988	$4,887,068	$44,411,725

OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Note: Paid amounts include dispensing fee

Last Updated: October 21, 2015

Drug Use Research & Management Program
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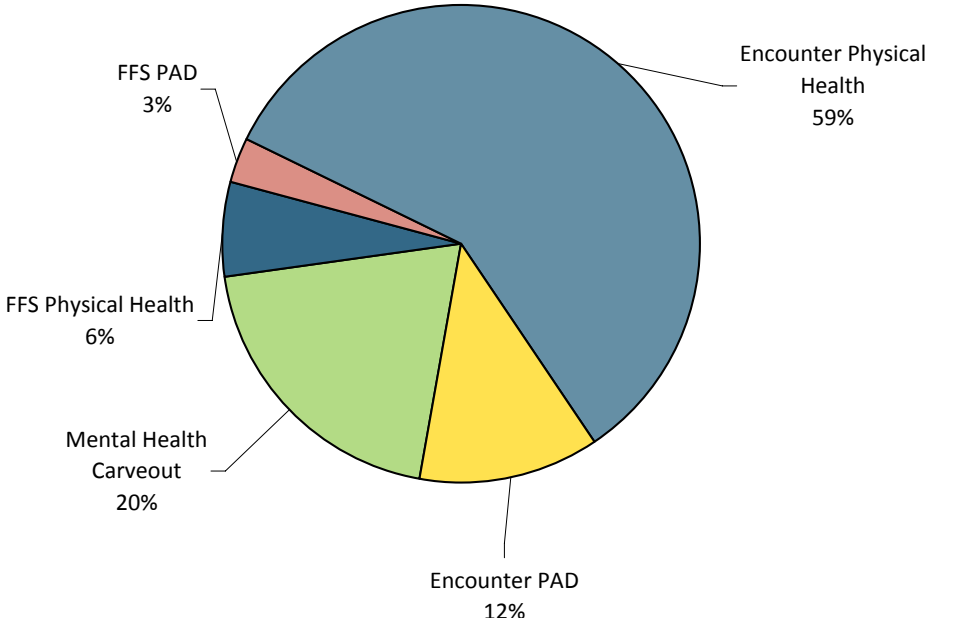
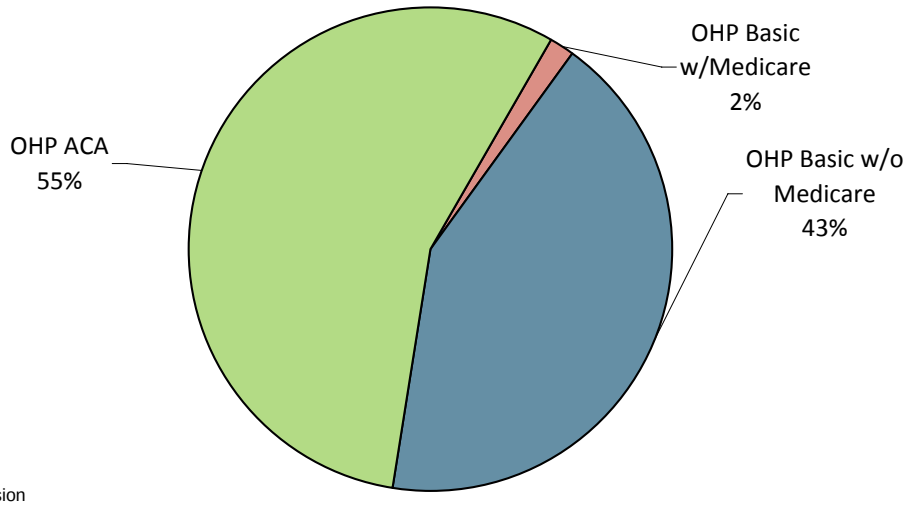
YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Note: Paid amounts include dispensing fee

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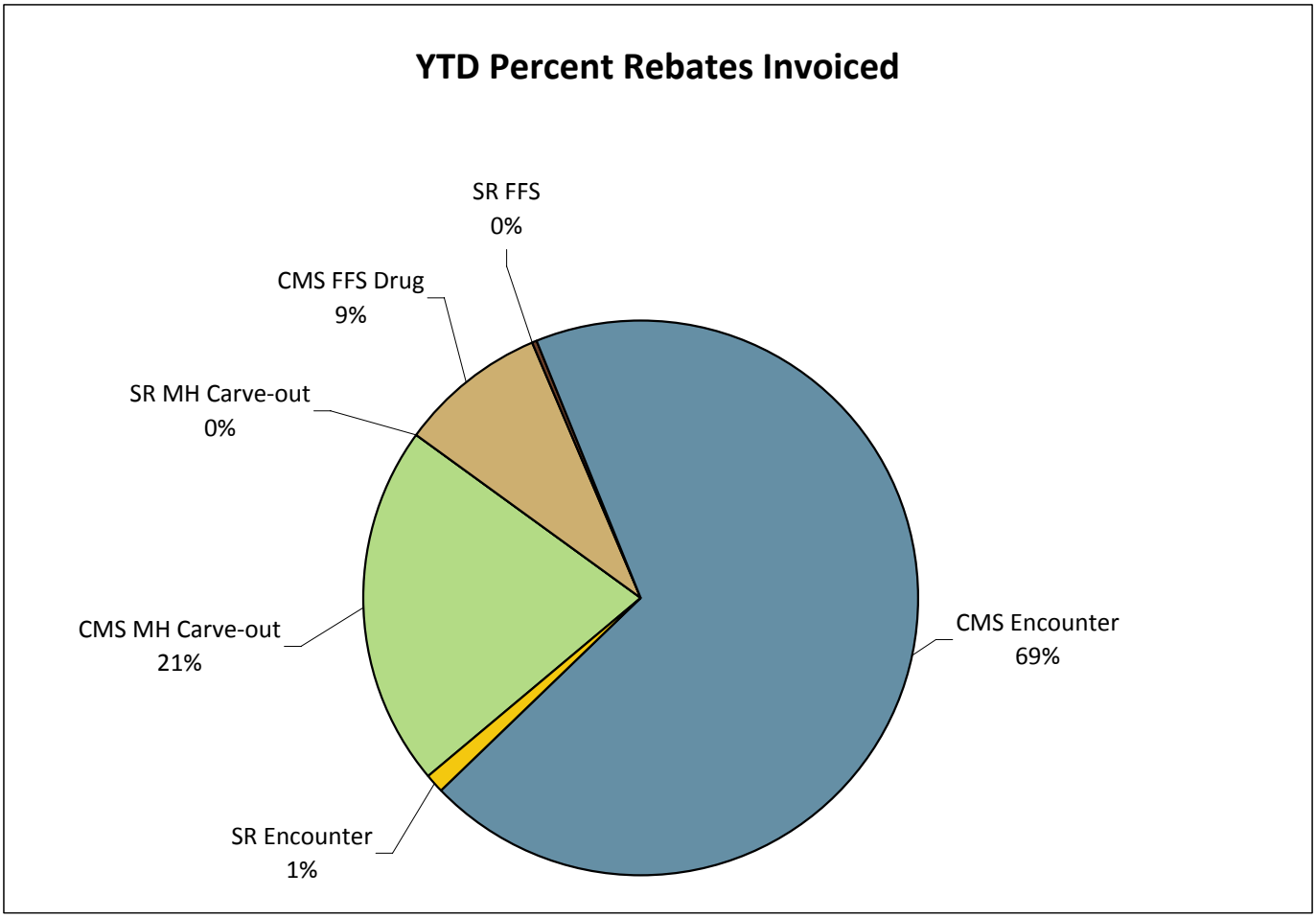
Pharmacy Utilization Summary Report: April 2014 - March 2015

Quarterly Rebates Invoiced	2014-Q2	2014-Q3	2014-Q4	2015-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$67,019,848	$69,307,450	$75,634,200	$90,684,023	$302,645,521
CMS MH Carve-out	$14,644,358	$15,135,883	$15,228,555	$18,471,786	$63,480,582
SR MH Carve-out	$62,641		$64,807		$127,447
CMS FFS Drug	$6,059,538	$6,062,304	$6,560,269	$7,314,929	$25,997,039
SR FFS	$236,982	$229,999	$257,828	$244,833	$969,642
CMS Encounter	$45,109,954	$47,080,661	$52,460,278	$63,769,129	$208,420,023
SR Encounter	$906,375	$798,603	$1,062,464	$883,346	$3,650,788

Quaterly Net Drug Costs	2014-Q2	2014-Q3	2014-Q4	2015-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$73,247,227	$88,748,081	$90,116,236	$86,461,091	$338,572,635
Mental Health Carve-Out Drugs	$15,633,674	$17,446,790	$17,529,654	$14,437,161	$65,047,279
FFS Phys Health + PAD	$8,176,573	$8,555,877	$8,140,584	$7,640,440	$32,513,474
Encounter Phys Health + PAD	$49,436,980	$62,745,414	$64,445,998	$64,383,489	$241,011,881



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

Last Updated: October 21, 2015

Drug Use Research & Management Program
DHS - Division of Medical Assistance Programs
500 Summer Street NE, E35, Salem, OR 97301-1079
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Pharmacy Utilization Summary Report: April 2014 - March 2015

PMPM Drug Costs (Excludes Rebate)	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$46.20	$49.07	$51.53	$54.12	$50.87	$53.74	$55.78	$50.98	$59.01	$57.36	$52.95	$59.41	$53.42
Mental Health Carve-Out Drugs	$10.59	$10.58	$10.61	$11.12	$10.61	$10.98	$11.32	$10.47	$11.04	$10.59	$9.95	$10.99	$10.74
FFS Physical Health Drugs	$24.23	$23.60	$24.45	$25.64	$22.99	$25.86	$25.95	$23.58	$27.10	$24.61	$23.13	$23.14	$24.52
FFS Physician Administered Drugs	$10.91	$10.40	$11.54	$10.42	$10.89	$13.75	$12.56	$9.68	$9.89	$11.33	$10.39	$12.77	$11.21
Encounter Physical Health Drugs	$28.66	$31.96	$34.53	$35.64	$34.31	$35.77	$37.10	$34.60	$41.43	$40.75	$37.44	$41.92	$36.18
Encounter Physician Administered Drugs	$7.04	$7.29	$7.20	$8.43	$6.99	$7.47	$8.25	$7.13	$8.33	$7.98	$7.04	$8.31	$7.62

Claim Counts	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Total Claim Count (FFS & Encounter)	879,470	903,745	914,248	944,871	914,947	958,673	1,008,538	874,488	978,481	1,018,294	952,137	1,064,695	951,049
Mental Health Carve-Out Drugs	130,358	134,503	134,086	140,589	136,822	142,387	148,426	132,301	151,810	148,740	139,076	154,423	141,127
FFS Physical Health Drugs	77,358	79,745	79,751	78,357	76,610	79,062	80,070	75,779	80,910	83,548	70,024	72,407	77,802
FFS Physician Administered Drugs	14,970	13,835	13,304	13,231	13,450	12,418	13,142	11,973	12,160	15,316	12,328	12,889	13,251
Encounter Physical Health Drugs	583,767	600,677	612,785	635,528	615,702	650,358	687,792	587,284	660,255	694,963	660,295	743,548	644,413
Encounter Physician Administered Drugs	73,017	74,985	74,322	77,166	72,363	74,448	79,108	67,151	73,346	75,727	70,414	81,428	74,456

Amount Paid per Claim (Excludes Rebate)	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$49.03	$52.23	$54.63	$56.23	$55.46	$56.52	$56.48	$57.00	$60.24	$57.89	$58.03	$59.12	$56.07
Mental Health Carve-Out Drugs	$75.78	$75.69	$76.68	$77.69	$77.39	$77.77	$77.87	$77.37	$72.65	$73.17	$74.65	$75.41	$76.01
FFS Physical Health Drugs	$43.01	$41.07	$41.99	$43.32	$42.06	$43.99	$43.08	$43.63	$46.87	$46.31	$46.53	$42.96	$43.74
FFS Physician Administered Drugs	$100.13	$104.26	$118.81	$104.23	$113.45	$148.86	$127.02	$113.34	$113.83	$116.23	$118.77	$133.27	$117.68
Encounter Physical Health Drugs	$39.07	$43.80	$46.90	$47.64	$47.77	$48.06	$47.91	$49.34	$53.90	$51.04	$51.18	$52.16	$48.23
Encounter Physician Administered Drugs	$76.77	$79.97	$80.70	$92.83	$82.78	$87.72	$92.66	$88.91	$97.52	$91.71	$90.27	$94.41	$88.02

Amount Paid per Claim - Multi Source Drugs (Excludes Rebate)	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$25.20	$26.62	$26.85	$26.72	$26.88	$26.89	$26.87	$27.07	$27.03	$26.25	$26.57	$26.52	$26.62
Mental Health Carve-Out Drugs	$60.25	$60.42	$60.92	$61.73	$61.30	$61.38	$61.69	$60.78	$54.71	$54.44	$55.76	$55.94	$59.11
FFS Physical Health Drugs	$21.72	$21.92	$21.99	$22.26	$22.10	$21.97	$21.46	$21.68	$22.00	$23.06	$22.50	$22.18	$22.07
Encounter Physical Health Drugs	$17.59	$19.44	$19.80	$19.27	$19.56	$19.65	$19.67	$19.88	$21.07	$20.38	$20.65	$20.64	$19.80

Amount Paid per Claim - Single Source Drugs (Excludes Rebate)	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$336.45	$369.87	$400.73	$414.92	$405.47	$387.42	$371.19	$399.85	$451.42	$421.83	$437.90	$447.86	$403.74
Mental Health Carve-Out Drugs	$437.96	$437.83	$452.20	$461.31	$458.94	$457.61	$452.85	$461.02	$472.86	$490.61	$489.82	$498.38	$464.28
FFS Physical Health Drugs	$308.60	$283.71	$297.29	$308.82	$298.61	$309.90	$301.38	$313.54	$353.42	$318.23	$344.94	$303.02	$311.79
Encounter Physical Health Drugs	$326.97	$373.08	$408.24	$422.77	$412.14	$388.53	$369.94	$403.32	$460.65	$426.45	$441.47	$455.91	$407.46

Multi-Source Drug Use Percentage	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Multi-Source Drug Use Percentage	93.5%	93.5%	93.5%	93.4%	93.3%	92.9%	92.6%	92.9%	93.1%	92.9%	93.2%	93.2%	93.2%
Mental Health Carve-Out Drugs	95.9%	96.0%	96.0%	96.0%	96.0%	95.9%	95.9%	95.9%	95.7%	95.7%	95.6%	95.6%	95.8%
FFS Physical Health Drugs	92.6%	92.7%	92.7%	92.7%	92.8%	92.4%	92.3%	92.5%	92.5%	92.1%	92.5%	92.6%	92.5%
Encounter Physical Health Drugs	93.1%	93.1%	93.0%	93.0%	92.8%	92.3%	91.9%	92.3%	92.5%	92.4%	92.7%	92.8%	92.7%

Preferred Drug Use Percentage	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Avg Monthly
Preferred Drug Use Percentage	86.23%	85.96%	86.03%	86.13%	86.08%	86.40%	86.49%	86.42%	86.47%	86.70%	86.58%	86.55%	86.3%
Mental Health Carve-Out Drugs	74.46%	73.35%	73.24%	73.12%	73.05%	75.82%	77.03%	77.11%	76.83%	76.96%	76.75%	76.94%	75.4%
FFS Physical Health Drugs	93.57%	93.66%	93.88%	94.36%	94.57%	94.46%	94.60%	94.83%	94.63%	95.01%	94.83%	94.63%	94.4%
Encounter Physical Health Drugs	88.29%	88.19%	88.23%	88.15%	88.08%	87.91%	87.76%	87.57%	87.79%	87.87%	87.86%	87.83%	88.0%

Note: Paid amounts include dispensing fee

Last Updated: October 21, 2015

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$11,448,630	25.5%	11,828	$968	V
2	LATUDA	Antipsychotics, 2nd Gen	$2,584,281	5.8%	3,047	$848	V
3	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,801,672	4.0%	3,123	$577	V
4	STRATTERA	ADHD Drugs	$1,602,619	3.6%	4,595	$349	Y
5	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,086,146	2.4%	748	$1,452	V
6	INVEGA	Antipsychotics, 2nd Gen	$931,831	2.1%	969	$962	V
7	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$700,723	1.6%	1,011	$693	V
8	DULOXETINE HCL	Antidepressants	$680,579	1.5%	23,678	$29	V
9	FLUOXETINE HCL	Antidepressants	$557,657	1.2%	31,023	$18	Y
10	BUPROPION XL	Antidepressants	$495,229	1.1%	16,562	$30	V
11	RISPERDAL CONSTA	Antipsychotics, Parenteral	$430,799	1.0%	602	$716	Y
12	SERTRALINE HCL	Antidepressants	$426,767	0.9%	36,897	$12	Y
13	ABILIFY MAINTENA	Antipsychotics, Parenteral	$416,022	0.9%	270	$1,541	V
14	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$404,272	0.9%	4,064	$99	Y
15	PRISTIQ ER	Antidepressants	$403,050	0.9%	1,526	$264	V
16	SAPHRIS	Antipsychotics, 2nd Gen	$399,379	0.9%	738	$541	V
17	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$397,673	0.9%	1,019	$390	V
18	HARVONI	Hepatitis C	$357,133	0.8%	15	$23,809	Y
19	AMITRIPTYLINE HCL	Antidepressants	$346,965	0.8%	17,160	$20	Y
20	TRAZODONE HCL	Antidepressants	$339,179	0.8%	36,741	$9	
21	Factor Viii Recombinant Nos	Physican Administered Drug	$302,052	0.7%	14	$21,575	
22	VENLAFAXINE HCL ER	Antidepressants	$297,598	0.7%	1,835	$162	V
23	LAMOTRIGINE	Antiepileptics (oral & rectal)	$288,815	0.6%	20,132	$14	Y
24	HUMIRA	Biologicals for RA, Psoriasis and Crohn's Disease	$279,456	0.6%	88	$3,176	Y
25	LANTUS	Diabetes, Insulins	$279,358	0.6%	814	$343	Y
26	CITALOPRAM HBR	Antidepressants	$271,361	0.6%	30,988	$9	Y
27	VENLAFAXINE HCL ER	Antidepressants	$263,421	0.6%	14,432	$18	Y
28	Anti-Inhibitor	Physican Administered Drug	$262,191	0.6%	2	$131,095	
29	VIIBRYD	Antidepressants	$254,990	0.6%	1,297	$197	V
30	ENBREL	Biologicals for RA, Psoriasis and Crohn's Disease	$232,183	0.5%	86	$2,700	Y
31	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$222,474	0.5%	572	$389	Y
32	ESCITALOPRAM OXALATE	Antidepressants	$221,882	0.5%	17,783	$12	Y
33	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$210,805	0.5%	11,580	$18	Y
34	BUPROPION HCL SR	Antidepressants	$204,885	0.5%	11,565	$18	Y
35	LORAZEPAM	Benzodiazepine Anxiolytics	$202,779	0.5%	21,210	$10	
36	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$199,577	0.4%	12,355	$16	
37	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$195,493	0.4%	3,712	$53	Y
38	NUVIGIL	ADHD Drugs	$193,580	0.4%	344	$563	V
39	Infliximab Injection	Physican Administered Drug	$188,725	0.4%	88	$2,145	
40	DIVALPROEX SODIUM	Antiepileptics (oral & rectal)	$180,990	0.4%	5,558	$33	Y
		Top 40 Aggregate:	**$30,563,220**		**350,071**	**$4,897**	
		All FFS Drugs Totals:	**$44,926,946**		**689,707**	**$447**	

Notes
- FFS Drug Costs only, rebates excluded
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amounts paid include dispensing fee

Last updated: October 21, 2015

ProDUR Alert Overview

DA Drug/Allergy Interaction: Triggers if there is an association between an ingredient and an allergy recorded in the recipient profile.

DC Inferred Disease Interaction: Triggers if there is a drug on the recipients profile that is indicated for a disease state that interacts with the drug being filled.

DD Drug to Drug Interaction: Triggers if there is an interaction between the drug being filled and another drug on the recipients profile.

ER Early Refill (Overutilization): Triggers if the drug being billed is too early based on previous billing and days supply. Allow filling when 80% of previous fill has been used.

HD High Dose: Triggers if the drug being billed, based on billed days supply, exceeds the maximum recommended daily quantity limit

ID Ingredient Duplication: Triggers if the drug being filled has a matching ingredient to another recently filled drug on the recipients profile.

LD Low Dose: Triggers if the drug being billed, based on billed days supply, is below the minimum recommended daily quantity limit.

LR Late Refill (Underutilization): Triggers if the drug being filled is late in being refilled for the recipient.

MC Drug to Disease Interaction: Triggers if there is a disease Diagnosis (ICD-10) on the recipients claim profile that interacts with the drug being filled.

MX Maximum Duration of Therapy: Triggers if the days supply on the claim is greater than the maximum days value.

PA Pediatric and Geriatric Age Limits: Triggers if the age of the recipient is less than the minimum (pediatric) or greater than the maximum (geriatric) age for the drug being billed.

PG Pregnancy/Drug Interaction: Triggers if the drug being filled is contraindicated for use in pregnancy and the patient profile indicates that the patient may be pregnant.

TD Therapeutic Duplication: Triggers if the class of drug being billed matches the drug class of another recently filled medication on the recipients profile.

Early Refill and Pregnancy/Drug Interaction are the only two ProDUR alerts set to deny claims for FFS Medicaid pharmacy claims.

Announcing New Version Release: Pregnancy Precautions Module™ (PREG) v2.0

FDB is pleased to announce the upcoming release of Pregnancy Precautions Module™ v2.0 (PREG 2.0) with the introduction of the following features:

- Additional FDB-based Pregnancy Precautions Severity Level values
- Pregnancy Precautions Boxed Warning Indicator
- Pregnancy Exposure Registry information
- Enhanced text citation capabilities
- Replacing existing Pregnancy Narratives with a more robust monograph capability

Background

The Food and Drug Administration (FDA) has introduced drug labeling rules that—effective June 30, 2015—will gradually phase out, over the course of five years, the use of FDA categories (A, B, C, D and X) as an expression of pregnancy risk and be replaced by narrative-based risk text.

Details

PREG 2.0 Features

- The newly released PREG 2.0 will have the following expanded severity levels which will enable much more specificity in the categorization of the labeling-based narrative-based pregnancy risk:

Severity Level	Description
1	Contraindicated
3	Generally Not Recommended
4	Assess risk/benefit. Human data limited or unavailable.
5	No known fetal/neonatal risk.

- The addition of a Pregnancy Precautions Boxed Warning Indicator enables the developer to strengthen the nature of the warning to the end-user in situations where the pregnancy warning extends to the Boxed Warning section of the drug label.

PREG 1.0

- As these replacements occur, FDB will update PREG 1.0 records with Severity Level 1 value "CONTRAINDICATED OR NOT RECOMMENDED" if deemed contraindicated. All others will be grouped within the broad Severity Level 2 value of "NO FDA RATING BUT MAY HAVE PRECAUTIONS OR WARNINGS." FDB has elected not to add additional Severity Level values within PREG 1.0, as it would force a disruptive mandatory reprogramming effort by our customers.
- **Note:** PREG 1.0 will continue to be supported by FDB for an indefinite time period and will continue to be distributed within the FDB MedKnowledge Enhanced package. It is not mandatory that developers replace PREG 1.0 with PREG 2.0. However, FDB does recommend that developers schedule a replacement of PREG 1.0 with PREG 2.0 content at a time that is convenient within their roadmap planning process, because over the next five years, PREG 1.0 records will be populated increasingly with broad severity level "2" records that are unable to provide a programmatic delineation of relative fetal or neonatal risk of the medication.

ProDUR Report for July through September 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	30	12	0	18	0.00%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,571	369	0	1,200	1.67%
DD (Drug/Drug Interaction)	Set alert/Pay claim	188	37	0	151	0.17%
ER (Early Refill)	Set alert/Deny claim	62,827	11,098	76	51,640	67.43%
ID (Ingredient Duplication)	Set alert/Pay claim	17,827	4,404	16	13,398	19.07%
LD (Low Dose)	Set alert/Pay claim	711	133	0	573	0.73%
LR (Late Refill/Underutilization)	Set alert/Pay claim	83	50	0	33	0.03%
MC (Drug/Disease Interaction)	Set alert/Pay claim	1,207	569	0	638	0.93%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	974	243	2	727	1.00%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	2,052	1,235	0	817	2.17%
TD (Therapeutic Duplication)	Set alert/Pay claim	5,713	1,607	1	4,079	6.03%
	Totals	**93,183**	**19,757**	**95**	**73,274**	**99.23%**

ProDUR Report for July through September 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	104	31	10,585	1.0%	29.8%	0.29%
	Haloperidol	164	41	2,208	7.4%	25.0%	1.86%
	Wellbutrin (Bupropion)	711	95	36,804	1.9%	13.4%	0.26%
DD	Geodon (Ziprasidone)	67	12	3,960	1.7%	17.9%	0.30%
ER	Remeron (Mirtazapine)	845	128	8,033	10.5%	15.1%	1.59%
	Hydrocodone/APAP	197	59	6,778	2.9%	29.9%	0.87%
	Oxycodone	211	84	5,422	3.9%	39.8%	1.55%
	Lorazepam	1,397	293	23,735	5.9%	21.0%	1.23%
	Alprazolam	1,182	228	18,606	6.4%	19.3%	1.23%
	Lamictal (Lamotrigine)	2,958	547	25,852	11.4%	18.5%	2.12%
	Abilify (Aripiprazole)	1,918	350	18,738	10.2%	18.2%	1.87%
	Seroquel (Quetiapine)	2,294	412	18,411	12.5%	18.0%	2.24%
	Risperdal (Risperidone)	1,658	310	13,568	12.2%	18.7%	2.28%
	Wellbutrin (Bupropion)	3,064	399	36,804	8.3%	13.0%	1.08%
	Zoloft (Sertraline)	3,997	683	41,793	9.6%	17.1%	1.63%
	Prozac (Fluoxetine)	2,988	406	34,362	8.7%	13.6%	1.18%
	Celexa (Citalopram)	2,697	333	34,162	7.9%	12.3%	0.97%
	Trazodone	3,960	610	40,355	9.8%	15.4%	1.51%
	Cymbalta (Duloxetine)	2,537	378	27,886	9.1%	14.9%	1.36%
ID	Lamictal (Lamotrigine)	941	240	25,852	3.6%	25.5%	0.93%
	Seroquel (Quetiapine)	1,285	382	18,411	7.0%	29.7%	2.07%
	Risperdal (Risperidone)	730	150	13,568	5.4%	20.5%	1.11%
	Zoloft (Sertraline)	1,010	271	41,793	2.4%	26.8%	0.65%
	Prozac (Fluoxetine)	782	148	34,362	2.3%	18.9%	0.43%
PG	Lorazepam	202	149	23,735	0.9%	73.8%	0.63%
	Alprazolam	198	139	18,606	1.1%	70.2%	0.75%
TD	Lamictal (Lamotrigine)	383	113	25,852	1.5%	29.5%	0.44%
	Depakote (Divalproex Sodium)	250	83	11,847	2.1%	33.2%	0.70%
	Seroquel (Quetiapine)	634	202	18,411	3.4%	31.9%	1.10%
	Zyprexa (Olanzapine)	394	100	11,924	3.3%	25.4%	0.84%
	Risperdal (Risperidone)	311	65	13,568	2.3%	20.9%	0.48%

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

Client	# of ER claims	Reason?	Notes
AD	18	Lost	MULTNOMAH COUNTY HLTH DEPT: Housing issue client
OV	16	Lost	MULTNOMAH COUNTY HLTH DEPT: Housing issue client
EU	7	Lost	MULTNOMAH COUNTY HLTH DEPT: Housing issue client
AM	7	Vacation	3 month supply mental health meds
EM	5	Vacation	3 month supply mental health meds
KB	7	Vacation	3 month supply mental health meds

Drug Use Research & Management Program
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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

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	25	28	20	10
		Profiles Sent	13	17	8	4
		Responses Received	4	1	2	2
		Response Rate	31%	6%	25%	50%
		Information Useful or Will Change Practice	2	1	0	1
		Patient Not With Office	1	0	0	0
		Already Scheduled	3	1	2	2
		Will Not Schedule	0	0	0	0
		Requested No Future Notifications	0	0	1	0
	Antipsychotic Metabolic Monitoring	Members Identified	639	0	703	0
		Profiles Sent	637	0	701	0
		Members With Response	144	0	173	0
		Response Rate	23%	0	25%	0
		Newly Scheduled	50	0	83	0
		Provider Contacted	265	0	244	0
		Provider Responses	68	0	73	0
		Provider Agreed with Recommendation	17	0	17	0
		Patient Not With Office	19	0	17	0
	Polypharmacy	Members Identified	0	254	0	0
		Profiles Sent	0	252	0	0
		Responses Received	0	23	0	0
		Response Rate	0	9%	0	0
		Information Useful or Will Change Practice	0	0	0	0
		Patient Not With Office	0	0	0	0

Drug Use Research & Management Program
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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

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	158	134	64	128
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	30	24	10	28
	Children under age 18 on any psychotropic	Profiles Reviewed	128	113	58	113
	Children under age 6 on any psychotropic	Profiles Reviewed	8	7	9	12
	Lock-In	Profiles Reviewed	46	7	35	15
		Letters Sent To Providers	3	0	1	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0
		Locked In	19	2	11	9
	Polypharmacy	Profiles Reviewed	10	56	18	0
		Letters Sent To Providers	1	2	0	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0

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Retro-DUR Intervention History by Quarter FFY 2014 - 2015

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Safety Net	ICS/LABA	Disqualified	0	18	15	2
		Enrolled in CCO	0	3	1	0
		Erroneous denial	0	10	4	1
		No Provider Info	0	2	5	1
		Other	0	1	1	0
		TPL coordination issue	0	2	4	0
		Faxes Sent	0	13	10	10
		Combination Inhaler prescribed	0	8	2	4
		Controller prescribed	0	1	0	1
		SABA prescribed	0	2	4	2
		No Subsequent Pulmonary Claims	0	2	4	3

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Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2014 - 2015

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	1,164	2,583	45%	1,183	2,617	45%	1,007	2,280	44%			
Five or more concurrent psychotropics	112	9,762	1%	92	10,739	1%	114	10,071	1%			
Three or more concurrent psychotropics	1,672	9,762	17%	1,546	10,739	14%	1,661	10,071	16%			
Two or More Concurrent Antipsychotics	93	9,762	1%	83	10,739	1%	80	10,071	1%			
Under 18 years old on any antipsychotic	2,590	9,762	27%	2,628	10,739	24%	2,290	10,071	23%			
Youth five years and younger on psychotropics	173	9,762	2%	173	10,739	2%	145	10,071	1%			

11/12/2015

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

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

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Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2014 - 2015

Metric	First Quarter Oct - Dec			Second Quarter Jan - Mar			Third Quarter Apr - Jun			Fourth Quarter Jul - Sep		
	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%	Numerator	Denominator	%
Children on Antipsychotics without diabetes screen	306	502	61%	374	586	64%	307	456	67%			
Five or more concurrent psychotropics	14	2,065	1%	17	2,534	1%	21	2,296	1%			
Three or more concurrent psychotropics	328	2,065	16%	277	2,534	11%	307	2,296	13%			
Two or More Concurrent Antipsychotics	11	2,065	1%	12	2,534	0%	5	2,296	0%			
Under 18 years old on any antipsychotic	503	2,065	24%	588	2,534	23%	457	2,296	20%			
Youth five years and younger on psychotropics	43	2,065	2%	43	2,534	2%	38	2,296	2%			

11/12/2015

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

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

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Treating UTIs with the Tried and True

Kate Unterberger, Pharm.D. Candidate 2016 and Andrew Gibler, Pharm.D., Oregon State University College of Pharmacy Drug Use Research and Management

Symptomatic urinary tract infections (UTIs) are the most frequent bacterial infection diagnosed by outpatient providers, and one of the most common indications for antibiotic prescriptions every year.[1,2] Despite availability of clinical practice guidelines, UTIs are commonly not managed appropriately.[3-5] Recent evidence suggests that in most cases, shorter courses of antibiotics are equally as effective as longer regimens, are associated with fewer adverse events, and have less potential to promote antibiotic resistance.[6-8] For adults eligible for outpatient management with oral antibiotics, a shorter course of treatment may be best.

Uncomplicated UTIs

Bacteria commonly implicated in uncomplicated cystitis and pyelonephritis are listed in Table 1. *Escherichia coli* remains the most common pathogen and accounts for 75-95% of infections in women.[2,9] Other gram-negative bacteria associated with UTIs include *Proteus mirabilis* and *Klebsiella* species.[9] Although gram-positive bacteria are less commonly associated with uncomplicated UTIs, *Staphylococcus saprophyticus* is associated with 5% to 15% of UTIs, most of which are cases of cystitis in younger women.[9]

Table 1. Pathogens Commonly Implicated in Uncomplicated Cystitis and Pyelonephritis[3,7]

*Escherichia coli**	*Klebsiella pneumoniae*
Staphylococcus saprophyticus	*Proteus mirabilis*

*Accounts for 75%-95% of all UTIs

Uncomplicated Cystitis

UTIs are considered uncomplicated in otherwise healthy, non-pregnant premenopausal women without urinary tract abnormalities.[2,10,11] Cystitis, which affects the bladder and urethra, is a diagnosis typically based on patient-reported symptoms.[1,3] Cystitis rarely develops into pyelonephritis and can be successfully cured with only a few days of antibiotic treatment (Table 2).[2]

Table 2. Antibiotic Recommendations for Uncomplicated Cystitis[2,3,9,12]

	Drug	Dose	Days
First-line therapy	Nitrofurantoin *(Macrobid)*	100 mg BID	5
	TMP-SMX *(Bactrim DS, Septra DS)*	160/800 mg BID	3
Second-line therapy	Ciprofloxacin *(Cipro)*	250 mg BID	3
	Levofloxacin *(Levaquin)*	250 mg Daily	3
	Fosfomycin *(Monurol)*	3 grams Once	1

Abbreviations: BID, twice daily; mg, milligrams; TMP-SMX, trimethoprim-sulfamethoxazole.

The Infectious Disease Society of America (IDSA) recommends either nitrofurantoin or trimethoprim-sulfamethoxazole (TMP-SMX) as first-line therapy for acute uncomplicated cystitis, though local antibiograms can be helpful to guide empiric therapy.[3,13] TMP-SMX has long been considered first-line therapy in the United States, and is very effective against susceptible pathogens. However, increasing rates of resistance have caused the IDSA to modify their recommendation to apply only to cases in which local resistance rates to TMP-SMX do not exceed 20%.[3] Antibiograms from local Portland hospitals report that about 78% of *Escherichia coli* pathogens cultured from infected patients are susceptible to TMP-SMX.[14,15] The most appropriate antibiotic for uncomplicated cystitis may also depend on patient antibiotic and medical history, potential for adverse drug effects, drug interactions and cost.[13]

Clinical trial results demonstrate a 5-day course of nitrofurantoin has comparable efficacy to a 3-day course of TMP-SMX for treating acute uncomplicated cystitis.[10] Nitrofurantoin is an appropriate alternative antibiotic because resistance rates continue to remain low. It is indicated exclusively for UTIs, specifically in women, because therapeutic concentrations are only achieved in the urine. Nitrofurantoin is a reasonable option for patients on warfarin since the drug-drug interaction is less pronounced than with TMP-SMX or fluoroquinolones. However, it should be avoided in patients with renal impairment (creatinine clearance less than 60 mL/min), and it is not recommended for UTI treatment in men due to inferior tissue penetration.[2]

Fluoroquinolones, such as ciprofloxacin and levofloxacin, should generally be avoided in treatment of relatively benign infections such as uncomplicated UTIs, though they have demonstrated good efficacy for treating uncomplicated cystitis.[2] Fluoroquinolones are especially susceptible to antibiotic resistance, and should be reserved for more serious infections that have fewer treatment options.[3] However, contrary to these guideline recommendations, fluoroquinolones continue to be the most frequently prescribed antibiotics in the U.S. for treatment of outpatient UTIs.[5]

Fosfomycin, administered as a single 3-gram dose, is another treatment option for uncomplicated cystitis. It has shown little resistance, but it is more expensive and may have inferior efficacy compared to other treatments.[3] Fosfomycin may be a more appropriate choice in areas known to have higher levels of antibiotic resistance to other therapies.

Uncomplicated Pyelonephritis

UTIs that affect the kidneys are classified as pyelonephritis, and although some cases result in hospital admission, most can be treated in the outpatient setting (Table 3). Symptoms more indicative of acute uncomplicated pyelonephritis include flank pain, costovertebral angle tenderness (Murphy's punch sign or Pasternacki's sign), fever, nausea, and vomiting.[7,12] Unlike cystitis, diagnosis normally involves a urinalysis.[3,12] Urine culture and susceptibilities should guide antibiotic treatment, but fluoroquinolones are often recommended for empiric treatment in regions where resistance to fluoroquinolones does not exceed 10%.[2,3,9] In the Portland area, about 85% of *E. coli* isolates are susceptible to fluoroquinolones,[14,15] so the patient's medical history is an important consideration.

Table 3. Oral Antibiotic Recommendations for Acute Uncomplicated Pyelonephritis[2,3,9,12]

Drug	Dose	Days
Ciprofloxacin (Cipro)	500 mg BID	7
Levofloxacin (Levaquin)*	500 mg Daily	7
TMP-SMX (Bactrim DS, Septra DS)	160/800 mg BID	14

Abbreviations: BID, twice daily; mg, milligrams; TMP-SMX, trimethoprim-sulfamethoxazole
*Infectious Diseases Society of America also recommends 750 mg daily for 5 days as an option.

Due to the growing presence of antibiotic resistance, several studies have been performed to evaluate the optimal duration of antibiotic treatment for acute uncomplicated pyelonephritis.[6-8] Results suggest that a 7-day course of ciprofloxacin is equally effective as a 14-day course in terms of cure rates.[6] Likewise, a 7-day course of ciprofloxacin appears to have superior bacteriologic and clinical cure rates compared to a 14-day TMP-SMX regimen.[7]

Complicated UTIs

More pathogens are implicated in complicated UTIs. Even though *E. coli* and other enterobacteriaceae, such as *Klebsiella*, *Proteus*, and *Enterobacter*, still cause the majority of infections, cultures of complicated UTIs can also reveal *Pseudomonas, Enterococcus,* and *Staphylococcus* species.[12]

Little evidence exists to support treatment recommendations for complicated cystitis and pyelonephritis. Complicated UTIs are associated with a co-morbid condition or urinary tract abnormality, examples of which can be found in Table 4.[12]

Table 4. Example Criteria for Complicated UTI Classification[9]

Pregnancy
Diabetes mellitus
Male gender
Immunosuppression with immunosuppressive medications
Functional urinary tract abnormality: indwelling catheter, neurogenic bladder, others
Structural urinary tract abnormality: kidney stones, fistula, polycystic kidney disease, kidney transplant, others

All UTIs in males are considered complicated. Most cases resolve after 7 days with a fluoroquinolone or TMP-SMX, though some conditions such as acute prostatitis may require at least 14 days of treatment.[9,12]

Likewise, UTIs that occur during pregnancy are considered complicated. Amoxicillin, amoxicillin/clavulanate, nitrofurantoin, fosfomycin, or cephalexin are reasonable oral antibiotics for the outpatient treatment of acute UTI during pregnancy.[12] TMP-SMX should be avoided during the 1st trimester because of potential risk for neural tube defects.[12] Fluoroquinolone antibiotics lack evidence for safety during pregnancy and should be avoided entirely.

Treatment duration varies by complication, but usually lasts 7 to 14 days.[11,12] Table 4 shows oral antibiotics that are commonly used for outpatient treatment of complicated UTIs.[16]

Table 5. Oral Antibiotic Treatment Options for *Complicated* UTIs[12,16]

Fluoroquinolones: ciprofloxacin (Cipro) or levofloxacin (Levaquin)
Broad spectrum Beta-lactams: amoxicillin/clavulanate (Augmentin), cefdinir (Omnicef), or ceftibuten (Cedax)
Trimethoprim-sulfamethoxazole (Bactrim DS, Septra DS)

Evidence Suggests Shorter is Better

As antibiotic resistance continues to increase, treating infections with the shortest effective duration becomes increasingly important. Shortening the duration of antibiotic therapy not only reduces resistance, but also reduces risk of adverse drug events and decreases cost of therapy.[17]

Serious adverse drug events, including *Clostridium difficile* infection, occur more frequently with prolonged use of antibiotics.[18] Risk of infection increases with use of broad-spectrum antibiotics, many of which are easy and effective choices for UTI treatment. Similarly, in the trial that demonstrated equivalent results in 7-day and 14-day regimens of ciprofloxacin for uncomplicated pyelonephritis, symptomatic *Candida* overgrowth was observed more frequently in patients who received the 14-day course.[6] Other notable risks associated with these antibiotics include prolonged QT-interval and tendon rupture with fluoroquinolones; photosensitivity and hyperkalemia with TMP-SMX; and vaginitis with fosfomycin.[13,16,19]

Conclusion

The evidence clearly shows shorter courses of antibiotics for acute treatments of uncomplicated UTIs are as effective as longer courses. Furthermore, using the shortest effective course of antibiotics is a public health priority: naturally, risk of adverse effects increases as the duration of antibiotic therapy increases; but also, overuse promotes widespread antibiotic resistance.

Local antibiograms can be helpful tools for guiding antibiotic selection. TMP-SMX remains an important first-line agent for uncomplicated cystitis, but local resistance rates are around 20%.[14,15] Fluoroquinolones are very effective at treating uncomplicated cystitis, but fluoroquinolones are especially prone to resistance with general use, and therefore should be reserved for pyelonephritis, complicated UTIs, or more serious infections. Nitrofurantoin should be used in female patients with uncomplicated cystitis and normal renal function. Lastly, fosfomycin is expensive but has a unique niche as a single-dose treatment option for uncomplicated cystitis.[3]

Peer Reviewed By: James Lewis, Pharm.D., Infectious Diseases Clinical Coordinator, Oregon Health & Science University and Tracy Klein, PhD, FNP, Assistant Professor, College of Nursing, Washington State University Vancouver

References:

1. Foxman B. Urinary tract infection syndromes: Occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am*. 2014;28(1):1-13.
2. Hooton TM. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366(11):1028-1037.
3. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the infectious diseases society of america and the european society for microbiology and infectious diseases. *Clinical Infectious Diseases*. 2011;52(5):e103-e120.
4. Shepherd AK, Pottinger PS. Management of urinary tract infections in the era of increasing antimicrobial resistance. *Med Clin North Am*. 2013;97(4):737-757.
5. Kallen AJ, Welch H,Sirovich BE. CUrrent antibiotic therapy for isolated urinary tract infections in women. *Archives of Internal Medicine*. 2006;166(6):635-639.
6. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: A randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. *The Lancet*. 2012;380(9840):484-490.
7. Talan DA, Stamm WE, Hooton TM,et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: A randomized trial. *JAMA*. 2000;283(12):1583-1590.
8. Eliakim-Raz N, Yahav D, Paul M, Leibovici L. Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection— 7 days or less versus longer treatment: Systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy*. 2013;68(10):2183-2191.
9. Lane DR, Takhar SS. Diagnosis and management of urinary tract infection and pyelonephritis. *Emerg Med Clin North Am*. 2011;29(3):539-552.
10. Gupta K, Hooton TM, Roberts PL,Stamm WE. SHort-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of Internal Medicine*. 2007;167(20):2207-2212.
11. Grigoryan L, Trautner BW,Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: A review. *JAMA*. 2014;312(16):1677-1684.
12. Grabe M, Bartoletti R, Bjerklund-Johansen T, et al. Guidelines on urological infections. *European association of urology*. Updated March 2015. Available at http://uroweb.org/guideline/urological-infections/. Accessed 11 May 2015.
13. Shepherd AK, Pottinger PS. Management of urinary tract infections in the era of increasing antimicrobial resistance. *Med Clin North Am*. 2013;97(4):737-757.
14. *OHSU adult outpatient antibiogram 2012*. OHSU Department of Pharmacy services; 2012. OHSU Drug Information/Drug Policy Services and OHSU Clinical Microbiology Laboratories, ed.
15. *Legacy health system adult outpatient antibiogram.* ; 2011. Legacy Health System Microbiology Department, ed.
16. DRugs for urinary tract infections. *JAMA*. 2014;311(8):855-856.
17. Esposito S, Esposito I, Leone S. Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections. *Journal of Antimicrobial Chemotherapy*. 2012;67(11):2570-2575.
18. Rice LB. The maxwell finland lecture: For the duration— rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. *Clinical Infectious Diseases*. 2008;46(4):491-496.
19. Drekonja DM, Okoye NC, Kuskowski MA,Johnson JR. APpropriateness of urinary tract infection diagnosis and treatment duration. *Archives of Internal Medicine*. 2010;170(5):489-490.

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New Hypertension Guidelines: Do Blood Pressure Goals Need to Change with Age?

By Samaneh Zhian, M.S., Pharm. D. Candidate, Leah Goeres, Pharm.D., Harleen Singh, Pharm.D. BCPS., Oregon State University College of Pharmacy

The later part of 2013, saw a new wave of hypertension (HTN) guidelines. The long awaited Eighth Report of the Joint National Committee (JNC8) was released along with several other guidelines.[1,2,3] These guidelines are not uniform in their recommendations and have varied blood pressure (BP) goals and pharmacological treatment recommendations. The focus of this newsletter is to highlight the key recommendations and controversies with JNC8 guidelines in the context of the scientific literature to date.

JNC8 Guidelines

There are nine general recommendations made in JNC 8 which are based on quantitative systematic reviews of randomized clinical trials (RCTs) summarized in **Table 1**. The quality of evidence and strength of recommendations were rated based on NHLBI grading format. The NHLBI appoints expert panels to conduct systematic evidence reviews to enable clinical practice guideline development. The NHLBI grading methodologies range from A – Strong evidence to support the recommendation to E – Expert Opinions support the recommendation and the evidence is not clear.

Table 1. JNC8 Recommendations for Management of Hypertension[1]

Recommendations	Grade
1. Population age ≥ 60 years, initiate therapy at BP ≥ 150/90 mm Hg to lower BP to <150/90 mmHg	A-Strong
2. Population age <60 years, initiate therapy at DBP ≥ 90 mm Hg to lower DBP to < 90 mmHg	A-Strong (age 30-59) E-Expert Opinion (age 18-29)
3. Population age < 60 years, initiate therapy at SBP ≥ 140 mmHg to lower SBP to <140 mmHg	E-Expert Opinion
4. Population age ≥ 18 years with CKD or Diabetes, initiate therapy at BP ≥140/90 mmHg to lower BP to < 140/90 mmHg	E-Expert Opinion
5. Population age ≥ 18 years with diabetes, initiate therapy at BP ≥140/90 mmHg to lower BP to < 140/90 mmHg	E-Expert Opinion
6. In nonblack population, initial antihypertensive treatment should include a thiazide, CCB, ACEI/ARB	B-Moderate
7. In black population, initial antihypertensive treatment should include a thiazide or CCB	B-Moderate (without diabetes) C-Weak (with diabetes)
8. Population age ≥ 18 years with CKD, regardless of race, initial antihypertensive treatment should include an ACEI/ARB	B-Moderate
9. If goal BP is not reached within 1 month, increase the dose or add second agent. If goal BP not reach with 2 drugs, add and titrate a third drug. Do not use an ACEI and an ARB together. If goal BP cannot be reached with recommended medications, antihypertensive drugs from other classes can be used. Referral to a hypertensive specialist may be indicated.	E-Expert Opinion

Abbreviations: ACEI- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, BP- blood pressure, CCB- calcium channel blocker, CKD- chronic kidney disease, DBP- diastolic blood pressure, SBP-systolic blood pressure

Treatment

The JNC8 recommendations for initial pharmacologic treatment are summarized in **Table 2**. Like the JNC7 panel, the JNC8 panel recommended thiazide-type diuretics as initial therapy for most patients. Although angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) are acceptable alternatives, thiazide-type diuretics still have the best evidence for outcomes such as decreased stroke and all-cause mortality. The JNC 8 panel does not recommended first-line therapy with beta-blockers (BB) and alpha-blockers due to higher rate of CV events when compared to ARBs and diuretics, respectively.

According to JNC8 guidelines, if the goal BP is not reached within 1 month of treatment initiation there are two recommended strategies: 1) the dose of the drug can be increased, 2) a second or third agent from the recommended drug classes can be initiated. The patient may be referred to a hypertension specialist if goal BP cannot be attained using the above strategies or for the management of complicated patients. The panel recommends that those who have achieved tighter BP control than the stated goal and are tolerating their treatment without adverse effects on health or quality of life can continue current treatment without adjustment.

The guidelines do not recommend the concomitant use of ACEI and ARB. This combination has not been shown to improve mortality and morbidity rates from cardiovascular (CV) causes and is associated with increased risk of side effects such as hypotension and renal impairment.[1]

Similar to JNC7, lifestyle modifications are strongly emphasized in JNC8 and include the Dietary Approaches to Stop Hypertension (DASH) eating plan, weight loss, sodium intake of less than 2.4 grams per day, and at least 30 minutes of aerobic activity most days of the week.

Table 2: Comparison of Goal BP and Initial Drug Therapy for Adults with Hypertension[1-3, 8]

Guideline	Population	Initiation Trigger (mm Hg)	Goal BP (mm Hg)	Initial Drug Treatment Options
JNC 8 (2013)	≥ 60 y	≥150/90	<150/90	Non-Black: thiazide, ACEI, ARB, or CCB Black: thiazide or CCB
	< 60 y	≥140/90	<140/90	
	Diabetes	≥140/90	<140/90	Thiazide, ACEI, ARB, or CCB
	CKD	≥140/90	<140/90	ACEI or ARB
CHEP (2014)	≥ 80	≥160/100	<150/90	Non-Black: thiazide, ACEI, ARB, or CCB Black: thiazide, ARB, BB, CCB
	<80	≥160/100	<140/90	
	Pt w/ CV risk or target organ damage	≥140/90	<140/90	ACEI or ARB
	Diabetes	≥130/80	<130/80	Thiazide, ACEI, ARB, or CCB
ASH/ ISH	< 80 y	≥140/90	<140/90	Non-Black (<60 y): ACEI or ARB Non-Black (≥60 y): CCB or thiazide (may consider ACEI or ARB) Black (all ages): CCB or thiazide
	≥ 80 y	≥150/90	<150/90	
	Diabetes	≥ 140/90	< 140/90	ACEI or ARB (black can consider CCB or thiazide)
	CKD	≥140/90	<140/90	ACEI or ARB
AHA/ACC /CDC	General population	≥140/90	<140/90	CAD/Post MI: BB, ACEI Systolic HF: ACEI or ARB, BB, aldosterone-antagonist, thiazide Diastolic HF: ACEI or ARB, BB, thiazide Diabetes: ACEI or ARB, thiazide, BB, CCB CKD: ACEI or ARB Stroke/TIA: thiazide or ACEI

Abbreviations: BB- beta-blocker, ACEI- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, CAD - coronary artery disease, CCB - calcium channel blocker, CKD- chronic kidney disease, HF- heart failure, MI- myocardial infarction, TIA- transient ischemic attack.

Special Therapeutic Consideration

The JNC8 recommends ACEI or ARBS for all patients with chronic kidney disease (CKD) and HTN, regardless of their ethnic background or diabetes status, to protect kidney function. One exception is noted for patients over the age of 75. The panel cited that ACEIs and ARBs may increase serum creatinine and risk of hyperkalemia. As a result, thiazide-type diuretics or CCBs are an acceptable alternative for patients over the age of 75 with decreased renal function.

Discussion

Even with the grade A rating, there is some controversy regarding the first recommendation which raises the BP goal in the general population of adults 60 years of age and older. For these patients, without diabetes or CKD, JNC8 recommends to initiate pharmacologic treatment when BP is ≥ 150/90 to a goal of < 150/90 mm Hg. Currently, most guidelines are in agreement for BP goals of < 150/90 mm Hg for the oldest adults (those 80 years old or older); however, there remains controversy on BP goals in "young" older adults (65-80 years old).

There were six key studies used to support the goal blood pressure recommendations for the JNC8 guideline. The HYpertension in the Very Elderly Trial (HYVET), is the only study to date that demonstrated that antihypertensive treatment to a SBP goal of <150 mm Hg in individuals aged 80 years and older is associated with reduction in CV outcomes.[4] Three other RCTs (JATOS, VALISH, CARDIO-SIS) cited by JNC8 compare different SBP goals on CV outcomes among older adults. In the Japanese Trial to Assess Optimal Systolic BP in Elderly Hypertensive Patients (JATOS), the benefit of SBP reduction to <140 mmHg (strict control) versus 140 to 159 mm Hg (mild-treatment) was evaluated in 4418 individuals aged 65 to 84 years with SBP ≥160 mm Hg at baseline. Differences in outcomes and mortality were not statistically significant.[5] In another trial the benefit of SBP reduction to <140 mmHg (strict control) versus 140 to 149 mm Hg (moderate-treatment) was evaluated in individuals aged 70 to 84. [6] In both trials the incidences of CV outcomes were not significantly different across randomized arms. It is important to note that the lengths of study in both trials were relatively short and study cohorts were relatively healthy. Therefore, these trials had inadequate statistical power to detect benefits of the lower SBP goals. Additionally, generalizability of the Japanese trials to other patient populations is limited.

Recent guidelines from Europe[7] and Canada[8] have concluded that the appropriate cut point for an age-related differential SBP goal is 80 years or older and not 60 years, recommending a BP goal of <140/90 mm Hg for patients aged 60-80 years (see Table 1). The American College of Cardiology Foundation /American Heart Association (ACCF/AHA) 2011, is the only guideline specifically tailored to hypertension in older adults and suggested that a target BP of <140/90 mm Hg in persons aged 65 to 79 years and a target SBP of 140 to 145 mm Hg in persons aged 80 years and older, if tolerated.[9] The authors of each of these guidelines have emphasized that very limited data exist to make definitive recommendations on the target BP goal in the elderly.

The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension emphasized that available randomized trials of antihypertensive treatments in the elderly showed a reduction in cardiovascular disease (CVD) events by lowering BP but the average SBP achieved in trials was never <140 mm Hg. Therefore, they suggested that elderly individuals with HTN should be treated to SBP levels of 140-149 mm Hg. In "fit" persons, aged less than 80 years, a SBP goal <140 mm Hg may be considered, whereas in frail elderly individuals, they recommended that SBP goals be adapted to individual tolerability.[7]

The Canadian Hypertension Education Program (CHEP) guideline, is in agreement with ESH/ESC and recommends BP targets of SBP <150 mm Hg for patients aged 80 years or older. However, it is a grade C recommendation based on low-quality trials, invalidated surrogate outcomes, or results from non-randomized observational studies.[8]

Although these trials provide new knowledge about hypertensive treatment in the elderly, the optimal BP goal for the "young" elderly population remains unknown. Further studies, with longer durations of follow-up and populations with comorbidities are needed to guide clinical practice. Some experts believe increasing the target BP goal will reduce the intensity of antihypertensive treatment in a large population at high risk for CVD. This change would apply to populations who are underrepresented in the literature and considered to be at higher cardiovascular risk: African Americans, people with multiple chronic conditions, and those with established CVD. Some experts speculate that a higher SBP goal in individuals aged 60 years and older may reverse the decades-long trend of declining in CVD in particularly vulnerable American populations.[10] Adding to the complexity of getting the elderly to their blood pressure goal is the issue of adverse effects, such as dehydration, orthostatic hypotension and renal insufficiency, which can be more pronounced in the elderly.

Conclusion

Clinical guidelines set out to identify, summarize, and evaluate quality evidence with the aim of guiding clinical decisions. However, high quality evidence regarding hypertension treatment goals remains limited, especially in special populations. There remains a critical knowledge gap on the optimal SBP target and a single SBP goal may not be appropriate for all older adults.

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References:

[1] James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2013.

[2] Go AS, Bauman M, Coleman King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory From the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *J Am Coll Cardiol.*2014;63(12):1230-1238.

[3] Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. A statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens* 2013.

[4] Bulpitt CJ, Beckett NS, Cooke J, et al. Hypertension in the Very Elderly Trial Working Group. Results of the pilot trial for the Hypertension in the Very Elderly Trial. *J Hypertens*. 2003;21:2409–17.

[5] JATOS Study Group. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS): protocol, patient characteristics, and blood pressure during the first 12 months. *Hypertens Res*. 2005;28:513–20.

[6] Ogihara T, Saruta T, Rakugi H, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension*. 2010;56:196–202.

[7] Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–357.

[8] DG, Quinn RR, Ravani P, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2013; 29:528–542.

[9] Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2011;123:2434–506.

[10] Lackland DT, Roccella EJ, Deutsch AF, et al, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, and Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014; 45:315-53.

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Is Long-Term Proton Pump Inhibitor Treatment for GERD Worth the Risk?

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New Funding Placement of GERD Treatment

Proton Pump Inhibitors (PPI) are a major economic burden for the healthcare system; not necessarily because of the cost of the drugs but because of the overprescribing of these drugs for minor symptoms without clear indications, as well as the increasing long-term use of PPIs. PPIs and histamine-2 receptor antagonists (H2RA) were associated with nearly $500,000 annual net cost in the Oregon Health Plan (OHP) fee-for-service (FFS) program and $2.13 million annual net cost in the coordinated care organizations during the 2014 calendar year.[1] The Health Evidence Review Committee placed long-term (greater than 8 weeks) medical treatment of gastro-esophageal reflux disease (GERD) below the OHP funding line on the Prioritized List of Services effective January 1, 2015.[2] Dyspepsia continues to be a non-funded condition. However, other U.S. Food and Drug Administration (FDA) approved indications for PPIs and H2RAs (e.g., gastrointestinal ulcers, pathological hyper-secretory conditions, *Helicobacter pylori* eradication) remain funded.

This article will review the evidence for long-term PPI safety and efficacy, describe current FFS utilization trends, communicate FFS PPI policy changes, and present guidance to assist with weaning patients off of long-term PPIs.

Evidence for Long-term Safety and Efficacy of Proton Pump Inhibitors

Proton pump inhibitors are well tolerated and are generally thought to be safe. However, long-term use of PPIs is now commonplace despite lack of evidence for long-term safety or efficacy. Prescribers should consider the diagnosis prior to treatment. Clinical practice guidelines recommend only 4 weeks of PPI therapy for uninvestigated dyspepsia.[3,4] High quality evidence suggests only 8 weeks of PPI therapy is needed for GERD or erosive esophagitis, but diagnosis is dependent on endoscopy, and symptoms can be poorly correlated with endoscopic findings.[3,4] There is insufficient evidence for PPI use beyond 8 weeks for GERD, and patients who do not respond to 8 weeks of therapy should be referred for further evaluation. Despite lack of evidence, long-term maintenance therapy is sometimes recommended for cases of chronic, severe esophagitis.[3,4] However, symptoms typically fluctuate, and on-demand use of acid suppressants (ie, PRN dosing) has demonstrated to be effective and is the preferred method of treatment for chronic dyspepsia or GERD.[4,5]

Growing evidence demonstrates long-term use might not be as harmless as first considered, and the FDA periodically updates prescribing information of PPIs with new safety alerts (Table 1).[6] However, randomized controlled trials are not feasible for most of the potentially associated harms of PPIs. The majority of observed associations are based on observational cohort studies and case reports and requires careful interpretation.

Table 1. Post-marketing FDA Safety Alerts for Proton Pump Inhibitors.[6]

***Clostridium difficile* Infection**	An increased risk of *C. difficile*-associated diarrhea has been associated with PPI use.
Bone Fractures	An increased risk of osteoporosis and fractures of the hip, wrist and spine have been associated with long-term (1 year or longer) use of PPIs, high doses of PPIs, or multiple daily doses of PPIs.
Vitamin B-12 Deficiency	Long-term use of PPIs (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin due to sustained hypochlorhydria.
Low Magnesium	Use of PPIs for greater than 1 year increases risk of hypomagnesemia which may not be reversible with oral magnesium supplementation.

A systematic review evaluated all studies that investigated the risk of *Clostridium difficile* infection (CDI) between 1990 and 2010.[7] Together, 25 case-control studies and 5 cohort studies were identified, which presented very heterogeneous data.[7] Despite the heterogeneity, the results between case-control studies and cohort studies consistently demonstrated higher risk of CDI with PPI use. A meta-analysis of the data was performed and the investigators found PPI therapy was associated with a 2-fold increased risk of CDI (odds ratio [OR] = 2.15, 95% Confidence Interval [CI], 1.81 to 2.55).[7]

Evidence limited to 11 observational cohort or case-control studies composed of mostly older adults suggests use of PPIs is associated with a modest increased risk in hip fractures (relative risk [RR] = 1.30; 95% CI, 1.19 to 1.43) and spine fractures (RR 1.56; 95% CI, 1.31 to 1.85).[8] These associated risks persisted after stratifying data by sex or duration of PPI use.[8] PPI use for less than 1 year was associated with a RR for hip fracture of 1.39 (95% CI, 1.10 to 1.74) and PPI use greater than 1 year was associated with a RR of 1.24 (95% CI, 1.19 to 1.29).[8]

An association between chronic PPI use and iron and vitamin B-12 deficiency is still controversial.[9] Results from observational studies assessing chronic PPI use and iron deficiency are contradictory, and it is doubtful an association can be found with the available data.[9] Most studies assessing vitamin B-12 deficiency, however, suggest a definite association exists between chronic PPI use and vitamin B-12 deficiency or vitamin B-12 supplementation;[9] however, no meta-analysis has been performed to quantify whether the association is significant. None of the studies identified found an association between H2RA use and iron or vitamin B-12 deficiency.[9]

The potential association between PPIs and hypomagnesemia was investigated in a systematic review and meta-analysis.[10] Data from 9 studies with more than 100,000 patients were analyzed.[10] Patients using PPIs had higher rates of hypomagnesemia versus patients who did not use PPIs (27.1% vs. 18.4%, respectively; OR = 1.78; 95% CI, 1.08 to 2.92).[10] Though there appears to be an association between regular use of PPIs and hypomagnesemia, significant heterogeneity between the studies analyzed limit the interpretation of these results.[10]

The cardiovascular risk associated with PPIs outside high-risk cohorts has not been adequately studied. Recently, however, a novel population data-mining approach for pharmacovigilance was performed on multiple medical record data sets of adult patients with GERD diagnoses.[11] Patients were matched and balanced to controls based on several covariates.[11] The data demonstrated a positive association between GERD patients exposed to PPIs and risk for myocardial infarction (OR = 1.16; 95% CI, 1.09 to 1.24).[11] The investigators approached yielded 97.5% specificity and 39% sensitivity in discerning a true association, which according to the investigators, provided 89% accuracy.[11] When data were analyzed in a separate prospective cohort, increased risk for cardiovascular mortality among PPI users was also found despite the investigators accounting for cardiovascular comorbidities (hazard ratio [HR] = 2.00; 95% CI, 1.07 to 3.78).[11] There were no such associations found between GERD patients exposed to H2RAs.[11]

Studies conducted since 1987 that investigated the association between PPIs and community-acquired pneumonia (CAP) were systematically reviewed.[12] Two retrospective cohorts and 7 case-control studies were available totaling over 120,000 pneumonia cases.[12] Use of PPIs was associated with increased risk of CAP (OR = 1.39; 95% CI, 1.09 to 1.76).[12] A stronger association was observed with higher doses of PPIs (OR = 1.50; 95% CI, 1.33 to 1.68).[12] Interestingly, the highest risk was for short-term PPI use.[12] No association between long-term PPI use (>180 days) and CAP was found.[12]

It has been suggested that long-term use of PPIs could promote the development of pre-cancerous lesions in the stomach, which might then increase the

occurrence of stomach cancers in PPI patients. However, there is no clear evidence to support these suggestions, though increased thickening of the stomach lining (hyperplasia) has been observed with long-term PPI use.[13] Such a condition can rarely lead to benign gastric carcinoids.[13]

Findings of PPI Drug Use Evaluation in Oregon Health Plan

The Oregon Pharmacy and Therapeutics Committee reviewed FFS PPI and H2RA utilization patterns for calendar year 2014.[14] PPIs accounted for 90% of all acid suppression claims and 84% were for preferred generics (omeprazole and pantoprazole).[14] The preferred H2RA (ranitidine) was associated with 8% of claims and the remaining 2% were associated with generic famotidine and cimetidine.[14] Over 75% of all patients (n=6712) were on acid suppression therapy longer than 8 weeks.[14] Funded OHP conditions were associated with just 14% of patients on continuous long-term PPI therapy and treatment averaged over 230 days per patient in 2014.[14]

Given the extensive long-term use by OHP FFS patients, lack of associated funded diagnosis and known risks associated with PPIs, the current prior authorization (PA) policy will limit use of all PPIs beyond 8 weeks to documented funded diagnoses effective July 1, 2015.[15] Current patients on long-term PPIs will be automatically approved for 1 year to allow for tapering. Preferred H2RAs will remain with open access due to their low overall utilization and established safety profile. Updated PA criteria allows some exceptions for use of PPIs under the OHP.[15]

Strategies to Wean Off Proton Pump Inhibitors

It is well understood that rebound acid hypersecretion following cessation of PPIs can occur. However, there is insufficient evidence to suggest this is a consistent phenomenon.[16] Studies evaluating rebound acid hypersecretion are of low-quality and have yielded contradictory results based on duration of therapy.[16] Therapy for up to 4 weeks found no evidence of rebound acid hypersecretion while therapy for 8 weeks or longer found evidence of hypersecretion.[16] The clinical importance of this acid rebound following the treatment with acid-suppressive therapy is unclear, but it may make it more difficult to discontinue PPIs. Thus, tapering off a PPI seems more logical than abruptly discontinuing a PPI, especially after long-term therapy.

There is a lack of consensus and guidelines on how to best discontinue long-term PPI therapy. A small number of discontinuation strategies have been investigated in patients with dyspepsia or non-erosive esophagitis, but very few studies have evaluated a specific discontinuation method and their effect on successful long-term discontinuation rates.[17] Studies with the highest long-term success rates (range, 30-60% at 12 months) used a brief 2- or 3-week PPI taper using a half-dose once daily or a full-dose on alternate days, in addition to providing patients with both oral and written education on symptom management and offering alternate drug therapy for breakthrough symptoms.[17] Studies assessing abrupt discontinuation of the PPI without a taper had much less successful permanent discontinuation rates.[17] It is unknown if tapering regimens longer than 3 weeks lead to improved discontinuation rates. Certainly, randomized clinical trials comparing different PPI discontinuation strategies are needed to inform this practice.

Regardless of the discontinuation strategy, screening for *H. pylori* infection and other appropriate diagnostic workups, if not previously performed, will identify patients less likely to tolerate PPI withdrawal and ensure appropriate treatment is initiated. In addition, providing written and verbal education about lifestyle and environmental strategies[18] and alternative treatment options to manage dyspepsia (eg, H2RAs and/or antacids) will ease the transition off the PPI. OHP patients have open access to preferred drugs like ranitidine and calcium carbonate.[19]

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References:

1. 2014 Market Share Reports, Oregon Health Authority [internal]. Drug Use Research and Management Program, Oregon State University College of Pharmacy.

2. Highlights of the Changes Reflected in the January 1, 2015 Prioritized List. http://www.oregon.gov/oha/herc/PrioritizedList/Change%20Highlights%20for%201-1-2015.pdf. Accessed July 16, 2015.

3. Katz P, Gerson L, Vela M. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol*. 2013;108:308-328.

4. National Institute for Health and Care Excellence. Dyspepsia and gastro-oesophageal reflux disease. NICE Clinical Guideline 184. 2014. guideline.nice.org/uk/cg184.

5. Pace F, Tonini M, Pallotta S, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Parmacol Ther*. 2007;26:195-204.

6. Medical Product Safety Information. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/. Accessed July 16, 2015.

7. Deshpande A, Pant C, Pasupuleti V, et al. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:225-233.

8. Yu EW, Bauer SR, Bain PA, et al. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med*. 2011;124:519-526. doi: 10.1016/j.amjmed.2011.01.007.

9. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep*. 2010;12:448-457. doi:10.1007/s11894-010-0141-0.

10. Park CH, Kim EH, Roh YH, et al. The association between the use of proton pump inhibitors and the risk of hypomagnesemia: a systematic review and meta-analysis. *PLoS ONE*. 2014;9:e112558. doi: 10.1371/journal.pone.0112558.

11. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS ONE*. 2015;10:e0124653. doi:10.1371/journal.pone.0124653.

12. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. *Exp Rev Clin Pharmacol*. 2012;5:337-344. doi: 10.1586/ecp.12.20.

13. Song H, Zhu J, Lu D. Long-term proton pump inhibitor (PPI) use and the development of gastric pre-malignant lesions. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010623. doi: 10.1002/14651858.CD010623.pub2.

14. Ketchum KL. Drug Use Evaluation: Proton Pump Inhibitor (PPI) /Histamine-2 Receptor Antagonist (H2RA) Length of Therapy. March 26, 2015. http://www.orpdl.org/durm/meetings/meetingdocs/2015_03_26/archives/2015_03_26_ProtonPumpInhibitorsDrugUseEvaluation.pdf. Accessed April 10, 2015.

15. Oregon Medicaid PA Criteria. Pharmaceutical Services Program, Oregon Health Plan. Available at http://www.oregon.gov/oha/healthplan/Pages/pharmacy-policy.aspx. Accessed July 12, 2015.

16. Hunfeld NGM, Geus WP, and Kuipers EJ. Systematic review: rebound acid hypersecretion after therapy with proton pump inhibitors. *Aliment Pharmacol Ther*. 2006;25:39-46. doi:10.1111/j.1365-2036.2006.03171.x.

17. Haastrup P, Paulsen MS, Begtrup LM, et al. Strategies for discontinuation of proton pump inhibitors: a systematic review. *Family Practice*. 2014;31:625-630. doi:10.1093/fampra/cmu050.

18. Kahrilas PJ. Gastroesophageal reflux disease. *N Engl J Med*. 2008;359:1700-7.

19. Oregon Medicaid FFS Drug Class List. The Oregon Health Plan. Available at www.orpdl.org/drugs/. Accessed July 16, 2015.

Intranasal Allergy Drugs

Goals:

- Restrict use of intranasal allergy inhalers for conditions funded by the OHP and where there is evidence of benefit.
- Treatment for allergic or non-allergic rhinitis is funded by the OHP only if it complicates asthma, sinusitis or obstructive sleep apnea. Only intranasal corticosteroids have evidence of benefit for these conditions.

Length of Authorization:

30 days to 6 months

Requires PA:

- Preferred intranasal corticosteroids without prior claims evidence of asthma
- Non-preferred intranasal corticosteroids
- Intranasal antihistamines
- Intranasal cromolyn sodium

Covered Alternatives:

- Preferred alternatives listed at http://orpdl.org/drugs/
- Preferred intranasal corticosteroids, preferred second generation antihistamines, and first generation antihistamines DO NOT require prior authorization.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the prescribed drug an intranasal corticosteroid?	Yes: Go to #3	No: Pass to RPh; deny (not funded by OHP)
3. Is the prescribed drug a preferred product?	Yes: Go to #5	No: Go to #4
4. Will the prescriber consider switching to a preferred product? Note: Preferred products 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 provider of preferred alternatives; go to #5	No: Go to #5
5. Does patient have co-morbid conditions funded by the OHP? • Chronic Sinusitis (J320-J329) • Acute Sinusitis (J0100; J0110; J0120; J0130; J0140; J0190) • Sleep Apnea (G4730; G4731; G4733; G4739)	Yes: Document ICD10 code(s) and approve for up to 6 months for chronic sinusitis or sleep apnea and approve for no more than 30 days for acute sinusitis	No: Go to #6

Approval Criteria		
6. Is there a diagnosis of asthma or reactive airway disease in the past 1 year (J440-J4522; J45901-45998)?	Yes: Go to #7	No: Go to #8
7. Is there a claim for an *orally* inhaled corticosteroid in the past 90 days? <u>Note</u>: Asthma-related outcomes are not improved by the addition of an intranasal corticosteroid to an orally inhaled corticosteroid.	Yes: Pass to RPh; deny for medical appropriateness	No: Approve for up to 6 months
8. RPh only: Is the diagnosis funded by the OHP?	Funded: Deny for medical appropriateness. (eg, COPD; Obstructive Chronic Bronchitis; or other Chronic Bronchitis [J449; J40; J410-418; J42; J440-449] Use clinical judgment to APPROVE for 1 month starting today to allow time for appeal. Message: “The request has been denied because it is considered medically inappropriate; however, it has been APPROVED for 1 month to allow time for appeal.”	Not Funded: Deny, not funded by the OHP. (eg, allergic rhinitis (J300-J309); chronic rhinitis (J310-312); allergic conjunctivitis (H1045); upper respiratory infection (J069); acute nasopharyngitis (common cold) (J00); urticaria (L500-L509); etc.)

P&T / DUR Review: *11/15 (AG); 7/15; 9/08; 2/06; 9/04; 5/04; 5/02*
Implementation: *TBD; 8/25/15; 8/09; 9/06; 3/06; 5/05; 10/04; 8/02*

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Promote use that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LABA/ICS products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform provider of covered alternatives in class	No: Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J440-J4522, J45901-45998)?	Yes: Go to #7	No: Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist), or alternatively has the patient been assessed with GOLD C/D COPD?	Yes: Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.	No: Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	Yes: Go to #8	No: Pass to RPh; Deny, medical appropriateness
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate to severe persistent asthma (Step 3 or higher per NIH EPR 3)?	Yes: Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.	No: Pass to RPh; Deny, medical appropriateness

P&T/DUR Review: *11/15 (KS); 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *TBD; 1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist Combination (LAMA/LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Promote COPD therapy that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
    - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of preferred LAMA and LABA products in each class	No: Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J440-J4522, J45901-45998)?	Yes: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	No: Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Has the patient been assessed with GOLD C/D COPD?	Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.	No: Go to #7
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (ie, ipratropium/albuterol)?	Yes: Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	No: Pass to RPh. Deny; medical appropriateness.

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Standard Methods for Quality Assessment of Evidence

The methods described herein is the standard approach used by the Drug Use Research & Management faculty to assess quality of evidence incorporated into the evidence summaries for the Oregon Health Plan (OHP) Pharmacy and Therapeutics Committee. These evidence summaries inform the recommendations for management of the preferred drug list (PDL) and clinical prior authorization (PA) criteria. These methods support the principles of evidence-based medicine and will continue to evolve to best fit the needs of the Committee and stay current with best practices.

Recommendations in evidence summaries (ie, Drug Class Reviews, Updates, or Literature Scans) are determined primarily from high quality systematic reviews. High quality clinical practice guidelines and relevant clinical trials are also used as supplementary evidence. New Drug Evaluations are more focused and primarily rely on evidence from clinical trials.

Quality Assessment

Internally validity is assessed after determination of risk of bias. A bias is a systematic error, or deviation from the truth, in study results. It is not possible to determine the extent biases can affect results of a particular study, but flaws in study design, conduct and analysis of data are known to lead to bias. Biases vary in magnitude but can underestimate or overestimate the true effect of the intervention in clinical trials. Clinical trials used to assess new drugs will be assessed for risk of bias using the methods in **Appendix A**.

Assessment of applicability, or directness, to the OHP population is an important consideration. The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability. Clinical trials used to assess new drugs will also be assessed for applicability to the OHP population using guidance provided in **Appendix A**.

High quality systematic reviews and clinical practice guidelines with applicability to the OHP population, as assessed by the PICOS framework, are included in evidence summaries. The AMSTAR measurement tool is used to assess for methodological quality of systematic reviews and is provided in **Appendix B**. Clinical practice guidelines are considered for inclusion after assessment of methodological quality using the AGREE II global rating scale provided in **Appendix C**.

Grading Quality of Evidence

The overall quality of evidence is graded for clinically relevant outcomes of efficacy and harm: mortality, morbidity outcomes, symptom relief, quality of life, and functioning (physical, mental, or emotional). Surrogate outcomes are considered if directly linked to a clinically relevant outcome. Clinically meaningful changes in these outcomes are emphasized. Evaluation of evidence for each outcome of interest is graded as **high**, **moderate**, **low**, or **insufficient** based on the domains listed in **Appendix D**. Evidence grades are defined in **Table 1**. Major domains in the evidence considered include risk of bias (internal validity), indirectness (applicability), inconsistency, imprecision, and publication bias.

Table 1. Quality of Evidence Grades and Definitions.

GRADE	DEFINITION
High	High confidence that the estimated effects produced in the studies reflect the true effect. Further research is very unlikely to change the estimated effect.
Moderate	Moderate confidence that the estimated effects produced in the studies reflect the true effect. Further research may change the estimated effect.
Low	Limited confidence that the estimated effects produced in the studies reflect the true effect. Further research is likely to change the estimated effect.
Insufficient	Evidence is not available or too limited to permit any level of confidence in the estimated effect.

Final evidence summary recommendations account for the availability and quality of evidence for relevant outcomes and perceived clinical impact on the OHP population.

APPENDIX A. Methods to Assess Quality of Studies.

Table 1. Types of Bias: Cochrane Risk of Bias (modified).

Selection Bias	Selection bias refers to **systematic differences** between **baseline characteristics of the groups** that were compared. The unique strength of proper ***randomization*** is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants. Successful randomization depends on fulfilling several interrelated processes. A rule for allocating patients to groups must be specified, based on some chance (random) process. Furthermore, steps must be taken to secure strict implementation of that schedule of random assignments by preventing foreknowledge of the forthcoming allocations. This process if often termed ***allocation concealment***.
Performance Bias	Performance bias refers to **systematic differences** between groups in the **care provided**, or in exposure to factors other than the interventions of interest. After enrolment, ***blinding participants and investigators/care givers*** will reduce the risk that knowledge of which intervention was received affected the outcomes, rather than the intervention itself. Effective blinding ensures that all groups receive a similar amount of attention, ancillary treatment and diagnostic investigations. Therefore, risk of differences in intervention design and execution, care experiences, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations and study duration between study groups are minimized.
Detection Bias	Detection bias refers to **systematic differences** between groups in how **outcomes were assessed**. ***Blinding of outcome assessors*** will reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affected outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes (eg, degree of post-operative pain).
Attrition Bias	Attrition bias refers to **systematic differences** between groups in **withdrawals** (exclusions and attrition) from a study. ***Withdrawals*** from the study lead to incomplete outcome data. There are two reasons for withdrawals or incomplete outcome data in clinical trials. ***Exclusions*** refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to assessors. ***Attrition*** refers to situations in which outcome data are not available.
Reporting Bias	Selection bias refers to the **selective reporting of pre-specified outcomes**, on the basis of the results. Of particular concern is that statistically non-significant (negative) primary endpoints might be selectively reported while select positive secondary endpoints are over-emphasized. Selective reporting of outcomes may arise in several ways: 1) there can be selective omission of pre-specified outcomes (ie, only some of the pre-specified outcomes are reported); 2) there can also be selection of choice data for an outcome that differs from what was pre-specified (eg, there may be different time points chosen to be reported for an outcome, or different methods used to measure an outcome at the same time point); and 3) there can be selective analyses of the same data that differs from what was pre-specified (eg, use of continuous vs. dichotomous outcomes for A1c lowering, selection from multiple cut-points, or analysis of between endpoint scores vs. change from baseline).

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

It is important to consider the likely magnitude of bias and direction of effect. For example, if all methodological limitations of studies were expected to bias the results towards a lack of effect, and the evidence indicates that the intervention is effective, then it may be concluded that the intervention is effective even in the presence of these potential biases. Assess each domain separately to determine if risk of each bias is likely **LOW**, **HIGH** or **UNCLEAR** (**Table 2**). Unclear risk of bias will be interpreted as high risk of bias when quality of evidence is graded (**Appendix D**).

Table 2. Methods to Assess Risk of Bias in Clinical Trials: Cochrane Risk of Bias (modified).

SELECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Inadequate randomization	Sequence generated by: • Computerized random number generator • Random number table • Coin toss	Sequence generated by: • Odd or even date of birth • Rule based on date or admission date • Hospital or clinic number • Alternating numbers	Method of randomization not described or sequence generation process not described in sufficient detail for definitive judgment
Inadequate allocation concealment	Participants or investigators could not foresee assignment because: • Central allocation (telephone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Participants or investigators could possibly foresee assignment because: • Open random allocation • Envelopes without appropriate safeguards (eg, unsealed or not opaque) • Allocation based on date of birth or case record number • Alternating allocation	Method of concealment not described or not described in sufficient detail for definitive judgment
Unbalanced baseline characteristics	Important prognostic factors similar between groups at baseline	Important prognostic factors are not balanced, which indicates inadequate sequence generation, allocation concealment, or failed randomization. *Statistical tests of baseline imbalance are not helpful for randomized trials.	Important prognostic factors are missing from baseline characteristics (eg, co-morbidities, other medications, medical/surgical history, etc.)
PERFORMANCE BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Participants or investigators/care providers un-blinded	Participants or investigators/care givers could not identify study assignment because: • Blinding of participants was ensured and unlikely to be broken (ie, double-dummy design with matching descriptions) • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding	Participants or investigators/care givers could possibly identify study assignment because: • No blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, differences easily observed in appearance, taste/smell or adverse effects between groups)	Not described or insufficient information to permit definitive judgment
DETECTION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Outcome assessors un-blinded	Outcome assessors could not identify study assignment because: • Blinding of assessors was ensured and unlikely broken • No blinding or incomplete blinding, but effect estimate not likely influenced by lack of blinding (ie, objective outcomes)	Outcome assessors could possibly identify study assignment because: • No blinding or incomplete blinding, which likely influenced effect estimate • Blinding potentially broken, which likely influenced effect estimate (eg, substantial differences in efficacy or safety outcomes between groups)	Not described or insufficient information to permit definitive judgment

ATTRITION BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
High attrition or differential	• No missing data • Reasons for missing outcome data unlikely to influence effect estimates	• High Drop-out rate or loss to follow-up (eg, >10% for short-term studies; >20% for longer-term studies) • Differential drop-out or loss to follow-up >10% between groups	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
Missing data handled inappropriately	• Intention-to-treat analysis performed where appropriate (eg, superiority trials) • Intention-to-treat and per-protocol analyses performed and compared where appropriate (eg, non-inferiority trials) • Reasons for missing outcome data unlikely to influence effect estimates • Appropriate censoring rules applied depending on nature of study (eg, last-observation-carried-forward (LOCF) for curative conditions, or for treatments that improve a condition over time like acute pain, infection, etc.)	• As-treated analyses performed with substantial departure from randomized number • Per-protocol analyses or modified-intention-to-treat with substantial amount of missing data • Potentially inappropriate imputation of missing data (eg, LOCF for chronic, deteriorating conditions like HF, COPD, or cancer, etc.)	Not described or insufficient reporting of attrition/exclusions post-randomization to permit judgment
REPORTING BIAS			
Risk of Bias	**LOW**	**HIGH**	**UNCLEAR**
Evidence of selective outcome reporting	• Study protocol is available and was followed and all pre-specified primary and secondary outcomes are reported • Study protocol is not available, but it is clear that all expected outcomes are reported	• Not all pre-specified primary and secondary outcomes reported • Primary outcome(s) reported using measurements, analyses, or subsets of patients that were not pre-specified (eg, post-hoc analysis; protocol change without justification) • Primary outcome(s) not pre-specified (unless clear justification provided) • Failure or incomplete reporting of other outcomes of interest • Inappropriate over-emphasis of positive secondary outcomes in study with negative primary outcome	Insufficient information to make determination

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

The Patient, Intervention, Comparator, Outcome, and Setting (PICOS) framework is used to assess applicability (ie, directness) of the evidence to the OHP population (**Table 3**).

Table 3. PICOS Domains that Affect Applicability.

PICOS Domain	Conditions that Limit Applicability
Patient	• Narrow eligibility criteria and broad exclusion criteria of those with comorbidities • Large differences between the demographic characteristics between the study population and patients in the OHP • Narrow or unrepresentative severities in stage of illness or comorbidities (eg, only mild or moderate severity of illness included) • Run-in period with high exclusion rate for non-adherence or adverse effects • Event rates in study much lower/higher than observed in OHP population
Intervention	• Doses, frequency schedule, formulations or duration of intervention used in study not reflective of clinical practice • Intensity/delivery of behavioral interventions not feasible for routine use in clinical practice • Concomitant interventions likely over- or underestimate effectiveness of therapy
Comparator	• Inadequate dose or frequency schedule of comparator • Use of inferior or substandard comparator relative to alternative comparators that could be used
Outcomes	• Short-term or surrogate outcomes assessed • Composite outcomes used that mix outcomes of different significance
Setting	• Standards of care in study setting differ markedly from clinical practice • Monitoring/visit frequency not feasible for routine use in clinical practice • Level of care from highly trained/proficient practitioners in trial not reflective of typical clinical practice where intervention likely to be used

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

APPENDIX B. Methods to Assess Methodological Quality of Systematic Reviews.

A measurement tool for the "assessment of multiple systematic reviews" (AMSTAR) was developed and shown to be a validated and reliable measurement tool to assess the methodological quality of systematic reviews. There are 11 components addressed in the measurement tool below, and each question can be scored in one of four ways: "Yes", "No", "Can't Answer", or "Not Applicable". The AMSTAR is used as a guideline to identify high quality systematic reviews eligible for inclusion in DURM evidence summaries. High quality systematic reviews do not contain a "fatal flaw" (ie, comprehensive literature search not performed (#3); characteristics of studies not provided (#6); quality of studies were not assessed or considered when conclusions were formulated (#7 and #8)). In general, a high quality systematic review will score a "yes" on most components presented in the AMSTAR tool.

Ref. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*. 2007;7:10. doi: 10.1186/1471-2288-7-10 .

Systematic reviews or guidance identified from 'best sources' undergo methodological rigor considered to be of high quality and are not scored for quality. 'Best sources' include, but are not limited to: Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center; Agency for Healthcare Research and Quality (AHRQ); Cochrane Collaboration; National Institute for Health and Care Excellence (NICE); Institute for Clinical and Economic Review (ICER); U.S. Department of Veterans Affairs (VA); Canadian Agency for Drugs and Technologies in Health (CADTH); BMJ Clinical Evidence; and the University of York Centre for Reviews and Dissemination.

AMSTAR Quality Scoring Template	
1) Was an 'a priori' design provided? Note: the research question and inclusion criteria should be established before the conduct of the review and should be available.	□ Yes □ No □ Can't answer □ Not applicable
2) Was there duplicate study selection and data extraction? Note: there should be at least two independent persons for study selection and data extraction; a consensus process for disagreements is in place; at least one person checks the other's work.	□ Yes □ No □ Can't answer □ Not applicable
3) Was a comprehensive literature search performed? Note: at least 2 databases (eg, MEDLINE, CINAHL, Scopus) plus one supplementary source (ie, gray literature) are searched. The review must include years and names databases used. Key words and/or Medical Subject Headings (MeSH) are stated and, if feasible, the search strategy is provided. Current reviews, specialized registers, or experts in the field of study may also be consulted.	□ Yes □ No □ Can't answer □ Not applicable
4) Was the status of publication (ie, gray literature) used as an inclusion criterion? Note: "gray literature" or "unpublished literature" was searched. Dissertations, conference proceedings, and trial registries are all considered "gray literature" for this purpose. If a database was used that contained both gray literature and published literature, it was specified that gray literature was specifically searched. The authors should state whether any studies were excluded from the systematic review based on publication status, language, etc.	□ Yes □ No □ Can't answer □ Not applicable
5) Was a list of studies (included and excluded) provided? Note: a list of included and excluded studies should be provided or referenced. Alternatively, there is a live electronic link to the list.	□ Yes □ No □ Can't answer □ Not applicable
6) Were the characteristics of the included studies provided? Note: in an aggregated form (eg, a table), data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed (eg, age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases) should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7) Was the scientific quality of the included studies assessed and documented? Note: methods of assessment were provided *a priori*. For example, a quality scoring tool or checklist was used, such as a Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is NOT acceptable).	□ Yes □ No □ Can't answer □ Not applicable
8) Was the scientific quality of the included studies used appropriately in formulating conclusions? Note: interpretation and analysis of the methodological rigor and quality of the included studies should be clear stated in the conclusions and explicitly stated in formulating recommendations. For example, "results should be interpreted with caution due to poor quality of included studies" is a reasonable interpretation. Cannot score "yes" for this question if scored "no" for question #7.	□ Yes □ No □ Can't answer □ Not applicable
9) Were the methods used to combine the findings of studies appropriate? Note: for the pooled results, a test should be performed to test for heterogeneity (ie, Chi-squared test, I^2). If heterogeneity exists, a random effects model was used, an explanation for inability to combine study results due to heterogeneity was given, or the clinical appropriateness of combining individual study results was considered (ie, is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10) Was the likelihood of publication bias assessed? Note: an assessment of publication bias was made and a graphical aid was provided (eg, funnel plot) and/or statistical tests (eg, Egger regression test) were included. Alternatively, if few studies were included, the review mentions that publication bias could not be assessed.	□ Yes □ No □ Can't answer □ Not applicable
11) Was the conflict of interest stated? Note: potential sources of support should be clearly acknowledged in both the systematic review AND is acknowledged for the included studies.	□ Yes □ No □ Can't answer □ Not applicable

APPENDIX C. Methods to Assess Methodological Quality of Clinical Practice Guidelines.

Clinical practice guidelines are systematically developed statements that assist clinicians in making clinical decisions. However, guidelines can vary widely in quality and utility. The Appraisal of Guidelines, Research, and Evaluation (AGREE) Instrument is a global rating scale (GRS) (www.agreetrust.org) that assesses the methodologic rigor in which a guideline is developed and used. The AGREE II GRS is an updated instrument that has been validated. AGREE II GRS consists of 23 items in 6 domains (scope, stakeholder involvement, rigor of development, clarity, applicability, and editorial independence) to rate (**Table 1**). Because it is time-consuming to administer, a consolidated GRS was developed, and is generally a reasonable alternative to the original GRS if resources are limited. The consolidated AGREE II GRS instrument consists of only 5 items (**Table 2**). With both instruments, each item is rated on a 7-point scale, from 0=lowest quality to 7=highest quality. High quality clinical practice guidelines are eligible for inclusion in DURM evidence summaries. These guidelines will score 6-7 points for each component on rigor of development. In general, a high quality clinical practice guideline will score 5-7 points on most components presented in the AGREE II GRS and each component of the consolidated AGREE II GRS.

Table 1. AGREE II Global Rating Scale.

	ITEM	DESCRIPTION
SCOPE AND PURPOSE		
1	The overall objective(s) of the guideline is (are) specifically described.	The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem or health topic. **[SCORE:]**
2	The health question(s) covered by the guideline is (are) specifically described.	A detailed description of the health questions covered by the guideline should be provided, particularly for key recommendations, although they need not be phrased as questions. **[SCORE:]**
3	The population to whom the guideline is meant to apply is specifically described.	A clear description of the population (ie, patients, public, etc.) covered by a guideline should be provided. The age range, sex, clinical description, and comorbidities may be provided. **[SCORE:]**
STAKEHOLDER INVOLVEMENT		
4	The guideline development group includes individuals from all relevant professional groups.	This may include members of the steering group, the research team involved in selection and review of the evidence and individuals involved in formulation of the final recommendations. **[SCORE:]**
5	The views and preferences of the target population have been sought.	Information about target population experiences and expectations of health care should inform the development of guidelines. There should be evidence that some process has taken place and that stakeholders' views have been considered. For example, the public was formally consulted to determine priority topics, participation of these stakeholders on the guideline development group, or external review by these stakeholders on draft documents. Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of patient/public values, preferences or experiences. **[SCORE:]**
6	The target users of the guideline are clearly defined.	The target users should be clearly defined in the guideline so the reader can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopedic surgeons, rheumatologists, and physiotherapists. **[SCORE:]**
RIGOR OF DEVELOPMENT		
7	Systematic methods were used to search for evidence.	Details of the strategy used to search for evidence should be provided, which include search terms used, sources consulted, and dates of the literature covered. The search strategy should be as comprehensive as possible and executed in a manner free from potential biases and sufficiently detailed to be replicated. **[SCORE:]**
8	The criteria for selecting the evidence are clearly described.	Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. **[SCORE:]**
9	The strengths and limitations of the body of evidence are clearly described.	Statements that highlight the strengths and limitations of the evidence should be provided. This ought to include explicit descriptions, using informal or formal tools/methods, to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. **[SCORE:]**
10	The methods for formulating the recommendations are clearly described.	A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. For example, methods may include a voting system, informal consensus, or formal consensus techniques (eg, Delphi, Glaser techniques). **[SCORE:]**

11	The health benefits, adverse effects, and risks have been considered in formulating the recommendations.	The guideline should consider both effectiveness/efficacy and safety when recommendations are formulated. **[SCORE:]**
12	There is an explicit link between the recommendations and the supporting evidence.	An explicit link between the recommendations and the evidence on which they are based should be included in the guideline. **[SCORE:]**
13	The guideline has been externally reviewed by experts prior to its publication.	A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the guideline development group. Reviewers should include both clinical and methodological experts. **[SCORE:]**
14	A procedure for updating the guideline is provided.	A clear statement about the procedure for updating the guideline should be provided. **[SCORE:]**
CLARITY OF PRESENTATION		
15	The recommendations are specific and unambiguous.	A recommendation should provide a precise description of which option is appropriate in which situation and in what population. It is important to note that in some instances, evidence is not always clear and there may be uncertainty about the best practice. In this case, the uncertainty should be stated in the guideline. **[SCORE:]**
16	The different options for management of the condition or health issue are clearly presented.	A guideline that targets the management of a disease should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. **[SCORE:]**
17	Key recommendations are easily identifiable	Users should be able to find the most relevant recommendations easily. **[SCORE:]**
APPLICABILITY		
18	The guideline describes facilitators and barriers to its application.	There may be existing facilitators and barriers that will impact the application of guideline recommendations. **[SCORE:]**
19	The guideline provides advice and/or tools on how the recommendations can be put into practice.	For a guideline to be effective, it needs to be disseminated and implemented with additional materials. For example, these may include: a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, or computer/online support. **[SCORE:]**
20	The potential resource implications of applying the recommendations have been considered.	The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff or expensive drug treatment. These may have cost implications on health care budgets. There should be a discussion in the guideline of the potential impact of the recommendations on resources. **[SCORE:]**
21	The guideline presents monitoring and/or auditing criteria	Measuring the application of guideline recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the guideline (eg, HbA1c <7%, DBP <95 mm Hg). **[SCORE:]**
EDITORIAL INDEPENDENCE		
22	The views of the funding body have not influenced the content of the guideline.	Many guidelines are developed with external funding (eg, government, professional associations, charity organizations, pharmaceutical companies). Support may be in the form of financial contribution for the complete development, or for parts of it (eg, printing/dissemination of the guideline). There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations. **[SCORE:]**
23	Competing interests of guideline development group members have been recorded and addressed	There should be an explicit statement that all group members have declared whether they have any competing interests. **[SCORE:]**

Table 2. Consolidated AGREE II Global Rating Scale.

	ITEM	DESCRIPTION
1	Rate the guideline development methods. **[SCORE:]**	• Appropriate stakeholders were involved in the development of the guideline. • The evidentiary base was developed systematically. • Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs was made.
2	Rate the guideline presentation. **[SCORE:]**	• The guideline was well organized. • The recommendations were easy to find.
3	Rate the guideline recommendations. **[SCORE:]**	• The recommendations are clinically sound. • The recommendations are appropriate for the intended patients.
4	Rate the completeness of reporting, editorial independence. **[SCORE:]**	• The information is complete to inform decision making. • The guideline development process is transparent and reproducible.

APPENDIX D. GRADE Quality of Evidence.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) provides a framework to assess quality of evidence for an *outcome* that emphasizes transparency of how evidence judgments are made, though it does not necessarily guarantee consistency in assessment. Quality assessment in GRADE is 'outcome-centric' and distinct from quality assessment of an individual study. Information on risk of bias (internal validity), indirectness (applicability), imprecision, inconsistency, and publication bias is necessary to assess quality of evidence and overall confidence in the estimated effect size. The GRADE framework provides an assessment for each outcome.

DURM evidence summaries, unless a single drug is evaluated, depend on the whole body of available evidence. Evidence from high quality systematic reviews is the primary basis for recommendations in the evidence summaries. High quality evidence-based clinical practice guidelines and relevant randomized controlled trials are used to supplement the whole body of evidence.

High quality systematic reviews and clinical practice guidelines often use the GRADE framework to assess overall quality of evidence for a given outcome. In such cases, the grade of evidence provided in the respective report can be directly transferred to the DURM evidence summary. When an evidence summary includes relevant clinical trials, or when high quality systematic reviews or clinical practice guidelines that did not use the GRADE framework were identified, quality of evidence will be graded based on hierarchy of available evidence, homogeneity of results for a given outcome, and methodological flaws identified in the available evidence (**Table 1**).

Table 1. Evidence Grades for Benefit and Harm Outcomes When a Body of Evidence is Evaluated.

GRADE	TYPE OF EVIDENCE
High	• Evidence is based on data derived from multiple randomized controlled trials with homogeneity with regard to the direction of effect between studies AND • Evidence is based on multiple, well-done randomized controlled trials that involved large numbers of patients.
Moderate	• Evidence is based on data derived from randomized controlled trials with some conflicting conclusions with regard to the direction of effect between studies OR • Evidence is based on data derived from randomized controlled trials that involved small numbers of patients but showed homogeneity with regard to the direction of effect between studies OR • Some evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.)
Low	• Most evidence is based on data derived from randomized controlled trials with significant methodological flaws (eg, bias, attrition, flawed analysis, etc.) OR • Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with homogeneity with regard to the direction of effect between studies
Insufficient	• Evidence is based mostly on data derived from non-randomized studies (eg, cohort studies, case-control studies, observational studies) with some conflicting conclusions with regard to direction of effect between studies OR • Evidence is based on data derived from expert opinion/panel consensus, case reports or case series OR • Evidence is not available

New Drug Evaluations cannot depend on evidence from systematic reviews and clinical practice guidelines. A body of evidence that solely consists of one or more clinical trials is initially assigned 4 points. For every relevant limitation, points are deducted; but points are added for consistently large effect sizes between studies or for a consistent dose-response observed in the studies (**Table 2**). The quality of evidence is subsequently graded as shown:

QUALITY OF EVIDENCE GRADES:

- ≥4 points = **HIGH**
- 3 points = **MODERATE**
- 2 points = **LOW**
- ≤1 point = **INSUFFICIENT**

An example evidence grade assessment of individual randomized controlled trials is available in **Table 3**, with a template provided in **Table 4**.

Table 2. Domains to Grade Evidence for Benefit and Harm Outcomes from Clinical Trials: Cochrane Evidence Grades (modified).

DOMAIN	DESCRIPTION	SCORE DEMOTION/PROMOTION (start with 4 points)
Risk of Bias (internal validity)	Risk of bias is the likelihood to which the included studies for a given comparison and outcome has an inadequate protection against bias that affects the internal validity of the study. • *Did any studies have important limitations that degrade your confidence in estimates of effectiveness or safety?*	• No serious limitation: all studies have low risk of bias: **(0)** • Serious limitations: ≥1 trial has high or unclear risk of bias: **(-1)** • Very serious limitations: most studies have high risk of bias: **(-2)**
Indirectness (applicability)	Directness (applicability) relates to evidence that adequately compares 2 or more reasonable interventions that can be directly linked to a clinically relevant outcome in a population of interest. • *Do studies directly compare interventions of interest in populations of interest using outcomes of interest (use of clinically relevant outcomes)?*	• Direct: clinically relevant outcomes of important comparisons in relevant populations studied: **(0)** • Indirect: important comparisons missing; surrogate outcome(s) used; or population not relevant: **(-1)**
Inconsistency	Inconsistency (heterogeneity) is the degree to which reported effect sizes from included studies appear to differ in direction of effect. Effect sizes have the same sign (ie, are on the same side of ''no effect'') and the range of effect sizes is narrow. • *Did trials have similar or widely varying results? Can heterogeneity be explained by differences in trial design and execution?*	• Large magnitude of effect consistent between studies: **(+1)** • Dose-response observed: **(+1)** • Small magnitude of effect consistent between studies: **(0)** • 1 study with large magnitude of effect: **(0)** • 1 study with small magnitude of effect: **(-1)** • Inconsistent direction of effect across studies that cannot be explained: **(-1)**
Imprecision	Imprecision is the degree of uncertainty surrounding an effect estimate with respect to a given outcome (ie, the confidence interval for each outcome is too wide to rule out no effect). • *Are confidence intervals for treatment effect sufficiently narrow to rule out no effect?*	• Precise: all studies have 95% confidence intervals that rule out no effect: **(0)** • Imprecise: ≥1 study demonstrated 95% confidence interval fails to rule out no effect: **(-1)**
Publication Bias	Publication bias is the degree in which completed trials are not published or represented. Unpublished studies may have negative outcomes that would otherwise change our confidence in the body of evidence for a particular comparison and outcome. • *Is there evidence that important trials are not represented?*	• No publication bias: all important trials published or represented: **(0)** • Serious publication bias: ≥1 important trial(s) completed but not published: **(-1)**

Ref. *Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)*

Table 3. Example Grade Assessment of Evidence from Randomized Controlled Trials.

Summary of Findings							Evidence Profile					
Study (NCT)	n	Control Results	Intervention Results	Difference (95% CI)	NNT/NNH	Risk of Bias	Overall Risk of Bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Quality of Evidence
Outcome (1): Response (defined as achieve LDL <100 mg/dL and HDL >40 mg/dL)												
Montgomery NCT26240434	553	Placebo 89/277 (32.1%)	Megastatin 40 mg 115/276 (41.7%)	9.6% RR 1.30 (1.04 to 1.62)	10	High	-1 (40 mg) 0 (>40 mg)	-1 (all)	+2 (all)	-1 (40 mg) 0 (>40 mg)	-1 (all)	LOW (40 mg) HIGH (>40 mg)
Asnis NCT96123239	704	Placebo 51/175 (29.1%)	Megastatin 40 mg 64/176 (36.4%)	7.3% RR 1.25 (0.92 to 1.69)	NS	Low						
			Megastatin 80 mg 79/177 (44.9%)	15.8% RR 1.54 (1.16 to 2.04)	6							
			Megastatin 160 mg 85/176 (48.3%)	19.2% RR 1.66 (1.26 to 2.19)	5							
Unpublished NCT01034462	434	NR	NR									
Unpublished NCT00225511	590	NR	NR									
Outcome (2): Change in CRP from baseline												
Montgomery NCT26240434	553	Placebo -0.20 mg/L	Megastatin 40 mg -0.85 mg/L	0.65 mg/L (0.25 to 1.05 mg/L)	NA	High	-1 (40 mg) 0 (>40 mg)	-1 (all)	+1 (all)	-1 (40 mg) 0 (>40 mg)	-1 (all)	INSUFFICIENT (40 mg) MODERATE (>40 mg)
Asnis NCT96123239	704	Placebo +0.15 mg/L	Megastatin 40 mg -0.20 mg/L	0.35 mg/L (-0.05 to 0.60 mg/L)	NA	Low						
			Megastatin 80 mg -0.25 mg/L	0.40 mg/L (0.05 to 0.70 mg/L)	NA							
			Megastatin 160 mg -0.45 mg/L	0.60 mg/L (0.45 to 0.70 mg/L)	NA							
Unpublished NCT01034462	434	NR	NR									

Table 4. Grade Assessment Template for Randomized Controlled Trials.

Summary of Findings							Evidence Profile					
Study (NCT)	n	Control Results	Intervention Results	Difference (95% CI)	NNT/NNH	Risk of Bias	Overall Risk of Bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Quality of Evidence
Outcome (1):												
Outcome (2):												

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Standard Methods for Abbreviated Drug Reviews

Purpose of Abbreviated Drug Review:
A New Drug Evaluation is the standard evidence summary document used by the Drug Use Research and Management (DURM) faculty to research new drugs approved by the U.S. Food and Drug Administration (FDA). Significant time and resources are used to research and critically appraise the evidence for a new drug. However, some drugs are approved solely for conditions that are not funded under the Oregon Health Plan (OHP). In other cases, specialty drugs for very rare conditions are expeditiously approved by the FDA with limited evidence, but can have significant budgetary implications if used. Under these circumstances, it is reasonable to expend fewer resources by both DURM faculty and the OHP Pharmacy & Therapeutics (P&T) Committee to make an appropriate recommendation for the drug.

Standard recommendations for Abbreviated Drug Reviews will be:

Drug approved for non-funded conditions: Restrict use for OHP-funded conditions through Prior Authorization (PA) (see Appendix 1).
Specialty drug for very rare conditions: Require manual review and approval by the OHP Medical Director through PA (see Appendix 1).

Content of Abbreviated Drug Review:
Each Abbreviated Drug Review is a basic 1-page document that summarizes evidence and basic information about the drug, including:

- FDA-approved indications and off-label uses, if applicable
- Dosage information
- Background information on the disease condition
- Primary efficacy and safety data
- Evidence gaps and limitations of use
- OHP population estimation, net cost and number of claims for drugs identified (specialty drugs only)

Standard Procedure for Abbreviated Drug Review:
Drug approved for non-funded conditions: A literature search is conducted to determine if there is moderate- or high-quality evidence for conditions funded under the OHP. If there is only evidence to support use of the drug for conditions not funded under the OHP, an Abbreviated Drug Review is performed with a recommendation to PA the drug to determine if use is for a funded condition.

Specialty drug for very rare conditions: A literature search is conducted for drugs FDA-approved for very rare conditions to identify evidence for use of the drug. The drug is considered for an Abbreviated Drug Review if the perceived budgetary impact [(annual net cost of drug X predicted # OHP patients annually)/ total fee-for-service annual drug costs to OHP] is significant, but unpredictable due to rarity of the treated condition. Population estimation is based on epidemiological data or OHP diagnoses data, if available. If the drug is used for a rare condition and any number of claims would have a significant budgetary impact, an Abbreviated Drug Review is performed with a recommendation for manual review and approval by the OHP Medical Director.

A template for the Abbreviated Drug Review is presented below:

Drug Use Research & Management
Oregon State University College of Pharmacy

Abbreviated Drug Review

Trade Name (generic)		
Estimated OHP Population: [specialty drug only]	Claims: [specialty drug only]	Monthly Net Cost: [specialty drug only]
Indications		
•		
Dosage		
•		
Background		
[…]		
Efficacy		
[…]		
Safety		
[…]		
Evidence Gaps/Limitations		
[…]		
Recommendation		
[…]		
References		

Drugs for Non-funded Conditions

Goal:

- Restrict use of drugs reviewed by the Oregon Pharmacy & Therapeutics (P&T) Committee without evidence for use in Oregon Health Plan (OHP)-funded conditions.

Length of Authorization:

- Up to 6 months.

Requires PA:

- A drug restricted by the P&T Committee due to lack of evidence for conditions funded by the OHP.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug being used to treat an OHP-funded condition?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		

P&T / DUR Review: *11/15 (AG)*
Implementation *TBD*

Drugs Selected for Manual Review by Oregon Health Plan

Goal:

- Require specialty drugs selected by the Oregon Pharmacy & Therapeutics (P&T) Committee to be manually reviewed and approved by the Oregon Health Plan (OHP) Medical Director.

Length of Authorization:

- To be determined by OHP Medical Director.

Requires PA:

- A drug approved by the P&T Committee to be manually reviewed by the OHP Medical Director for approval.

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code
2. Pass to RPh. Deny; requires manual review and approval by the OHP Medical Director. Message: The P&T Committee has determined this drug requires manual review by the OHP Medical Director for approval.	

P&T / DUR Review: *11/15 (AG)*
Implementation *TBD*

New Drug Policy

Goal:

- Restrict coverage of selected new drugs until the Oregon Pharmacy & Therapeutics Committee can review the drug for appropriate coverage.

Length of Authorization:

- Up to 6 months

Requires PA:

- A new drug, identified by the reviewing pharmacist during the weekly claim processing drug file load, in a class where existing prior authorization policies exist or that is used for a non-funded condition on the Oregon Health Plan (OHP) List of prioritized services.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug being used to treat an OHP-funded condition?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP.
3. Pass to RPh. The prescriber must provide documentation of therapeutic failure, adverse event, or contraindication alternative drugs approved by FDA for the funded condition. Otherwise, the prescriber must provide medical literature supporting use for the funded condition. RPh may use clinical judgement to approve drug for up to 6 months or deny request based on documentation provided by prescriber.		
~~4. Client has documented therapeutic failure, adverse event or contraindication to 2 covered alternatives (CONSULT WITH PHARMACIST for appropriate covered alternatives).~~ ~~Document the drugs tried or contraindications.~~	~~Yes: Approve for 6 months or anticipated length of therapy; whichever is shorter.~~	~~No: Pass to RPH; Deny (Cost Effectiveness)~~

P&T / DUR Review: *11/15 (AG); 12/09*
Implementation: *TBD; 1/1/10*

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Prior Authorization Review: Botulinum Toxins

Background:
Currently, there are 3 botulinum toxin type A products (abobotulinumtoxina [Dysport®]; incobulinumtoxina (Xeomin®); onabotulinumtoxina (Botox®; Botox® Cosmetic) and one botulinum toxin type B product (rimabotulinumtoxinb [Myobloc®]) available commercially in the U.S. Indications and off-label uses for each of these products are listed in Table 1.

Table 1. Indications and Off-label Uses for Botulinum Toxins:[1]

Botulinum toxin type A: • abobotulinumtoxina (DYSPORT): cervical dystonia; glabellar lines; upper limb spasticity (off-label: achalasia; acquired nystagmus; anal fissures; hand dystonia; sialorrhea (drooling); spasticity of cerebral palsy; tardive dyskinesia; others) • incobulinumtoxina (XEOMIN): blepharospasm; cervical dystonia; glabellar lines (off-label: achalasia; sialorrhea; others) • onabotulinumtoxina (BOTOX; BOTOX COSMETIC): axillary hyperhidrosis; cervical dystonia; chronic migraine; glabellar lines; lateral canthal lines; overactive bladder; strabismus and blepharospasm associated with dystonia; upper limb spasticity; urinary incontinence due to detrusor overactivity (off-label: achalasia; anal fissures; hand dystonia; Raynaud phenomenon; sialorrhea; spasticity of cerebral palsy; tardive dyskinesia; others)
Botulinum toxin type B: • rimabotulinumtoxinb (MYOBLOC): cervical dystonia (off-label: sialorrhea)

The Health Evidence Review Commission (HERC) updated treatment guidelines within the Prioritized List of Health Services for use of chemodenervation for chronic migraine and for detrusor over-activity of the bladder.[2] Specifically, the notes address continuing funding only for positive response from chemodenervation for these conditions. The guideline changes are highlighted in *italics* below. The change will be in effect January 1, 2016.[2]

GUIDELINE NOTE XXX, CHEMODENERVATION FOR CHRONIC MIGRAINE[2]
Line 414
Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:

1. have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
2. has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, calcium channel blocker, anticonvulsant or tricyclic antidepressant)
3. treatment is administered in consultation with a neurologist or headache specialist.

Treatment is limited to two treatments given 3 months apart. Additional treatment requires documented positive response to therapy. *Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency*.

GUIDELINE NOTE XXX, CHEMODENERVATION OF THE BLADDER[2]

Line 331

Chemodenervation of the bladder (CPT 52287) is included on this line only for treatment of idiopathic detrusor over-activity or neurogenic detrusor over-activity (ICD-9 596.5x/ICD-10-CM N32.81) in patients who have not responded to or been unable to tolerate at least two urinary incontinence antimuscarinic therapies (e.g. fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, trospium). Treatment is limited to 90 days, with additional treatment only if the patient shows documented positive response. *Positive response to therapy is defined as a reduction of urinary frequency of 8 episodes per day or urinary incontinence of 2 episodes per day compared to baseline frequency*.

A clinical Prior Authorization (PA) for botulinum toxins was last approved by the Oregon Pharmacy & Therapeutics (P&T) Committee in September 2014 (see **Appendix 1**).

Recommendations:

- Changes to the current PA criteria are recommended to reflect updated Guideline Notes approved by the HERC.
- Evaluation of medical literature for use of botulinum toxins since the PA was last reviewed by the P&T Committee did not require any additional changes to the criteria. No further review or research needed at this time.

References:

1. Facts & Comparisons® eAnswers [internet database]. Indianapolis, IN: Wolters Kluwer, 2015 Clinical Drug Information LLC. Updated September 2015. Accessed October 12, 2015.
2. Value-based Benefits Subcommittee Meeting Archive; DRAFT minutes, October 1, 2015 meeting. Health Evidence Review Commission, Oregon Health Authority. Available at http://www.oregon.gov/oha/herc/CommitteeMeetingMaterials/VbBS%20Minutes%2010-1-2015.pdf. Accessed October 20, 2015.

Botulinum Toxins

Goal(s):

- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit (eg, dystonia or spasticity associated with certain neurological diseases).
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:

- From 90 days to 12 months

Requires PA:

- Use of botulinum toxins without associated dystonia or neurological disease diagnosis in last 12 months.

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 for management of migraine headache or detrusor over-activity (eg, overactive bladder)?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
3. Does patient have diagnosis of neurological-induced dystonia or spasticity in which a botulinum toxin is a first-line treatment option? Examples: • Genetic torsion dystonia 333.6x; • Acquired torsion dystonia 333.7x; • Blepharospasm 333.81; • Spasmodic torticollis 333.83; • Other fragments of torsion dystonia 333.89; • Paralysis associated with CVD 438.2x-432.5x; • Multiple sclerosis 340.xx; • Neuromyelitis optica 341.0; • Spastic hemiplegia, other specified hemiplegia 342.xx; • Cerebral palsy 343.xx; • Quadriplegia and quadraparesis 344.0x; • Paraplegia 344.1; • Diplegia of upper limbs 344.2; • Monoplegia of lower limb 344.3x; • Monoplegia of upper limb 344.4x; • Unspecified monoplegia 344.5; • Other specified paralytic syndrome 344.89; • Muscular dystrophies 359.0x-359.2x; or • Strabismus in other neuromuscular disorders 378.73.	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does patient have a diagnosis of chronic migraine with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #7
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny for medical appropriateness.

Approval Criteria		
6. Has the patient had an inadequate response, or has contraindications, to ≥1 drugs from each of the following 3 drug classes? • Beta-blockers: (propranolol; metoprolol; atenolol; nadolol; or timolol) • Tricyclic antidepressants: (nortriptyline or amitriptyline) • Anticonvulsants: (divalproex sodium/valproic acid; carbamazepine; topiramate; or gabapentin) • Calcium channel blockers (diltiazem; verapamil; or nimodipine)	**Yes:** Approve no more than 2 treatments given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny for medical appropriateness and recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Does patient have a diagnosis idiopathic or neurogenic detrusor over-activity (eg, overactive bladder syndrome) (ICD10-CM N32.81)?	**Yes:** Go to #8	**No:** Pass to RPh and go to #9
8. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (eg, fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass or RPh. Deny for medical appropriateness.

Approval Criteria

9. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
Neurologic conditions with none or minimally effective treatment or treatment not necessary (333.82; 333.84; 333.94-333.99); Facial nerve disorders (351.xx); Spastic dysphonia (478.79); Anal fissure (565.0); Disorders of sweat glands (eg, focal hyperhidrosis) (705.xx); Other disorders of cervical region (723.xx, EXCEPT 723.4): Disorders of sweat glands (705.0-705.1; 705.21-705.9; 780.8); Acute and chronic disorders of the spine without neurologic impairment (724.1; 724.2; 724.4-724.6; 727.70-724.9); Disorders of soft tissue (729.0-729.2); Headaches (307.81; 339.xx; 784.0); Gastroparesis (536.3)
Deny for medical appropriateness for the following conditions; evidence of benefit is insufficient
Dysphagia (787.2x); Other extrapyramidal disease and abnormal movement disorders (333.xx, EXCEPT 333.6x; 333.7x; 333.81; 333.83; 333.89); Other disorders of binocular eye movements (eg, esotropia, exotropia, mechanical strabismus, etc.) (378 EXCEPT 378.73); Tics (307.2x); Laryngeal spasm (478.75); Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (723.0 and 723.4); Spasm of muscle in absence of neurological diagnoses (728.85); Contracture of tendon (sheath) in absence of neurological diagnoses (727.81); Amyotrophic sclerosis (335.20); Clinically significant spinal deformity or disorders of spine with neurological impairment (724.00-724.09; 724.4); Hyperplasia of prostate (600.xx)

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a reduction of ≥7 headache days per month compared to baseline headache frequency?	**Yes:** Approve for up to 12 months Baseline:____ headaches/month Current:____ headaches/month	**No:** Pass to RPh. Deny for medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of idiopathic or neurogenic detrusor over-activity?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months Baseline:____ episodes/day Current:____ episodes/day	**No:** Pass to RPh. Deny for medical appropriateness

P&T / DUR Review: *11/15 (AG); 9/14 (KK); 7/14 (KK)*
Implementation : *TBD*

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New Drug Evaluation: ivabradine tablet, oral

Date of Review: September 2015
Generic Name: ivabradine
PDL Class: not applicable

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): CORLANOR® (Amgen, Inc.)
Dossier Received: yes

Research Questions:

1. What is the current evidence for the efficacy of ivabradine to reduce to reduce mortality and cardiovascular (CV) morbidities; and if available, how does the drug's efficacy compare to other drugs used to manage chronic heart failure with reduced ejection fraction (HFrEF)?
2. Based on the evidence available, does ivabradine have a clear place in therapy for management of chronic HFrEF?
3. How well is ivabradine tolerated in patients; and if available, how does the safety of ivabradine compare to other drugs used to manage chronic HFrEF?
4. Are there subgroups of patients in which ivabradine may be safer or more effective than other drugs used to manage chronic HFrEF?

Conclusions:

- Evidence for use of ivabradine is based on one 23-month clinical trial (n=6,505) with low overall risk bias.[1] The study was composed of patients with stable, mildly symptomatic HFrEF (New York Heart Association [NYHA] Classes II and III) with a mean ejection fraction (EF) of 32% in normal sinus rhythm with a minimum resting heart rate (HR) of 70 beats-per-minute (BPM).[1] Patients in the study remained on standard HF therapy, which typically included an ACE-inhibitor [ACE-I] or angiotensin-2 receptor blocker [ARB]), beta-blocker, diuretic(s), and an aldosterone antagonist.[1]
- There is low quality evidence, based on a secondary endpoint, that ivabradine 5-7.5 mg twice daily (BID) may reduce risk of hospitalizations for heart failure (HF) by 4.7% compared to placebo (15.9% vs. 20.6%, respectively; Hazard Ratio [HR]=0.74; 95% Confidence Interval [CI], 0.66-0.83; p<0.0001; number needed-to-treat [NNT] =22).[1] However, ivabradine does not appear to be any different from placebo in regards to ability to reduce all-cause or CV-related mortality in these patients.[1]
- Overall, studies that evaluated other populations provide moderate quality evidence that ivabradine does not reduce CV outcomes or mortality in patients with HFrEF in normal sinus rhythm when baseline resting HR is not considered,[2] or in CAD patients without HF.[3]
- There is moderate quality evidence ivabradine can cause asymptomatic and symptomatic bradycardia.[1–3] Negative chronotropic drugs such as non-dihydropyridine calcium channel blockers (i.e., diltiazem and verapamil), or amiodarone increases risk for adverse events with ivabradine.[4]
- There is moderate quality evidence ivabradine increases risk for development of atrial fibrillation.[1,3] Ivabradine should be avoided in patients with atrial fibrillation and should be discontinued if it develops after starting the drug.[4]

Recommendation:

- Restrict use of ivabradine to populations where it has demonstrated some efficacy. See **Appendix 2** for the proposed prior authorization criteria.

Background:

The goals of management of HFrEF (ie, systolic HF) are to prevent hospital admission and improve survival, and to relieve signs (eg, edema) and symptoms (eg, dyspnea).[5] The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[5,6] The most well-studied system in the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has shown to have a significant impact on the pathophysiology and progression of HF.[5,6] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[5,6] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a select beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralcorticoid (aldosterone) receptor antagonist (spironoloactone or eplerenone).[5,6]

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[5,6] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD.[6] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[5] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[5,6] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[6] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[7] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[5,6] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[6] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials that were designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see Table 1).[5,6]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[5]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-35 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg Qday • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation

* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

There are also other therapeutic options for management of HFrEF that do not inhibit RAAS or other components of neurohormonal activation. Hydralazine and isosorbide dinitrate has shown to decrease morbidity and mortality in self-identified African-Americans/Blacks with NYHA class III-IV and reduced EF.[6] Digoxin has no effect on survival, but it can have a modest effect on reducing hospitalizations regardless of the underlying rhythm or cause of HF (ischemic or non-ischemic cardiomyopathy).[6] Ivabradine inhibits I_f channels in the sinoatrial node of the heart, which acts as a pacemaker by slowing the heart rate; but unlike beta-blockers, ivabradine does not have an effect on myocardial contractility or intracardiac conduction.[4] In Europe, consideration for ivabradine is given to

reduce HF hospitalization in patients in normal sinus rhythm with HFrEF (EF ≤35%), a baseline resting HR of 70 BPM or more, and persistent symptoms (NYHA class II-IV) despite a recommended dose of a beta-blocker, an ACE-I/ARB and an aldosterone antagonist.[5] Ivabradine was recently approved by the U.S. Food and Drug Administration for a similar indication as that recommended in Europe.[4]

Previous evidence has shown increased HR, even at relatively low rates of 77-82 BPM, in patients with CAD is associated with higher higher CV mortality and CV complications.[8] In patients with HF with preserved EF (HFpEF), every increase in HR by 10 BPM was associated with a statistically significant 7% increased risk of all-cause mortality, and 8% increased risk of CV death or hospital admission for HF.[9] In patients with confirmed CAD and HFrEF, a baseline resting HR of 70 BPM or higher was associated with 34% higher risk for CV death, 53% increase in hospital admission for HF, and 46% increase in hospital admission for myocardial infarction (MI), which were statistically significant differences relative to a baseline resting HR lower than 70 BPM.[10] Patients with symptomatic HFrEF (NYHA Class II or higher) with high resting HR (≥87 BPM) were at a 3.5-fold higher risk for death from HF, and almost 2-fold higher risk for all-cause mortality and CV mortality than patients with a resting HR under 72 BPM.[11] However, decreasing HR may not necessarily improve CV risk. For example, sustained-release metoprolol succinate reduced mortality and hospitalizations independent of resting baseline HR, change in HR from baseline, or the HR achieved at the end of study follow-up.[12]

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 first large trial (median duration 19 months; n=10,917) of ivabradine was a fair-quality study called "morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left-ventricULar dysfunction" (i.e., "BEAUTIFUL").[2] The study was a multi-centered, double-blind, randomized, controlled trial (RCT) that compared ivabradine 5 mg twice daily (BID), titrated up to 7.5 mg BID if tolerated, to placebo in mostly males with NYHA Class II HF. Most patients enrolled into the study were on appropriate concurrent HF therapies, including ACE-Is or ARBs (90%), beta-blockers (84%), aspirin or other antithrombotic agent (94%), and lipid lowering therapy (i.e., statins) (90%). Patients enrolled into the study had a mean left-ventricular ejection fraction (LVEF) of 32% and had stable CAD, defined as previous MI at least 6 months prior to enrollment, previous interventional coronary revascularization at least 6 months prior to enrollment, or patients with evidence of at least 1 major coronary artery with at least 50% occlusion. In addition, patients had to be in normal sinus rhythm with a resting HR of at least 60 BPM. The mean age in the study was 65 years and 82% were males. The primary endpoint was a composite of CV death, hospital admission for MI, or hospital admission for new-onset or worsening HF. CV death was defined as sudden cardiac death, death from a vascular procedure, death from arrhythmia, death from stroke, death from any vascular event, or sudden death from an unknown cause. The primary endpoint occurred in 15.4% of patients receiving ivabradine (mean dose 6.18 mg BID) and 15.3% of patients receiving placebo (hazard ratio [HR] =1.00 (95% confidence interval [CI], 0.91 to 1.10; p=0.94). In addition, there was a no significant difference in all secondary outcomes measured, including all-cause mortality, cardiac death, CV death (defined above), coronary revascularization, hospital admission for HF, and hospital admission for MI. The protocol was amended to evaluate a subgroup of patients with a resting HR of at least 70 BPM as data became available that ivabradine may be more beneficial in these patients. The subgroup analysis found a significant reduction in 2 secondary endpoints: hospital admission for MI, admission to hospital for MI or unstable angina, or coronary revascularization. There was no statistically significant difference between ivabradine and placebo for all other study endpoints, including the composite primary endpoint. Bradycardia was the most commonly associated adverse event (13%) attributed to ivabradine.[2]

The second trial (median duration 22.9 months) of ivabradine was a fair-quality study that evaluated the drug in patients (n=6505) with stable, symptomatic chronic HF (NYHA Classes II and III) with systolic dysfunction (LVEF ≤35%) and was titled the "Systolic Heart failure treatment with the If inhibitor ivabradine

Trial" (i.e., "SHIFT").[1] It was a multi-centered, double-blind, RCT that compared ivabradine 5 mg BID, titrated up to 7.5 mg BID if tolerated, to placebo in mostly White male subjects. Most patients enrolled into the study were on appropriate concurrent heart failure therapies, including ACE-I/ARBs (91%), and beta-blockers (89%); however, only 26% of the patients enrolled in the study were on target beta-blocker doses and under half (49%) were receiving 50% or more of the targeted beta-blocker dose, per the European Society of Cardiology (ESC).[5] No data were provided on the proportion of patients receiving target doses of ACE-Is or ARBs. Patients enrolled into the study had a LVEF of 29% and 84% regularly received diuretics. Only 2% were classified with NYHA Class IV HF. The mean age in the study was 60 years and 76% were males, mostly of Eastern European descent (no U.S. sites). The primary endpoint was a composite of CV death or hospital admission for worsening HF. CV death was defined as any sudden death unless an unequivocal non-CV cause of death was established. At 28 days, HR in patients on ivabradine fell by a mean 15.4 BPM compared to pre-treatment, which was a net reduction of 10.9 BPM (95% CI, 10.4-11.4) relative to placebo. The primary endpoint occurred in 24.5% of patients receiving ivabradine (mean dose 6.5 mg BID) and 28.7% of patients receiving placebo (absolute difference of 4.2%; HR =0.82 (95% CI, 0.75 to 0.90; p<0.0001; NNT=26 for 1 year). These data were driven by a reduction in the number of hospital admissions for worsening HF (15.9% vs. 20.6%; HR=0.74, 95% CI 0.66-0.83; p<0.0001) and not CV death (13.9% vs. 15.0%; HR=0.91, 95% CI 0.80-1.03; p=0.128). A sub-group analysis found that patients with a baseline resting HR of less than 77 BPM had a significant reduction in the composite primary endpoint, but there was no difference between the groups in patients with HR of 77 BPM or higher. Other secondary outcomes that demonstrated statistically significant reductions with ivabradine use included death attributed to HF (3.5% vs. 4.6%; HR=0.74, 95% CI 0.58-0.94; p=0.014), hospital admissions due to any CV reason (30.1% vs. 34.4%; HR=0.85, 95% CI 0.78-0.92; p=0.0002), and all-cause hospitalizations (38.0% vs. 41.5%; HR=0.89, 95% CI 0.75-0.90; p=0.003). However, there was no statistically significant difference in all-cause mortality between those receiving ivabradine (15.5%) and those receiving placebo (16.9%). In addition, there was no statistically significant difference in the primary endpoint in patients who were on at least 50% of the target beta-blocker dose as recommended by the ESC – a pre-specified secondary endpoint. A sub-group analysis of the study found there to be a direct association between HR achieved at 28 days and subsequent cardiac outcomes.[11] Patients with HRs lower than 60 BPM at 28 days on treatment had fewer primary composite endpoint events in the study (17.4%, 95% CI 15.3-19.6) than did patients with higher HRs.[11] However, there were statistically significant baseline differences in some confounding factors: patients enrolled into the study with lower baseline resting HRs were younger, had lower rates of current smoking status, had a higher LVEF, and lower NYHA classification status than patients with much higher baseline HRs.[11] Notable adverse events included symptomatic and asymptomatic bradycardia, which occurred at a statistically significantly greater extent with ivabradine.[1] More patients on ivabradine also experienced atrial fibrillation (9.5% vs. 7.7%), which occurred significantly more often than in patients receiving placebo (number needed to harm = 55 patients).[1]

The third trial (median duration 27.8 months) of ivabradine was a good-quality study that evaluated the drug in patients (n=19,102) with stable CAD but without any evidence of clinical HF and was titled "Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease" (i.e., "SIGNIFY").[3] The study was a multi-centered (no U.S. sites), double-blind, RCT that compared ivabradine 7.5 mg BID, adjusted to 5 mg, 7.5 mg or 10 mg BID if tolerated, to placebo in mostly White males without HF. Eligible patients had stable CAD, were in normal sinus rhythm, and a LVEF greater than 40% with a resting HR of 70 BPM or greater. However, patients had to have either activity-limiting angina pectoris (Canadian Cardiovascular Scale [CCS] class II or higher), a history of myocardial ischemia in the past year or were hospitalized for a coronary event in the past year. Otherwise, if patients did not meet one of the previous 3 criteria, they had to meet at least 2 other criteria put them at risk for a cardiac event, such as dyslipidemia, diabetes mellitus, current smoker, age 70 years or older, or peripheral artery disease. Most patients enrolled into the study were receiving ACE-I/ARBs (82.8%), beta-blockers (83.1%), aspirin or other antithrombotic agent (91.6%), and lipid lowering therapy (i.e., statins) (92.2%). Patients enrolled into the study had a mean age of 65 years and 72.4% were males. About 73% had a previous MI, 68% had a history of coronary revascularization, and 63% had activity-limiting angina. The primary endpoint was a composite of nonfatal MI and multiple outcomes under the umbrella term "cardiovascular death". CV death was defined as sudden cardiac death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause), death from a vascular procedure, fatal stroke, or non-sudden death from an unknown cause. The primary endpoint occurred in 6.8% of patients receiving ivabradine (mean dose 8.0 mg BID) and 6.4% of patients receiving placebo (HR =1.08; 95% CI, 0.96 to 1.20; p=0.20). In addition, there was a non-statistically significant difference in all secondary outcomes measured, including all-cause

mortality, cardiac death, CV death (defined above), fatal/non-fatal MI, coronary revascularization, and hospital admission for HF. Overall, the addition of ivabradine did not reduce CV events in patients with stable CAD without HF.[3]

Based on the evidence provided from these 3 trials, the FDA granted approval for the use of ivabradine to reduce risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with a LVEF of 35% or less, who are in sinus rhythm with a resting HR of 70 BPM or more and either on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.[4] The approval was based on the efficacy demonstrated as a secondary endpoint in SHIFT, which showed a statistically significant 4.7% reduction in hospitalizations for worsening HF with ivabradine relative to placebo. Thus, 22 patients would need to be treated with ivabradine for nearly 2 years (22.9 months) to prevent 1 hospitalization for worsening HF. Based on the evidence available, patients that do not fit the criteria within the FDA approval will likely not benefit from ivabradine.

Clinical Safety:
A summary of the clinical safety of ivabradine will focus on the stable but symptomatic chronic HF population enrolled in SHIFT[1], which is the population for which the FDA has approved use of the drug. A summary of common adverse events associated with ivabradine is available in Table 2.

In SHIFT, symptomatic and asymptomatic bradycardia was more frequent in the ivabradine group than in patients taking placebo (both $p<0.001$).[1] The rate of bradycardia was 6.0% per patient-year in patients on ivabradine (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Bradycardia resulted in premature withdrawal from the study in 48 (1.5%) of patients on ivabradine and 10 (0.3%) of those on placebo.[1] Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, or amiodarone).[4] In addition, sinus arrest and heart block have occurred with use of ivabradine.[4] Therefore, patients on ivabradine should be monitored closely for signs and symptoms of bradycardia, especially early in therapy.

In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients on ivabradine and 3.9% per patient-year in patients treat with placebo. The manufacturer advises discontinuing ivabradine if atrial fibrillation develops.[4]

Table 2. Adverse Events with Rates ≥1% Higher with Ivabradine than Placebo Occurring in >1% of Patients Enrolled in SHIFT.[1,4]

Adverse Event	Ivabradine (n=3260)	Placebo (n=3278)
Bradycardia	10%	2.2%
Hypertension; Increased Blood Pressure	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes, Visual Brightness	2.8%	0.5%

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images. Phosphenes are typically triggered by sudden variations in light intensity.[4]

According to the SHIFT investigators, there were no relevant between-group differences in laboratory parameters (unpublished data).[1]

Animal studies have shown ivabradine to result in embryo-fetal toxicity and cardiac teratogenic effects. It can therefore be assumed ivabradine may cause fetal toxicity when administered to pregnant women and it is advised females on ivabradine use effective contraception.[4]

Look-alike / Sound-alike Error Risk Potential: The Institute for Safe Medication Practice (ISMP) has not updated their List of Confused Drug Names since approval of ivabradine.[13]

Pharmacology and Pharmacokinetic Properties:

Table 3. Basic Pharmacology and Pharmacokinetic Properties of Ivabradine.

Parameter	
Mechanism of Action	Specific inhibitor of the I_f current in the sinoatrial node, decreasing heart rate without affecting blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarization.[4]
Oral Bioavailability	40% due to extensive first-pass metabolism and elimination in the gut and liver.[4]
Distribution and Protein Binding	Volume of distribution at steady state is about 100 L; approximately 70% of the drug in plasma is bound to protein.[4]
Elimination	Total clearance is 24 L/h, with renal clearance of about 4.2 L/h (4% unchanged in urine).[4]
Half-Life	Effective half-life is about 6 hours.[4]
Metabolism	Extensively metabolized in the liver and intestines by CYP 3A4-mediated oxidation.[4] The major metabolite is a N-desmethylated derivative that is as potent as ivabradine and circulates at about 40% that of ivabradine.[4]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality (all-cause, secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptom-relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality-of-life

Primary Study Endpoints:
1) Composite (cardiovascular death*, hospital admission for MI, or hospital admission for HF)
2) Composite (cardiovascular death* or hospital admission for HF)
3) Composite (cardiovascular death* and nonfatal MI)

*Cardiovascular death was also a composite of several outcomes, which are defined individually in the Comparative Evidence Table.

Table 4. Comparative Evidence of Ivabradine.

Ref./ Study Design	Drug Regimens/ Median Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. BEAUTIFUL[2] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR ≥60 BPM (I) 2. Placebo (P) 19 months	Demographics: -Mean Age 64.6 y -82% Males -Mean HR 79.2 BPM -Mean LVEF 32% -NYHA I 14% -NYHA II 59% -NYHA III 27% -ACE-I/ARB 90% -Beta-blocker 84% Key Inclusion Criteria: -Age ≥55 y (or ≥18 years if have DM) -CAD (previous MI, previous coronary revascularization, or evidence ≥1 major coronary artery narrowed by ≥50%) -LVEF <40% -Normal sinus rhythm -Resting HR ≥60 BPM Key Exclusion Criteria: -MI or coronary revascularization previous 6 months -Stroke/TIA previous 3 months -Implanted pacemaker, cardioverter or defibrillator -Valvular disease -Sick sinus syndrome -Sinoatrial block -Congenital long QT -Complete AV block -Uncontrolled HTN -NYHA Class IV	ITT: I: n=5479 P: n=5438 Attrition: I: 28% P: 16%	Primary Endpoint: CV Death, Hospital Admission for MI, or Hospital Admission for HF: I: 15.4% vs. P: 15.3%; HR=1.00 (95% CI, 0.91-1.10; p=0.94) Secondary Endpoints: All-cause Mortality: I: 10.4% vs. P: 10.1%; HR=1.04 (95% CI, 0.92-1.16; p=0.55) Cardiac Death (death from MI, HF or cardiac surgery): I: 2.5% vs. P: 2.8%; HR=0.89 (95% CI, 0.71-1.12; p=0.33) CV Death (cardiac death, or death from vascular procedure, arrhythmia, stroke, other vascular event, or sudden death of unknown cause): I: 8.6% vs. P: 8.0%; HR=1.07 (95% CI, 0.94-1.22; p=0.32) Coronary Revascularization: I: 2.8% vs. P: 3.4%; HR=0.83 (95% CI, 0.67-1.02; p=0.078) Hospital Admission for HF: I: 7.8% vs. P: 7.9%; HR=0.99 (95% CI, 0.86-1.13; p=0.85) Hospital Admission for MI: I: 3.6% vs. P: 4.2%; HR=0.87 (95% CI, 0.72-1.06; p=0.16)	NS NS NS NS NS NS	Any Serious AE: I: 23% P: 23% P=NS Discontinuation due to AE: I: NR P: NR Bradycardia: I: 705 (13%) P: 79 (2%) P=NR Cardiac disorders: I: 18% P: 15% P<0.001	NS NR 11%/NR 3%/33	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographic characteristics evenly matched. Performance: (mod) allocated by interactive web-response system to ensure allocation remained concealed; blinding not described. Detection: (mod) 2 major protocol amendments; power assumptions described; censoring rules appropriate; ITT analysis performed; assessors blinded. Attrition: (mod) high attrition, w/ 12% higher attrition w/ ivabradine but controlled w/ ITT. **Applicability**: Patient: patients w/ mild symptomatic HF; mostly male; unknown racial makeup; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.). Intervention: mean dose of 6.18 mg BID; 40% remained on 7.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; clinically relevant individual outcomes; AEs only described by body system except for bradycardia. Setting: outpatient visits at 2 weeks, 1, 3 and 6 months; and every 6 months thereafter. **Analysis**: The drug sponsor used a subgroup analysis that found patients w/ HR ≥70 BPM may benefit from the following outcomes w/ ivabradine: hospital admission for MI, or hospital admission for coronary revascularization. The analysis was used to test the hypothesis in the SHIFT trial.

2. SHIFT[1] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR >60 BPM; dose reduced by 2.5 mg if HR <50 BPM or symptomatic (I) 2. Placebo (P) 22.9 months	Demographics: -Mean Age 60.4 y -Male 76% -HR 79.9 BPM -LVEF 29% -NYHA II 48.7% -NYHA III 49.5% -NYHA IV 1.7% -Ischemic etiology 68% -Non-ischemic etiology 32% -Hypertension 67% -ACE-I/ARB 91% -Beta-blocker 89% -Diuretics 84% -Aldosterone antagonists 60% Key Inclusion Criteria: -Age ≥18 y -Stable, symptomatic HF ≥4 weeks -LVEF ≤35% -Normal sinus rhythm -Resting HR ≥70 BPM -Optimal and stable background HF therapy x ≥4 weeks -Previous hospitalization for HF in last 12 months Key Exclusion Criteria: -Recent MI <2 months -CVA/TIA <4 weeks -Ventricular or atrioventricular pacing operative ≥40% of day -Atrial fib/flutter -Symptomatic hypotension -HF from congenital disease or severe valvular disease -diltiazem/verapamil -Class I antiarrhythmic	mITT: I: n=3241 P: n=3264 Attrition: I: 21% P: 19%	Primary Endpoint: CV Death or Hospital Admission for HF: I: 24.5% vs. P: 28.7%; HR=0.82 (95% CI, 0.75-0.90; p<0.0001) Secondary Endpoints: CV Death or Hospital Admission for HF in Patients on ≥50% Target Beta-blocker Dose per the ESC*: I vs. P data NR; HR=0.90 (95% CI, 0.77-1.04; p=0.155) All-cause Mortality: I: 15.5% vs. P: 16.9%; HR=0.90 (95% CI, 0.80-1.02; p=0.092) Death from HF: I: 3.5% vs. P: 4.6%; HR=0.74 (95% CI, 0.58-0.94; p=0.014) CV Mortality: I: 13.9% vs. P: 15.0%; HR=0.91 (95% CI, 0.80-1.03; p=0.128) Hospital Admission for HF: I: 15.9% vs. P: 20.6%; HR=0.74 (95% CI, 0.66-0.83; p<0.0001) Hospital Admission for any CV reason: I: 30.1% vs. P: 34.4%; HR=0.85 (95% CI, 0.78-0.92; p=0.0002) All-cause Hospitalization: I: 38.0% vs. P: 41.5%; HR=0.89 (95% CI, 0.75-0.90; p=0.003)	4.2%/24 NS 1.4%/NS 1.1%/91 1.1%/NS 4.7%/22 4.3%/24 3.5%/29	Serious AEs: I: 1450 (45%) P: 1553 (48%) p=0.025 Discontinuation due to AE: I: 467 (14%) P: 416 (13%) p=0.051 Symptomatic Bradycardia: I: 150 (4.6%) P: 32 (1.3%) p<0.0001 Asymptomatic Bradycardia: I: 184 (5.7%) P: 48 (1.5%) p<0.0001 Atrial Fibrillation: I: 306 (9.5%) P: 251 (7.7%) p=0.012 Phosphenes (transient enhanced brightness in a restricted area of the visual field): I: 89 (2.8%) P: 17 (0.5%) p<0.0001 Blurred Vision: I: 17 (1%) P: 7 (<1%) p=0.042	NA NS 3.3%/30 4.2%/23 1.8%/55 2.3%/43 0.3%/333	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization with well-balanced demographics. Performance: (low) allocated by interactive web-response system to ensure allocation remained concealed; placebo identical in appearance, ensuring blinding maintained. Detection: (mod) power assumptions described; modified ITT analysis performed after 2 centers' data removed due to misconduct; imputation of missing data unclear; censoring rules unclear. Attrition: (low) 2% more patients on ivabradine (n=682) withdrew vs. placebo (n=605) (HR=1.14; 95% CI, 1.02-1.27; p=0.017). **Applicability**: Patient: majority White males w/ Class II or III NYHA HF; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.), similar doses between groups; only 26% in each grp at target dose of beta-blocker. Intervention: mean dose 6.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary endpoint driven by decreased hospitalizations for HF; primary endpoint not significantly reduced in patients w/ baseline HR <77 BPM; primary endpoint also favors age <65 years; ivabradine resulted in a net HR reduction of 8.1 (95% CI, 8.5-9.7) BPM vs. placebo by end of study; all deaths categorized as CV deaths unless unequivocal non-CV cause established. Setting: no USA sites, mostly Eastern Europe (66%); outpatient clinic visits every 4 months. **Analysis**: Results of the trial were considered by the FDA to grant approval of the drug with specific criteria for use.

3. SIGNIFY[3] MC, R, DB, PC PG	1. Ivabradine 7.5 mg BID (5 mg BID if age ≥75 y). Dose adjusted to 5, 7.5 or 10 mg BID per HR (goal 55-60 BPM) and bradycardia symptoms (I) 2. Placebo (P) 27.8 months	Demographics: -Mean Age 65 y -72.4% Males -Mean HR 77.2 BPM -Mean LVEF 56.4% -73.3% previous MI -67.8% previous coronary revascularization -63.1% w/ activity-limiting angina (CCS class ≥II) Key Inclusion Criteria: -Age ≥55 y -Stable CAD w/o HF -LVEF >40% -Normal sinus rhythm -Resting HR ≥70 BPM And either: -≥1 major adverse prognostic factor: • angina pectoris (CCS class ≥2) • myocardial ischemia past 1 y • hospitalization for coronary event past 1 y -Or 2 minor adverse prognostic factors: • HDL <40 mg/dL or LDL >160 mg/dL (on meds) • T1DM or T2DM • PAD • Current smoking • Age ≥70 y Key Exclusion Criteria: -NYHA class II or higher -MI, coronary revascularization, stroke/TIA w/i 3 months	ITT: I: n=9550 P: n=9552 Attrition: I: 20.6% P: 14.5%	Primary Endpoint: Death from CV cause or nonfatal MI: I: 6.8% vs. P: 6.4%; HR=1.08 (95% CI, 0.96-1.20; p=0.20) Secondary Endpoints: All-cause mortality: I: 5.1% vs. P: 4.8%; HR=1.06 (95% CI, 0.94-1.21; p=0.35) Coronary Death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause): I: 2.8% vs. P: 2.6%; HR=1.06 (95% CI, 0.89-1.26; p=0.52) CV Death (coronary death; death from CV procedure; fatal stroke; non-sudden death of unknown cause): I: 3.4% vs. P: 3.2%; HR=1.10 (0.94-1.28; p=0.25) MI (fatal/non-fatal): I: 4.1% vs. P: 3.9%; HR=1.06 (95% CI, 0.92-1.22; p=0.43) Coronary Revascularization: I: 5.9% vs. P: 5.9%; HR=1.00 (95% CI, 0.89-1.12; p=0.98) Hospital Admission for HF: I: 2.3% vs. P:1.9%; HR=1.20 (95% CI, 0.99-1.46; p=0.07)	0.4%/NS 0.3%/NS NA/NS NA/NS NA/NS 0%/NS NA/NS	Serious AEs: I: 37.6% P: 35.4% p=0.001 Discontinuation due to AE: I: 13.2% P: 7.4% P<0.001 Symptomatic Bradycardia: I: 7.9% P: 1.2% p<0.001 Asymptomatic Bradycardia: I: 11.0% P: 1.3% p<0.001 Discontinuation due to Asymptomatic Bradycardia: I: 272 (2.8%) P: 17 (0.2%) p<0.001 Discontinuation due to Symptomatic Bradycardia: I: 194 (2.0%) P: 33 (0.3%) p<0.001 Atrial Fibrillation: I: 5.3% P: 3.8% p<0.001 Phosphenes: I: 5.4% P: 0.5% p<0.001	2.2%/45 5.8%/17 6.7%/14 9.7%/10 2.6%/38 1.7%/58 1.5%/66 4.9%/20	**Quality Rating**: GOOD **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographics well-balanced between groups. Performance: (low) allocated by interactive voice/web-response system to ensure allocation remained concealed; matching placebo, ensuring blinding maintained. Detection: (mod) power assumptions described; true ITT analysis performed; data assessors remained blinded during study; censoring rules unclear. Attrition: (low) attrition high for ivabradine, w/ 6.1% more ivabradine patients who withdrew from study vs. placebo. **Applicability**: Patient: population studied different from previous trials (no HF); majority White males w/moderate angina but stable CAD; notable concurrent meds were beta-blockers (83.1%), ACE-I/ARB (82.8%), statins (92.2%), ASA (91.6%), diltiazem/verapamil (4.4%). Intervention: mean dose 8.2 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; ivabradine resulted in HR of 60.7 BPM at 3 months vs. 70.6 BPM w/ placebo; difference in HR maintained to end of study. Setting: no USA sites; outpatients visits at 1,2,3 and 6 months and every 6 months thereafter. **Analysis**: Well performed study confirmed lack of efficacy of ivabradine in CAD patients with preserved EF.

Abbreviations [alphabetical order]: ACE-I = ACE Inhibitors; AE = adverse events; ARB = angiotensin receptor blockers; ARR = absolute risk reduction; ASA = aspirin; AV = atrioventricular; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society scale I-IV; CI = confidence interval; CV = cardiovascular; DB = double-blind; DM = diabetes mellitus; DF = ejection fraction; ESC = European Society of Cardiology; HDL = high-density lipoprotein cholesterol; HR = heart rate or hazard ratio; HTN = hypertension; ITT = intention to treat; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MC = multi-centered; 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; NR = not reported; NS = not significant; NYHA = New York Heart Association; PAD = peripheral artery disease; PC = placebo-controlled; PG = parallel-group; R = randomized; T1DM; type-1 diabetes mellitus; T2DM = type-2 diabetes mellitus; TIA = transient ischemic attack.

*Target doses: carvedilol: 25-50 mg BID; metoprolol succinate: 200 mg Qday; bisoprolol 10 mg Qday; nebivolol 10 mg Qday.[5]

References:

1. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885. doi:10.1016/S0140-6736(10)61198-1.

2. Fox K, Ford I, Steg P, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807-816. doi:10.1016/S0140-6736(08)61170-8.

3. Fox K, Ford I, Steg P, Tardif J, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. *New England Journal of Medicine*. 2014;371:1091-1099. doi:10.1056/NEJMoa1406430.

4. Corlanor (ivabradine) [prescribing information]. Thousand Oaks, CA: Amgen Inc., April 2015.

5. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *European Journal of Heart Failure*. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

6. Yancy C, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239. doi:http://dx.doi.org/10.1016/j.jacc.2013.05.019.

7. van Veldhuisen D, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-2158. doi:10.1016/j.jacc.2009.02.046.

8. Diaz A, Bourassa M, Guertin M, Tardif J. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J*. 2005;26:967-674. doi:10.1093/eurheartj/ehi190.

9. Pocock S, Wang D, Pfeffer M, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27:65-75. doi:10.1093/eurheartj/ehi555.

10. Fox K, Ford I, Steg P, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008;372:817-821. doi:10.1016/S0140-6736(08)61171-X.

11. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886-894. doi:10.1016/S0140- 6736(10)61259-7.

12. Gullestad L, Wikstrand J, Deedwania P, et al. What resting heart rate should one aim for when treating patients with heart failure with a beta-blocker? Experiences from the metoprolol controlled release/extended release randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol*. 2005;45:252-259. doi:10.1016/j.jacc.2004.10.032.

13. ISMP's List of Confused Drug Names, Updated 2015. Institute for Safe Medication Practices. Available at www.ismp.org/Tools/confuseddrugnames.pdf. Accessed July 6, 2015.

Appendix 1: Highlights of Prescribing Information[4]

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

CORLANOR (ivabradine) tablets, for oral use
Initial U.S. Approval: 2015

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

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use. (1)

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

- Starting dose is 5 mg twice daily. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. (2)
- In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily. (2)

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

Tablets: 5 mg, 7.5 mg (3)

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

- Acute decompensated heart failure (4)
- Blood pressure less than 90/50 mmHg (4)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present (4)
- Resting heart rate less than 60 bpm prior to treatment (4)
- Severe hepatic impairment (4)
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) (4)
- In combination with strong cytochrome CYP3A4 inhibitors (4)

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

- Fetal toxicity: Females should use effective contraception. (5.1)
- Monitor patients for atrial fibrillation. (5.2)
- Monitor heart rate decreases and bradycardia symptoms during treatment. (5.3)
- Not recommended in patients with 2nd degree AV block. (5.3)

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

Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-772-6436 (1-800-77-AMGEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- CYP3A4 inhibitors increase Corlanor plasma concentrations and CYP3A4 inducers decrease Corlanor plasma concentrations. (7.1)
- Negative chronotropes: Increased risk of bradycardia, monitor heart rate. (7.2)
- Pacemakers: Not recommended for use with demand pacemakers set to rates ≥ 60 beats per minute. (7.3)

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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2015

Ivabradine (Corlanor®)

Goals:

- Restrict use of ivabradine to populations in which the drug has demonstrated efficacy.
- Encourage use of ACE-inhibitors or angiotensin II receptor blockers (ARBs) with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.
- Encourage use of with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ivabradine (Corlanor®)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on ivabradine)?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have current documentation of New York Heart Association Class II or III heart failure with reduced ejection fraction less than 40% (LVEF <40%)?	Yes: Go to #4	No: Pass to RPh. Deny for medical appropriateness
4. Is the patient in normal sinus rhythm with a resting heart rate of 70 beats per minute or greater (≥70 BPM)?	Yes: Go to #5	No: Pass to RPh. Deny for medical appropriateness

Approval Criteria		
5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at these target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness
6. Is the patient currently on a maximally tolerated dose of an ACE-inhibitor or an ARB; and if not, is there a documented intolerance or contraindication to both ACE-inhibitors and ARBs?	Yes: Approve for up to 6 months	No: Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Is the patient in normal sinus rhythm with no documented history of atrial fibrillation since ivabradine was initiated?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail*. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *11/15 (AG)*
Implementation: *TBD*

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: Lumacaftor/Ivacaftor

Date of Review: November 2015
Generic Name: Lumacaftor/Ivacaftor
PDL Class: Cystic Fibrosis Medications

End Date of Literature Search: September 2015
Brand Name (Manufacturer): Orkambi® (Vertex)
Dossier Received: Yes

Research Questions:

1. Is there evidence that lumacaftor/ivacaftor (LUM/IVA) improves clinically relevant outcomes in patients with cystic fibrosis (CF) homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, including lung function, quality of life, frequency of pulmonary exacerbations, hospitalizations, and mortality with a clinically significant magnitude of benefit?
2. Is there evidence that LUM/IVA is safe in patients with CF homozygous for the F508del mutation in the CFTR gene?
3. Are there any additional mutations in which LUM/IVA has safely demonstrated efficacy?

Conclusions:

- Treatment with LUM/IVA is approved for patients with CF homozygous for the F508del mutation in the CFTR gene. Lifelong therapy is used to slow lung function decline. Treatment has not been demonstrated to be curative.
- There is moderate quality evidence from two randomized controlled trials (RCTs) that short-term use of LUM/IVA 400/250 mg twice daily improves percent-predicted FEV1 compared to placebo over 24 weeks (mean difference 2.8% to 3.3% with LUM 400 mg/IVA twice daily and LUM 600 mg/IVA twice daily, respectively) in CF patients homozygous for the F508del mutation in the CFTR gene;[1] however, the clinical significance of this improvement is unknown. The magnitude of effect (2.8%) was considerably less than that produced by IVA alone versus placebo in patients with G115D mutation (11%) at 24 weeks, [2] and similar to that for IVA alone in the F508del mutation for which IVA was decided to be not efficacious.[3] There is insufficient and inconsistent evidence that LUM/IVA improves body mass index (BMI).[1] Changes in the quality of life questionnaire (CFQ-R respiratory domain) and pulmonary exacerbations were not statistically significant compared to placebo due to hierarchal design, but there was a nominal decrease in pulmonary exacerbations (LUM 400 mg RR 0.61; 95% CI 0.49 to 0.76 for and LUM 600 mg RR 0.70; 95% CI 0.56 to 0.87), and was confounded by other concomitant pre-modulation therapies. [1]
- An area of clinical uncertainty remains whether the combination of LUM/IVA provides more benefit than IVA monotherapy which was found to be deleterious in F508del homozygotes adults in previous clinical trials.[3] With phase 2 trials demonstrating a dose dependent decrease in $PPFEV_1$ with LUM alone, LUM/IVA treatment effect similar to IVA monotherapy, and LUM monotherapy not included as a comparator in confirmatory studies, the clinical significance of the combination agent remains uncertain.
- It is unclear from existing data whether the LUM/IVA combination is superior to IVA alone; evidence so far is insufficient to support use of IVA monotherapy in patients homozygous for the F508del mutation as the drug did not significantly improve percent-predicted FEV1.[3] Although statistically significant, the

small FEV1 effect seen with LUM/IVA in CF patients homozygous for the F508del mutation was similar to that for IVA alone (2-3%).[1,3] The individual components of the drug were not included in phase 3 studies, so it is unknown to what degree each medication contributes to its efficacy.

- There is low quality evidence that LUM/IVA produces a numerical decrease in sweat chloride of about 10 mmol/L, which is a much smaller decrease compared to that observed with IVA alone in patients with the G551D and R117H mutations (50 and 24 mmol/L, respectively). However, change in sweat chloride is not known to be clinically relevant to decline in respiratory function.
- Minor and reversible elevations of transaminases were seen across all groups and significant elevations occurred only in 5.1% of placebo patients and 5.2% of LUM/IVA patients. Serious adverse events related to abnormal liver function were not observed in the placebo group and were reported for seven patients in the LUM/IVA groups. Due to hepatic and respiratory related safety concerns, transaminases and pulmonary function should be monitored throughout therapy; this is particularly important in pediatric patients receiving therapy who will be potentially receiving therapy for years to come.
- LUM/IVA did not demonstrate a significant effect in patients who were heterozygous for the F508del mutation and therapy should not be used in patient populations outside of those homozygous for the F508del mutation.
- More data are needed to determine the long-term effects of LUM/IVA on survival and quality of life as well as the applicability of LUM/IVA in real-world settings, including criteria that define treatment success and time to response after initiation.

Recommendations:

- Maintain LUM/IVA as non-preferred and update PA criteria as presented in Appendix 3. Continue to monitor for patient adherence and adopt clinical criteria as needed to adequately assess clinical response as further data become available.

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[4] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[5] Important outcomes for treatment include reduction in mortality, frequency of pulmonary exacerbations, and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used outcome in clinical trials. The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for the respiratory symptom domain.[6] Weight is also a commonly measured secondary outcome in trials of CF children, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, and increased morbidity and mortality in children with CF. [6] The nutritional status of patients with CF is strongly associated with pulmonary function, respiratory status and survival. Sweat chloride level is the gold standard for a diagnosis of CF. Normal individuals typically have levels < 40 mmol/L but patients with CF have elevated levels > 60 mmol/L.[7] More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.[8] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of ivacaftor.[9] Although initial studies showed a reduction in the sweat chloride levels to values below the diagnostic threshold for CF (60 mmol/L), there is no evidence that sweat chloride is correlated with meaningful clinical benefits and it has not shown to correlate with improvement in FEV_1. [7] Clinical severity of CF is dependent on other factors in addition to CFTR function, and what aspect of CFTR function is affected depends on the specific combination of mutations in the individual.

CF is caused by mutations in the CFTR gene, found on the surface of cells in a variety of tissues where it functions as a regulator of chloride ion channel.[10] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[8] The F508del mutation results in

misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR to open channels at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ion.[8] There are three common alleles at the poly-T locus of the *R117H* gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.[11] Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype. The most common CFTR mutation is the *F508del*, which accounts for approximately two thirds of the recognized mutations, and carries the most severe prognosis. .[3]

Ivacaftor is a potentiator of CFTR and is indicated for the management of CF in patients in patients 2 years of age and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.* [2,12–14] Compared to placebo, the effects of IVA demonstrated in trials of the G115D mutation were an 10.6% absolute increase in FEV1 which was seen within 2 weeks of treatment, a 26% absolute decrease in respiratory exacerbations, a reduction in sweat chloride values by 50-60 mmol/L and a weight gain of 2.7 kg.[2] However the two-week endpoint was noted in post hoc analysis; the study design aimed at outcomes at 24 weeks. Ivacaftor is proposed to treat the underlying cause of CF by influencing the basic gene defect which can normalize airway surface liquid and help re-establish mucociliary clearance.[15,16] Ivacaftor is designed to increase the time that activated CFTR channels at the cell surface remain open. [15,16] The FDA recently approved LUM/IVA, a combination drug that contains a new molecular entity (LUM). The exact mechanism of LUM is unknown, but it may promote more functional folding of the defective F508del CFTR protein, allowing it to get to the cell surface. Previous studies of IVA did not demonstrate a clinical improvement in lung function in patients with an F508del mutation.[3] However, the combination of LUM/IVA was approved after phase III trials demonstrated it had efficacy for the management of CF in patients 12 years of age and older homozygous for the F508del mutation in the CFTR gene.[1] Phase II trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[17]

Worsening of liver function has been reported and use of LUM/IVC should be used in caution in patients with advanced liver disease. Liver enzymes should be monitored prior to therapy, every 3 months during the first year of treatment, and annually thereafter.

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:

Approval of LUM/IVA was based on 2 Phase III, randomized, double-blinded, placebo-controlled trials (TRAFFIC AND TRANSPORT) that compared LUM/IVA to placebo over 24 weeks (n=1122) in patients with CF who were homozygous for the F508del CFTR mutation.[1] Each trial had three parallel arms: lumacaftor 600 mg once daily/ivacaftor 250 mg twice daily, lumacaftor 400 mg/ivacaftor 250 mg twice daily, and placebo twice daily. The trials had identical designs with the exception of ambulatory electrocardiography in TRAFFIC, and adolescent pharmacokinetic assessments in TRANSPORT. The primary endpoint was an absolute change in percent-predicted FEV1 ($PPFEV_1$) at week 24, with studies demonstrating a difference from placebo of about 3%. Previous phase II dose-ranging studies of LUM/IVA demonstrated modest reductions in sweat chloride (-9.5 mmol/L; 95% CI -15.1 to -3.9) for LUM 600 mg daily and -11.0 (95% CI -18.3 to -3.7) with LUM 400 mg twice daily.[18] This is a much smaller effect than what was observed with IVA therapy in G551D and R117H mutations (50 and 24 mmol/L, respectively).[11,19] The individual components of the drug were not included in phase III studies, so it is unknown to what degree each medication contributes to its efficacy. Results of the FDA analysis demonstrated a small FEV1 improvement similar to that for IVA monotherapy with a similar exacerbation rate ratio (0.6) those homozygous for the F508del CFTR mutation.[18] LUM monotherapy demonstrated a dose-dependent decrease in lung function and was not included as an arm in confirmatory studies, raising the concern of unknown biological plausibility of the combination of both agents resulting in significant improvements.[20]

A pre-specified hierarchical testing for key secondary endpoints was done to test for significance. If a test failed, all subsequent tests were considered not statistically significant. In TRAFFIC, the absolute change in $PPFEV_1$ from baseline was 2.2% , with a mean difference from placebo of 2.6% (95% CI 1.2 to 4.0) with LUM 400 mg/IVA twice daily. Similarly, in TRANSPORT, the change from baseline was 2.9% with a difference from placebo of 3.0% (95% CI 1.6 to 4.4). The mean difference versus placebo with the higher dose of LUM (600 mg twice daily) was 4.0% (95% CI 2.6 to 5.4) in TRAFFIC and 2.6 (95% CI 1.2 to 4.1) in TRANSPORT. Thirty nine percent of patients achieved a 5% or greater increase in the PPFEV1 (OR 2.22; $p<0.001$) compared to placebo. There was no significant difference in change in BMI in TRAFFIC, and therefore the remaining secondary endpoints were not tested and considered not significant. In TRANSPORT there was a statistically significant difference in change in BMI between LUM/IVA and placebo (0.4; 95% CI 0.2 to 0.5), but no statistically significant difference in absolute change in CFQ-R. The remaining secondary outcomes were not statistically significant. There was a nominal improvement in exacerbation rates in pooled data from TRAFFIC AND TRANSPORT with both doses of LUM/IVA compared to placebo (0.8 per 48 weeks vs. 1.14;RR 0.7; 95% CI 0.5-0.9 for LUM 600mg/IVA twice daily and 0.7 vs. 1.14; RR 0.61; 95% CI 0.4 to 0.8 for TRAFFIC and TRANSPORT, respectively, NNT 4-6), with a reduction in rate of about 34% compared to placebo. However, this is confounded by the other pre-modulation therapies received by patients. Sweat chloride or other biomarkers were not evaluated in the phase III trials. There does not seem to be a dose-response, as for many outcomes the combination including 400 mg LUM was more effective than 600 mg LUM.

Differences between these 2 studies and the study of IVA alone, which demonstrated no effect in this population, were duration (24 weeks vs. 16 weeks), the use of hypertonic saline was not allowed in the IVA trial, and lower baseline $PPFEV_1$ in the LUM/IVA trials. The FDA did not find evidence that LUM/IVA is superior to IVA alone with respect to improvement in $PPFEV_1$ and pulmonary exacerbations.[18]

Drug-drug interactions between LUM (a strong CYP3A inducer) and IVA (CYP3A substrate and weak inhibitor) necessitate higher doses of IVA. These properties also create potential difficulty with the fixed combination of these agents and may be one explanation for the numerically similar effect size of a 2-3% increase in $PPFEV_1$ seen with the combination compared to IVA alone.[21]

Clinical Safety:
Overall, any adverse event was reported in 95% of patients and it was generally well tolerated with low discontinuation rates. The most common adverse drug reactions that occurred in 5% of more of patients were generally respiratory and are included in the following table:

Table 1: Incidence of Adverse Drug Reactions in ≥5% of ORKAMBI-Treated Patients Who are Homozygous for the *F508del* Mutation in the *CFTR* Gene in 2 Placebo-Controlled Phase 3 Clinical Trials of 24 Weeks Duration		
Adverse Reaction (Preferred Term)	**ORKAMBI N=369 (%)**	**Placebo N=370 (%)**
Dyspnea	48 (13)	29 (8)
Nasopharyngitis	48 (13)	40 (11)
Nausea	46 (13)	28 (8)
Diarrhea	45 (12)	31 (8)
Upper respiratory tract infection	37 (10)	20 (5)
Fatigue	34 (9)	29 (8)
Respiration abnormal	32 (9)	22 (6)
Blood creatine phosphokinase increased	27 (7)	20 (5)
Rash	25 (7)	7 (2)
Flatulence	24 (7)	11 (3)
Rhinorrhea	21 (6)	15 (4)
Influenza	19 (5)	8 (2)

Serious adverse events were reported in 28.6% of patients in the placebo group and 22.8% of the patients in the LUM/IVA groups; infective pulmonary exacerbation was the most common serious adverse event observed (13% in pooled treatment group and 24.1% in placebo group). Minor elevations (> 3x the upper limit of normal range) of liver transaminases occurred in 5.1% of placebo patients and 5.2% of LUM/IVA patients. Serious adverse events related to abnormal liver function were not observed in the placebo group but were reported in 7 patients in the LUM/IVA group, of which 6 returned to baseline following discontinuation.

Withdrawals due to adverse events occurred at a higher percentage in the active treatment groups, but rates were low in all study arms.

Pharmacology and Pharmacokinetic Properties[22]:

Parameter	
Mechanism of Action	Improves the conformational stability of F508-del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface; facilitating increased chloride transport.
Oral Bioavailability	Exposure 3 times higher when administered with fat-containing foods compared to a fasting state.
Distribution and Protein Binding	Lumacaftor is 99% bound to plasma proteins, primarily albumin with a VD of 86L Ivacaftor is 99% protein bound, primarily to alpha 1-acid glycoprotein and albumin
Elimination	Majority of lumacaftor eliminated unchanged in feces. Majority of ivacaftor eliminated in feces after metabolic conversion.
Half-Life	25.2 hr (lumacaftor); 9 hr (ivacaftor)
Metabolism	Lumacaftor not extensively metabolized. Ivacaftor is primarily metabolized by CYP3A

Abbreviations:

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Weight Gain (BMI)
2) Mortality
3) Hospitalizations
4) Frequency of pulmonary exacerbations
5) Quality of Life and Pulmonary symptoms

Primary Study Endpoint:
1) Absolute change in PPFEV1 from baseline at week 24

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. TRAFFIC[1] Phase III, RCT, DB, PC, PG	1. LUM/IVA 600 mg Q24H / 250 mg Q12H 2. LUM/IVA 400 mg/ 250 mg Q12H 3. Placebo 24 weeks	Demographics: Homozygous for the *F508del-CFTR* mutation; mean baseline FEV1 61%; mean age 26 Key Inclusion Criteria: Sweat chloride >60 mmol/L or chronic sinopulmonary disease, FEV1 40-90% of predicted, ≥12 y/o Key Exclusion Criteria: Cirrhosis, portal HTN, risk factors for torsades de pointes, Hg < 10 g/dL, abnormal LFTs (≥3x ULN), GFR < 50 ml/min, QTcF > 450 msec, alcohol or drug abuse including cannabis, cocaine, and opiates, use of strong inhibitors, moderate inducers, or strong inducers of CYP3A4, pregnant or nursing females	mITT: 1. 185 2. 187 3. 187 Attrition: 1. 11 2. 10 3. 8	Change in $PPFEV_1$ from baseline: 1. 3.6 % 2. 2.2% 3. -0.44% Treatment difference: 1 vs. 3: 4.0%; 95% CI 2.6-5.4; p<0.001 2 vs. 3: 2.6%; 95% CI 1.2-4.0); p<0.001 Absolute change from baseline in BMI: 1. 0.35 kg/m2 2. 0.32 kg/m2 3. 0.19 kg/m2 Difference vs. placebo: NS Pulmonary Exacerbations : 1. 79 (43%) 2. 73 (40%) 3. 112 (61%) 1 vs. 3: RR 0.72; 95% CI 0.52-1.00; p=0.05* 2 vs. 3: RR 0.66; 95% CI 0.47 to 0.93; p=0.02* *Considered not significant due to statistical hierarchy	 NA NA NS NA NA	Discontinuations due to Adverse Events: 1. 8 (4.4%) 2. 6 (3.3%) 3. 4 (2.2%) NS Serious Adverse Events: 1. 33 (18%) 2. 33 (18.1%) 3. 49 (26.6%)	 NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Low RoB; Appropriate randomization and allocation concealment; baseline characteristics similar Performance: Low RoB; Double-blind design; matching placebo Detection: Low RoB; site personnel, site monitor, and study team blinded Attrition: modified ITT analysis done using FAS including all randomized subjects who received any amount of study drug. Attrition overall low (<10%) and similar between grps. **Applicability**: Patient: Significant exclusion criteria limits generalizability to patient population; Only 58.1% on hypertonic saline and 64.5% on inhaled antibiotics Intervention: new fixed drug combination Comparator: Individual component comparator needed to assess contribution of LUM Outcomes: The literature remains uncertain on clinical outcomes best to assess gene therapy targeting the CFTR gene; Pulmonary exacerbations were defined as a new or change in antibiotic therapy for 4 or more of the following symptoms: new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection Setting: Multinational (North America, Europe, Australia) **Analysis**: Good internal validity with little magnitude of effect and uncertain clinical significance. Funded by manufacturer.

2. TRANSPORT[1] Phase III, RCT, DB, PC, PG	1. LUM/IVA 600 mg/ 250 mg Q12H 2. LUM/IVA 400 mg/ 250 mg Q12H 3. Placebo 24 weeks	Demographics: Homozygous for the *F508del-CFTR* mutation; mean baseline FEV1 61%; mean age 26 Key Inclusion Criteria: Sweat chloride >60 mmol/L or chronic sinopulmonary disease, PPFEV1 40-90%, age ≥12 y Key Exclusion Criteria: Cirrhosis, portal HTN, risk factors for torsades de pointes, Hg < 10 g/dl, abnormal LFTs (≥3x ULN), GFR < 50 ml/min, QTcF > 450 msec, alcohol or drug abuse including cannabis, cocaine, and opiates, use of strong inhibitors, moderate inducers, or strong inducers of CYP3A4, pregnant or nursing females	ITT: 1. 187 2. 189 3. 187 FAS: 1. 185 2. 187 3. 187 Attrition: 1. 9 2. 15 3. 5	Change in $PPFEV_1$ from baseline: 1. 2.5 % 2. 2.9% 3. -0.15% Treatment difference: 1 vs. 3: 2.5%; 95% 1.2-4.1; p<0.001 2 vs. 3: 3.0%; 95% CI 1.6-4.4); p<0.001 Absolute change from baseline in BMI: 1. 0.48 kg/m2 2. 0.43 kg/m2 3. 0.07 kg/m2 Treatment Difference: 1 vs. 3: 0.41; 95% CI 0.23-0.59; p<0.001 2 vs. 3: 0.36; 95% CI 0.17-0.54; p<0.001 Pulmonary Exacerbations (Rate Ratio): 1. 94 (51%) 2. 79 (42%) 3. 139 (74%) 1 vs. 3: RR 069; 95% CI 0.52-0.92; p=0.01* 2 vs. 3: RR 0.57; 95% CI 0.42 to 0.76; p=<0.001* *Considered not significant due to statistical hierarchy	 NA NA NA NA ARR 23/ NNT 5 ARR 32/ NNT 4	Discontinuations due to Adverse Events: 1. 6 (3.2%) 2. 11 (5.9%) 3. 2 (1.1%) Serious Adverse Events: 1. 51 (27.4%) 2. 31 (16.6%) 3. 57 (30.6%)	 NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Low RoB; Appropriate randomization and allocation concealment; baseline characteristics similar Performance: Low RoB; Double-blind design; matching placebo Detection: Low RoB; Site personnel, site monitor, and study team blinded Attrition: modified ITT analysis done using FAS including all randomized subjects who received any amount of study drug. Attrition overall low (<10%) and similar between groups. **Applicability**: Patient: Significant exclusion criteria limits generalizability to patient population; Only 58.1% on hypertonic saline and 64.5% on inhaled antibiotics Intervention: OK Comparator: Individual component comparator needed to assess contribution of LUM Outcomes: Unclear on clinical outcomes best assess gene therapy targeting the CFTR gene. Pulmonary exacerbations were defined as a new or change in antibiotic therapy for 4 or more of the following symptoms: new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection Setting: Multinational (North America, Europe, Australia) **Analysis**: Good internal validity with little magnitude of effect and uncertain clinical significance. Funded by manufacturer.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CFTR = Cystic Fibrosis Transmembrane Conductance Regulator; FAS = full analysis set; GFR = glomerular filtration rate; Hg = hemoglobin; HTN = hypertension; mITT = modified intention to treat; IVA = ivacaftor; LUM= lumacaftor; 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; $PPFEV_1$ = percent-predicted forced expiratory volume in one second; RCT = randomized controlled trial; RoB = risk of bias; ULN = upper limit of normal; y = years.

References:

1. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *N Engl J Med*. May 2015. doi:10.1056/NEJMoa1409547.

2. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672. doi:10.1056/NEJMoa1105185.

3. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. 2012;142(3):718-724. doi:10.1378/chest.11-2672.

4. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2014;18(18):1-106. doi:10.3310/hta18180.

5. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. *American Journal of Respiratory and Critical Care Medicine*. 2013;187(7):680-689. doi:10.1164/rccm.201207-1160OE.

6. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest*. 2009;135(6):1610-1618. doi:10.1378/chest.08-1190.

7. Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest*. 2013;143(1):14-18. doi:10.1378/chest.12-1430.

8. O'Reilly R, Elphick HE. Development, clinical utility, and place of ivacaftor in the treatment of cystic fibrosis. *Drug Des Devel Ther*. 2013;7:929-937. doi:10.2147/DDDT.S30345.

9. Accurso FJ, Van Goor F, Zha J, et al. Sweat chloride as a biomarker of CFTR activity: proof of concept and ivacaftor clinical trial data. *J Cyst Fibros*. 2014;13(2):139-147.

10. Kumar S, Tana A, Shankar A. Cystic fibrosis--what are the prospects for a cure? *Eur J Intern Med*. 2014;25(9):803-807. doi:10.1016/j.ejim.2014.09.018.

11. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *Lancet Respir Med*. June 2015. doi:10.1016/S2213-2600(15)00201-5.

12. Aherns R, Rodriguez S, Yen K. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D -CFTR mutation (abstract) Pediatr Pulmonol 2011;(suppl 34):283.

13. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219-1225. doi:10.1164/rccm.201301-0153OC.

14. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. March. March 2015.

15. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *Ann Pharmacother*. 2012;46(7-8):1065-1075. doi:10.1345/aph.1R076.

16. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2015;3:CD009841. doi:10.1002/14651858.CD009841.pub2.

17. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respir Med*. 2014;2(7):527-538. doi:10.1016/S2213-2600(14)70132-8.

18. Food and Drug Administration. Pulmonary-Allergy Drugs Advisory Commitee Meeting FDA Presentation. May 12, 2015. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm447290.htm.

19. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014;13(6):674-680. doi:10.1016/j.jcf.2014.09.005.

20. FDA Center for Drug Evaluation and Research. Summary Review. Application Number: 206038Orig1s000. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

21. Robertson SM, Luo X, Dubey N, et al. Clinical drug-drug interaction assessment of ivacaftor as a potential inhibitor of cytochrome P450 and P-glycoprotein. *J Clin Pharmacol*. 2015;55(1):56-62. doi:10.1002/jcph.377.

22. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. July 2015.

Appendix 1: Highlights of Prescribing Information

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

ORKAMBI™ (lumacaftor/ivacaftor) tablets, for oral use
Initial U.S. Approval: 2015

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

ORKAMBI is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene. (1)

Limitations of Use:
The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation. (1)

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

- Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. (2.1)
- Reduce dose in patients with moderate or severe hepatic impairment. (2.2, 8.6, 12.3)
- When initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce ORKAMBI dose for the first week of treatment. (2.3, 7.1, 12.3)

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

- Tablets: lumacaftor 200 mg and ivacaftor 125 mg. (3)

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

- None. (4)

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

- Use in patients with advanced liver disease: ORKAMBI should be used with caution in these patients and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced. (2.2, 5.1, 6.1)
- Liver-related events: Elevated transaminases (ALT/AST) have been observed in some cases associated with elevated bilirubin. Measure serum transaminases and bilirubin before initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Interrupt dosing in patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution, consider the benefits and risks of resuming dosing. (5.2, 6.1)
- Respiratory events: Chest discomfort, dyspnea, and respiration abnormal were observed more commonly during initiation of ORKAMBI. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. (5.3, 6.1)
- Drug interactions: Use with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index may decrease systemic exposure of the medicinal products and co-administration is not recommended. Hormonal contraceptives should not be relied upon as an effective method of contraception and their use is associated with increased menstruation-related adverse reactions. Use with strong CYP3A inducers may diminish exposure of ivacaftor, which may diminish its effectiveness; therefore, co-administration is not recommended. (5.4, 6.1, 7, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor, a component of ORKAMBI. Baseline and follow-up examinations are recommended in pediatric patients initiating ORKAMBI. (5.5)

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

The most common adverse reactions to ORKAMBI (occurring in ≥5% of patients with CF homozygous for the *F508del* mutation in the *CFTR* gene) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza. (6.1)

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

See Full Prescribing Information for a complete list. (2.3, 7, 12.3)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 07/2015

Oral Cystic Fibrosis Modulators

Goals:

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

Length of Authorization:

- 60 days to 6 months

Requires PA:

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

Preferred Alternatives:

- No preferred alternatives at this time.

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on ivacaftor or lumacaftor/ivacaftor)?	Yes: Go to **Renewal Criteria**	No: Go to #2
2. What is the diagnosis?	Record ICD-9 code and go to #3	
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPH; Deny (medical appropriateness)
4. What is the patient's baseline sweat chloride level?	Document and go to #5; If no baseline level, request a baseline level before approving therapy.	
5. Is the request for ivacaftor (Kalydeco®)?	**Yes:** Go to #6	**No:** Go to #9
6. Does the client have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #7	**No:** Pass to RPH; Deny (medical appropriateness)

7. Does the patient have a documented G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Go to #12	**No:** Go to #8 If unknown, there needs to be a FDA cleared CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation)
8. Does the patient have a documented R117H mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Pass to RPH. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Pass to RPH; Deny (medical appropriateness) If unknown, there needs to be a FDA cleared CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation)
9. Is the request for lumacaftor/ivacaftor (Orkambi)?	**Yes:** Go to #10	**No:** Pass to RPH; Deny (medical appropriateness)
10. Does the client have a diagnosis of cystic fibrosis and is 12 years of age or older?	**Yes:** Go to #11	**No:** Pass to RPH; Deny (medical appropriateness)
11. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Go to #12	**No:** Pass to RPH; Deny (medical appropriateness) If unknown, there needs to be a FDA cleared CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are

		heterozygous for the F508del mutation)
12. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated **or** not appropriate based on age (<6 y/o) and normal lung function: • Dornase alfa, AND • Hypertonic saline, AND • Inhaled or oral antibiotics (if appropriate)	**Yes:** Go to #13	**No:** Pass to RPH; Deny (medical appropriateness)
13. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #14
14. Does the patient have decreased liver function, defined as elevated levels (ie, ≥3x the upper limit of normal) in ≥3 of the following levels: ALT, AST, AP, GGT, total bilirubin? Note: This was an additional exclusion criteria from the trials	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #15
15. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 60 days Note: Approve for 60 days to allow time for patient to have a sweat chloride test done after 30 days of treatment (see **Renewal Criteria**)	**No:** Pass to RPH; Deny (medical appropriateness)

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal?	**Yes:** Go to #2	**No:** Go to #3
2. Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment as defined as below? • Sweat chloride test has decreased by at least 20 mmol/L	**Yes:** Go to #6	**No:** Pass to RPH; consider patient's adherence to therapy and repeat test in 2 weeks to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness.
3. Does the patient have documented response to therapy as defined as below? For patients ≥ 6 y/o • A lack of decline in lung function as measured by the FEV_1 when the patient is clinically stable, OR • A reduction in the incidence of pulmonary exacerbations, OR • A significant improvement in BMI by 10% from baseline For patients 2-5 y/o (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline OR • Improvement in exacerbation frequency or severity OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline	**Yes:** Go to #4	**No:** Pass to RPH; Deny (medical appropriateness)

4. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #5	**No:** Pass to RPH; Deny (medical appropriateness)
5. If within first year of treatment, are liver function tests (AST/ALT) within normal limits in the past 3 months? If after 1 year of treatment, are liver function tests (AST/ALT) within normal limits in past 1 year? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	**Yes:** Go to #6	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is ivacaftor dosed appropriately based on age, weight, and co-administered drugs (See dosing and administration below)?	**Yes:** Approve for additional 4 months (total of 6 months since start of therapy)	**No:** Pass to RPH; Deny (medical appropriateness)

Dosage and Administration:

Ivacaftor:

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

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with ivacaftor	Co-administered drug category	Recommended dosage adjustment for ivacaftor
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce ivacaftor dose to 1 tablet or 1 packet of oral granules **twice weekly** (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazamine	CYP3A4 moderate inhibitors	Reduce ivacaftor dose to 1 tablet or 1 packet of oral granules **once daily (**half of normal dose)
Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

Lumacaftor/ivacaftor:

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

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Class Review: Cross-sex Hormone Therapy

Date of Review: November 2015

Purpose for Class Review:
Cross-sex hormone therapy (CSHT) is the standard treatment for individuals who wish to assume the gender opposite of their biological sex. The Oregon Health Plan (OHP) funds treatment to delay onset of puberty in adolescents with gender dysphoria (GD) and funds CSHT for adolescents and adults who meet eligibility criteria. The focus of this review is to present the treatments available for these purposes and evaluate comparative effectiveness and safety of the available regimens.

Research Questions:
1. What is the comparative effectiveness and safety of gonadotropin-releasing hormone (GnRH) analogs used for puberty suppression in adolescents with GD?
2. What is the comparative effectiveness and safety of CSHT for adolescents and adults with GD?
3. Are there any subgroups that would particularly benefit or be harmed from suppression therapy or hormone therapy for GD?

Conclusions:
- There is insufficient evidence on the comparative efficacy of hormone therapy in individuals with GD. No randomized controlled trials have studied the efficacy and safety of hormone therapy (CSHT or GnRH analogs) in this population. Hormones used for GD are based on studies used for other indications (e.g., hormone replacement, contraception, and hypogonadism).
- There is insufficient evidence on the effect of CSHT and GnRH analogs on long-term safety outcomes, such as: mortality, cardiovascular risk, bone density changes and psychological effect of sex reassignment.
- There is low strength of evidence from published guidelines to use GnRH therapy to suppress puberty in adolescents who meet eligibility criteria.[1-3]
- There is low strength of evidence from published guidelines to initiate CSHT (estrogen or testosterone) in adolescents and adults who satisfy eligibility criteria.[1-3] Replacement therapy should target estrogen and testosterone levels of desired gender.

Recommendations:
- There are no GnRH analogs on the preferred drug list (PDL) and no changes are recommended. Include all GnRH analogs in the existing prior authorization (PA) criteria for leuprolide (Appendix 3). The criteria will be applied to all GnRH treatments for adolescents with GD to ensure they are used appropriately for puberty suppression.
- Allow patients with GD access to testosterone treatments, subject to clinical PA criteria (Appendix 3). No changes to the PDL are recommended.

- No changes to the PDL recommended for estrogen derivatives. Require clinical PA criteria for estrogen derivatives when requested for use in patients 18 years of age or younger.

Background:
Harry Benjamin and Magnus Hirschfield were the first to recognize individuals desiring to assume the gender opposite of their biological designation and went on to define this population as transsexuals.[1] The prevalence of transsexualism ranges from 1:11,900 to 1:45,000 for male-to-female (MtF) individuals and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals.[2] The Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) has updated the diagnosis of transgender individuals from gender identity disorder (GID) to gender dysphoria (GD).[4] Gender dysphoria is the conflict and stress presented by a discrepancy in a person's sex assigned at birth and a person's gender identity. Gender dysphoria can present from childhood all the way through adulthood.[1] Only 6-27% of GD cases in children are maintained through adolescence and continue as adults.[4] Adolescents with GD have a higher likelihood of GD that persists into their adult years. Adolescents must have reached at least Tanner stage 2 puberty and have symptoms consistent with GD receive a diagnosis.[1,2,3] Due to the psychological or psychiatric issues that commonly accompany GD, guidelines recommend that a diagnosis be made by a mental health professional.[1,2] Commonly used terms for transgender individuals and GD are outlined in table 1.

Table 1. Definitions Used For Transgender Individuals[1-4]

Gender Identity	Person's fundamental sense of being a man, women, or of indeterminate sex.
Gender Identity Disorder (GID)	Psychiatric diagnosis is given when a strong and persistent cross-gender identification, combined with a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causes clinically significant distress.
Gender Dysphoria (GD)	DSM-IV-TR diagnosis in patients with distress and unease experienced when gender identity and sex are not completely congruent.
Gender identity disorder not otherwise specified (GIDNOS)	DSM-IV-TR diagnosis in patients with a disorder in gender identity not otherwise classified.
Gender Nonconformity	Person's gender identity, role or expression differs from the cultural norms prescribed for people of a particular sex.
Gender Variance (GV)	Any degree of cross genders identification in gender role behavior not dependent on GD or GIDNOS diagnosis.
Sex Reassignment	Complete treatment procedure for those who want to adapt their bodies to the desired sex.
Transgender	Individual deviates from commonly defined categories of gender and identifies with a gender identity different from gender at birth.
Transsexual	People identify as, or desire to live and be accepted as, a member of the gender opposite to that assigned at birth; the term male-to-female (MtF) transsexual person refers to a biological male who identifies as, or desires to be, a member of the female gender; female-to-male (FtM) transsexual person refers to a biological female who identifies as, or desires to be, a member of the male gender.

Gender reassignment is helpful in treating GD.[2,3] Treatment of GD may include psychotherapy, puberty suppression, CSHT and sex reassignment surgery (SRS).[2,3] Interventions to treat GD fall into three categories: fully reversible, partially reversible and irreversible.[2] Using GnRH analogs, medroxyprogesterone, and spironolactone are examples of fully reversible interventions. The use of CSHT is partially reversible, for example deepening of the voice with testosterone is not reversible upon discontinuation of treatment. Surgical procedures are irreversible.[2] Delaying puberty in adolescents with GD is recommended to prevent stress associated with body changes during this time.[1-4] Delaying puberty has also been shown to benefit physical changes once CSHT is initiated. GnRH analogs causes discontinuation of gonadal sex steroid production within 4-12 weeks of initiation and persists up to 3 months after discontinuing therapy.[3] Long-acting GnRH analogs are used to prevent the onset of puberty by blocking the release of sex hormones. GnRH agonists (leuprolide, histrelin, triptorelin and goserelin acetate), testosterone inhibitors (spironolactone), antiandrogens (cyproterone acetate [not available in the US]) and 5α-reductase inhibitors (finasteride) are used for

hormone-suppressive therapy (Table 2).[4] Flutamide is only recommended for the treatment of excessive seborrhea due to risk of hepatotoxicity and the ability to increase testosterone and estradiol levels.[5]

Adults and adolescents, age 16 years and older, who are considering sex reassignment are candidates for CSHT (Table 2).[1] Estrogen formulations are used for MtF CSHT. Oral and intramuscular (IM) formulations of estradiol valerate, oral estradiol and IM estradiol cypionate are used in treatment regiments.[4] 17-β-estradiol can be easily measured which is important in making sure estrogen concentrations are <200 pg/mL.[5] The preferred route is transdermal estrogen as it is associated with a lower incidence of VTE and cardiovascular disease.[5] CSHT for transsexual males include IM testosterone undecanoate, IM testosterone enanthate or cypionate, testosterone gel 1%, testosterone patches or oral methyltestosterone.[5] Progestins, commonly injectable medroxyprogesterone 150 mg every 3 months, can be given with testosterone to cease menstruation. Due to lack of data on effectiveness of progestins in MtF individuals and risks associated with treatment, it is not recommended.[5]

Cross-sex hormone therapy and GnRH treatment are associated with adverse events ranging from mild to severe. Common adverse reactions to GnRH therapy are sterile abscess, hot flashes, leg pains, headache and weight gain.[1,4] Limited data suggest that long-term use of GnRH therapy in men is linked to decreased bone mass. Additional research is needed to determine the effects of delaying puberty on the development and bone growth of adolescents.[4] Thrombosis is the most concerning adverse event associated with estrogen supplementation. Data from the use of ethinyl estradiol, which is no longer recommended, has demonstrated an increased risk in cardiovascular mortality and VTEs in transsexual females. Studies need to be done with currently recommended estrogen therapies to determine cardiac and embolic risk. In transsexual males, testosterone supplementation has been associated with increased lipid levels. The effect of lipid parameter changes on cardiovascular outcomes is unknown, as data from epidemiologic and randomized controlled trials have been inconclusive in men taking testosterone for hypogonadism.[4]

Concerns over reduced bone mass with CSHT have been inconclusive and fracture risk has not been studied. Cancer risk, especially breast and prostate, is potentially concerning in transsexual males and females, but limited evidence suggests similar prevalence as in the general population. The long-term risks of CSHT and psychological risks of sex reassignment in adults is unknown.[4] Effects of treatment on fertility should also be discussed as both testosterone and estrogen can cause reduced fertility or infertility.[1-4]

Objective treatment outcomes for GD have not been developed or quanitified.[3] The main outcomes for hormone therapy used for transgender patients is clinical degree of masculine or feminine change, psychosocial benefits, patient satisfaction, quality of life and regrets of therapy.[3,4] Outcomes related to the risk of treatment associated with CSHT (e.g., VTE, cardiovascular, bone loss, cancer) should be tracked; however, high-quality studies have not been performed. Most of the evidence for GnRH and CSHT treatment comes from retrospective evidence and data from randomized, double-blind clinical trials is lacking.[2,3] Additionally, studies performed in this population have been done in a manner that subjects the evidence to a high degree of bias, limiting the ability to draw conclusions.

Commonly used therapies for GD and CSHT are listed in Table 2 and summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. Indications[+] and Dosing[1,4]

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Finasteride	Hormone-suppressive therapy	Oral	5 mg/day
Goserelin acetate	Hormone-suppressive therapy	Parenteral	3.6 mg sc every 4 weeks
Histrelin	Hormone-suppressive therapy	Implant	50 mg – delivers 65 µg/day released over a period of 12 months
Leuprolide	Hormone-suppressive therapy	Parenteral	3.75-15 mg im every month or 11.25 to 30 mg every 3 months
Triptorelin	Hormone-suppressive therapy	Parenteral	3.75 mg im every month
Estradiol patch	MtF Regimen	Transdermal	0.1 -0.4 mg twice weekly
Estradiol	MtF Regimen	Oral	2.0-6.0 mg/day
Estradiol valerate or cypionate	MtF Regimen	Parenteral	5-20 mg im every 2 weeks or 2-10 mg im every week
Spironolactone	MtF Regimen and hormone-suppressive therapy	Oral	100-200 mg/day
Cyproterone acetate*	MtF Regimen and hormone-suppressive therapy	Oral	50-100 mg/day
GnRH agonists	MtF Regimen	Subcutaneous	3.75 mg monthly
Methyltestosterone	FtM Regimen	Oral	50-100 mg/day
Testosterone undecanoate*	FtM Regimen	Oral	160-240 mg/day
Testosterone enanthate or cypionate	FtM Regimen	Parenteral	100-200 mg im every 2 weeks or 50% weekly
Testosterone undecanoate	FtM Regimen	Parenteral	1000 mg every 12 weeks
Testosterone gel 1%	FtM Regimen	Transdermal	2.5-10 g/day
Testosterone patch	FtM Regimen	Transdermal	2.5-7.5 mg/day

* Not available in the United States, [+] No hormone treatments have been approved by the Food and Drug Administration for GD/transgender indications
Abbreviations: FtM – female-to-male transsexual; g – gram, im - intramuscular; mg – milligram; MtF – male-to-female transsexual; sc - subcutaneous

Summary of Pivotal Studies Completed

Due to major limitations in study design (e.g., non-randomized, observational, retrospective, small populations, and short term follow up) nine studies were identified but not included.[6-14]

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.

Systematic Reviews:
Two systematic reviews were identified but not included due to the lack of availability of high quality evidence available for analysis. Both reviews considered the evidence as being "very low quality".[15,16]

Guidelines:
Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline
In 2009, the Endocrine Society (ES) released a clinical practice guideline on the management of transsexual individuals.[1] Recommendations are evidence-based using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Evidence included in the recommendations was found to be low or very low. The Guidelines recommend that patients considering GnRH analogs or CSTH are appropriate candidates for treatment by completing eligibility and readiness criteria. Diagnosis of gender identity disorder (GID) should be done by a mental health professional (strongly recommended based on low quality of evidence).[1]

GnRH analogs are used to suppress puberty until it is appropriate to initiate hormone therapy. For those adolescents who meet eligibility criteria, it is strongly recommended that they receive puberty suppressing therapy.[1] This is based on evidence of high GID remission rates after the onset of puberty, making it appropriate to delay initiation of CSHT in prepubertal children. Hormonal suppressive therapy begins when physical changes of puberty, confirmed by estradiol and testosterone levels, are present and no earlier than Tanner stage 2-3 (strong recommendation based on low quality of evidence).[1] Long-acting analogs are the preferred therapy for pubertal suppression. Patients should receive follow-up outlined in table 3.

Table 3. Monitoring Recommendations for Puberty Suppressive Therapy[1]

Every 3 months	- Height - Weight - Sitting height - Tanner stages	- LH - FSH - Estradiol/testosterone
Annually	- Renal and liver function - Lipids - Glucose - Insulin - Glycosylated hemoglobin	- Bone density (dual energy x-ray absorptiometry) - Bone age (x-ray of left hand)
Abbreviations: FSH – follicle stimulating hormone, LH – luteinizing hormone		

Initiation of puberty for the adolescent desiring to assume the opposite sex should be considered at age 16 and done by gradually increasing the dosing schedule of CSHT (based on a weak recommendation of very low quality evidence).[1] Induction of female puberty should be done with 17-β estradiol and intramuscular

(im) testosterone for induction of male puberty. The same monitoring parameters listed in table 1 apply to induction therapy, with the addition of endocrinology labs every three months.

Goals of treatment for a transsexual patient wishing to assume the opposite gender are to suppress endogenous hormone secretion of the patient's biological gender and maintain sex hormone levels within the normal range of the desired sex.[1] GID should be confirmed by an endocrinologist prior to treatment with CSHT. Females wishing to take on male sexual characteristics should be offered similar hormone replacement as prescribed for male hypogonadism.[1] Parenteral or transdermal testosterone preparations are recommended to obtain normal male testosterone values of 320-1000 ng/dL. To reduce estrogen levels and halt menses before treatment with testosterone, GnRH analogs or depot medroxyprogesterone can be used. Estrogen and antiandrogen therapy (i.e. spironolactone) is recommended for female transsexuals.[1] The estrogen component of the female transsexual regimen is given as 17-β estradiol in an oral, transdermal or parenteral formulation. Testosterone and serum estradiol levels should be maintained at the level of a premenopausal woman, at <55 ng/dL and <200 pg/mL, respectively. All patients should have lab assessments every 3 months for the first year and then annually or biannually thereafter (Table 4). Prolactin levels are recommended in female transsexuals being treated with estrogen.[1]

Table 4. Monitoring Recommendations for CSHT[1]

Every 2-3 months*	- Signs of feminization/ masculinization	- Adverse reactions
Every 3 months	- Estradiol - Testosterone	- Serum electrolytes (if taking spironolactone)
General Recommendations	- Cancer screening (breast, colon, prostate) - Bone density testing at baseline for those at risk of osteoporotic fracture	
* Monitor 1-2 times per year after first year		

There is limited data on the adverse effects of GnRH and CSHT in transgender patients. Adults and adolescents should understand the impact treatment might have on fertility. GnRH analogs will prevent the production of viable sperm but the effects can be reversed after cessation of treatment.[1] Adolescent female fertility should not be affected by suppressive analogs. All individuals undergoing hormone therapy should be evaluated for cardiovascular risk factors. If transsexual persons are at risk for osteoporosis, bone mineral density (BMD) testing is recommended. Patients that have undergone gonadectomy and have stopped hormone therapy may be at increased risk of osteoporosis. Breast cancer screening in transsexual females should follow recommendations for those who are women from birth.[1] Female transsexuals who are treated with estrogens should be screened for prostate disease according to recommendations for testing of biological men. Individuals with contraindications to hormone therapy (smoking history, diabetes diagnosis, liver disease) should carefully weigh the risks and benefits of CSHT.

<u>The 2011 World Professional Organization for Transgender Health Standards of Care</u>

The World Professional Organization for Transgender Health (WPATH) produces Standards of Care (SOC) guidance for the management of transsexual individuals. The original guidance was produced in 1979, with the 2011 version being the 7th edition.[2] Guidance recommends that the degree of GD be accessed by a mental health professional and that an endocrinologist prescribe hormone therapy. Mental health professionals should also determine the eligibility of the patients for CSHT and refer if appropriate. It is recommended that adolescents wait until at least Tanner stage 2 before starting puberty suppressive therapy. Criteria for adolescents wishing to take puberty suppression hormones are listed in Table 5. Adult CSHT eligibility is based on well-documented GD, ability to make decisions and consent for treatment, and well-controlled comorbidities (mental or physical) (Table 6).[2]

Table 5. Criteria for Adolescents Desiring Puberty-Suppression Hormones[2]

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (suppressed or expressed).
2. Gender dysphoria emerged or worsened with the onset of puberty.
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment.
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Adapted from The World Professional Association for Transgender Health. Standards of Care for the Health of the Transsexual, Transgender, and Gender-Nonconforming People. Versions 7. Available at: www.WPATH.org.

Table 6. Criteria for Patients Desiring Hormone Therapy[2]

1. Persistent and well documented gender dysphoria.
2. Capacity to make a fully informed decision and to consent to treatment (at least 16 years of age).
3. Age of majority in a given country (if younger follow SOC outlined for adolescents).
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Adapted from The World Professional Association for Transgender Health. Standards of Care for the Health of the Transsexual, Transgender, and Gender-Nonconforming People. Versions 7. Available at: www.WPATH.org.

The goals for puberty-suppression differ for males and females. Males from birth (natal) should be given GnRH analogs to prevent testosterone secretion.[2] Progestins and other medications, which block and/or neutralize the effect of testosterone can also be used. Natal females can be treated with GnRH analogs to suppress estrogen and progesterone production. Oral contraceptives can also be used to prevent menstruation. Physical development of patients should be followed closely by a pediatric endocrinologist to ensure height and BMD are adequate.

There are commonly accepted hormone regimens for GD despite lack of controlled, comparative clinical trials of efficacy or safety. Thus, WPATH guidance does not endorse any specific CSHT regimen.[2] Physical changes of CSHT can take months to years to be realized. If the patient has undergone gender reassignment surgery consisting of oophorectomy or orchiectomy, lifelong CSHT is recommended, unless contraindicated.[2] Initial and follow-up labs are recommended for all patients considering and taking CSHT. The goal of CSHT is maintenance of testosterone and estrogen levels within the normal range for FtM transsexuals and MtF transsexuals, respectively. Commonly used agents for CSHT are displayed in Table 6. The use of progestins besides cyproterone is not universally recommended due to increased risk of adverse reactions (breast cancer and cardiovascular risk) without proven benefit. Bioidentical compounds used in postmenopausal hormone replacement have not been shown to be more effective or safer than approved therapies.[2]

Table 6. Hormones for Feminizing and Masculinizing Therapy[2]

Hormone	Formulation	Comments
Feminizing Therapy (MtF)		
Estrogen	Oral ethinyl estradiol	- Shown to increase risk of VTE and not recommended
	Transdermal	- Recommended for those at increased risk of VTE
Anti-Androgens*	Spironolactone	- blocks androgen secretion and binding
	GnRH agonists [e.g., goserelin, triptorelin, and buserelin (not available in the US)]	- blocks the GnRH receptor - only available as injectables or implants
	5-alpha reductase inhibitors	- blocks conversion of testosterone
	Cyproterone acetate	- progestin - not available in US due to hepatotoxicity concerns
Masculinizing Hormones (FtM)		
Testosterone	Oral testosterone	- buccal formulation available
	Transdermal	- similar effects as IM preparation but slower onset
	Intramuscular (IM)	- concentration levels may vary
Progestins	Medroxyprogesterone	- used for a limited duration to aid in stopping menstrual cycle
* Commonly used with estrogen		

The most commonly associated adverse effects with treatment of feminizing hormones are VTE, hypertriglyceridemia, gallstones, elevated liver enzymes, weight gain, and cardiovascular disease. Feminizing hormones may also increase the risk of hypertension, hyperprolactinemia or prolactinoma and type 2 diabetes mellitus (T2DM).[2] The risk of developing breast cancer with the use of feminizing hormones is not clear. Masculinizing hormones are associated with polycythemia, weight gain, acne, balding and sleep apnea. They may also be associated with elevated liver enzymes, hyperlipidemia, destabilization of certain psychiatric disorders (bipolar and schizophrenia), cardiovascular disease, hypertension, and T2DM.[2] There is inconclusive risk associated with masculinizing hormones for loss of bone density, breast cancer, cervical cancer, ovarian cancer, and uterine cancer. Contraindications to feminizing hormones are previous VTE related to a hypercoagulable condition, history of estrogen-sensitive neoplasm and end-stage chronic liver disease. Masculinizing hormones should not be used in individuals who are pregnant, have unstable coronary artery disease, or untreated polycythemia with a hematocrit of 55% or higher. Those with a history of breast cancer or other estrogen-dependent cancers should seek further guidance before starting CSHT.

<u>American Psychiatric Association – Task Force on Treatment of Gender Identity Disorder</u>

The American Psychiatric Association (APA) formed a task force to develop treatment recommendations for GD in 2012.[3] Due to the lack of high-quality evidence, recommendations were based on clinical consensus. Treatment recommendations were divided into children, adolescents, adults and disorders of sexual development (DSD). Treatment of children is confined to non-pharmacological therapy, with the focus being on diagnosis and addressing mental health concerns. As with other guidelines, the APA recommends that if adolescents (defined as ages 12-18 years) opt for hormone therapy, fully reversible options are recommended.[3] In the US, sex reassignment surgery is not allowed until 18 years of age. Data from case reports suggest that adolescents that wish to utilize puberty suppression therapy have positive results overall. Consensus recommendations for treatment are:

- Psychological and psychiatric assessment of adolescents wishing for sex reassignment
- Psychotherapy
- Assessment of indications and readiness for suppression of puberty and/or cross sex hormones

- Psychoeducation of family members and institutions regarding GD
- Safety of environment and discussion of protective measures

Cohort and longitudinal evidence has shown that adults wishing to use hormone or surgical treatments had good outcomes if they first engaged in psychotherapy and a staged transition period.[3] Recommendations for adults are:

- DSM diagnosis of gender concerns (e.g., GD)
- Diagnosis of coexisting psychopathology
- Distinguishing between GID with concurrent psychiatric illness and gender manifestations that are not part of GID
- Engaging in psychotherapy with gender variant individuals as indicated
- Explanation of physical, psychological, and social implications of treatment options
- Determining eligibility and readiness for hormone and surgical therapy
- Education of family members, employers, and institutions about GD and gender variance (GV)
- Obtain documentation from endocrinologists and surgeons that facilitates communication and third party reimbursement and tax deductions

Individuals with DSD have congenital conditions that affect chromosomal, gonadal and/or genital sexual development.[3] Similar to GD, there are no high-quality data to guide the care of individuals with DSD. Recommendations for DSD patients consist of guidance by an expert mental health specialist to assist in addressing the needs of disparity between gender identity compared to biological sex.

The task force concludes that mental health care, hormone therapy and SRS are recommended for eligible patients with GD.[3]

References:

1. Hembree W, Cohen-Kettenis P, Delemarre-van de Waal H, et al. Endocrine treatment of transsexual persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2009; 94: 3132-3154.
2. WPATH.
3. Byne W, Bradley S, Coleman E, et al. Report of the American Psychiatric Association task force on treatment of gender identity disorder. *Arch Sex Behav* 2012; 41:759-796.
4. Smith K, Madison C and Milne N. Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. *Pharmacotherapy* 2014;34(12):1282-1297.
5. Fabris B, Bernardi S, Trombetta C. Cross-sex hormone therapy for gender dysphoria. *J Endocrinol Invest* 2015;38:269-282.
6. Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med* 2014;11:3002-3011.
7. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J of Nerv and Ment Dis* 2013;201: 996-1000.
8. Van Caenegem, Wierckx K, Taes Y, et al. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol* 2015;172: 163-71.
9. Klink D, Caris M, Heijboer A, et al. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab* 2015;100: E270-275.
10. Mueller A, Zollver H, Kronawitter D, et al. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 2011;119: 95-100.
11. Ott J, Kaufamann U, Bentz E, et al. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril* 2010;93:1267-72.
12. Ruetsche A, Kneubuehl R, Birkhaeuser M, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int* 2005;16:791-798.
13. Haraldsen I.R., Haug E, Falch J, et al. Cross-sex pattern of bone mineral density in early onset gender identity disorder. *Hormones and Behavior* 2007;52: 334-343.
14. Wierckx K, Van Caenegem E, Schreiner T, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med* 2014;11: 1999-2011.
15. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endo* 2010;72: 214-231.
16. Elamin M, Garcia MZ, Murad MH, et al. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analysis. *Clin Endo* 2010; 72:1-10.
17. Supprelin LA (histrelin acetate) [Prescribing Information]. Chadds Ford, PA: Endo Pharmaceutical Solutions, Inc., April 2013.
18. Leuprolide Acetate for injection [Prescribing Information]. Princeton, NJ: Sandoz, August 2011.
19. Trelstar (triptorelin pamoate for inj) [Prescribing Information]. Parsippany, NJ: Actavis Pharma, Inc., July 2014.
20. Zoladex (goserelin acetate for inj) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals, February 2015.
21. Premarin (conjugated estrogen tablets) [Prescribing Information]. Philadelphia, PA: Wyeth Pharmaceuticals, December 2014.
22. Alora (estradiol tablets) [Prescribing Information]. Corona, CA: Watson Pharma, Inc., May 2005.
23. Premarin (conjugated estrogens for inj) [Prescribing Information]. Philadelphia, PA: Wyeth Pharmaceuticals, April 2012.

24. Premarin (conjugated estrogens cream) [Prescribing Information]. Philadelphia, PA: Wyeth Pharmaceuticals, February 2012.
25. Aveed (testosterone undecanoate for inj) [Prescribing Information]. Malvern, PA: Endo Pharmaceuticals, Inc., May2015.
26. Androderm (testosterone transdermal system) [Prescribing Information]. Parsippany, NJ: Actavis Pharma, Inc., May 2015.
27. Axiron (testosterone topical solution) [Prescribing Information]. Indianapolis, IN: Lily USA, LLC., May 2015.
28. Natesto (testosterone nasal gel) [Prescribing Information]. Malvern, PA: Endo Pharmaceuticals, Inc. May 2015.

Appendix 1: Specific Drug Information

Table 8. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Histrelin[17]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	Unknown	• Unknown
Leuprolide[18]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	CYP450 Urine <5%	• Half-life: 3 hours
Triptorelin[19]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	CYP450 Urine 42%	• Half-life: 3 hours
Goserelin[20]	Inhibits gonadotropin release, suppressing ovarian and testicular steroidogenesis	NA	Hydrolysis; CYP450 Urine >90% Liver <10%	• Half-life: 2.3 hours (female), 4.2 hours (male)
Estrogen (oral)[21]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours (estrone)
Estrodiol (patch)[22]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 1.7 hours (estrone)
Estrogen (topical)[23]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours
Estrogen (IM)[24]	Binds to estrogen receptors, developing and maintaining female sex characteristics	Water soluble through skin, mucous membranes and GI tract	CYP450: 3A4 Urine excretion	• Half-life: 4-18 hours
Testosterone (IM)[25]	Development of male sex organs and maintenance of secondary sex characteristics	NA	Metabolized to 17-keto steroids by 2 pathways Metabolized to 17-keto steroids by 2 pathways 90% urine 6% feces	• Half-life: 8 days
Testosterone (patch)[26]	Development of male sex organs and maintenance of secondary sex characteristics	Continually absorbed through the skin over 24 hours	Metabolized to 17-keto steroids by 2 pathways 90% urine	• Half-life: 10-100 minutes

			6% feces	
Testosterone (topical)[27]	Development of male sex organs and maintenance of secondary sex characteristics	Continually absorbed through the skin over 24 hours. Only 10% of product is absorbed	Metabolized to 17-keto steroids by 2 pathways 90% urine 6% feces	• Half-life: 10-100 minutes
Testosterone (nasal)[28]	Development of male sex organs and maintenance of secondary sex characteristics	Development of male sex organs and maintenance of secondary sex characteristics	Development of male sex organs and maintenance of secondary sex characteristics	• Half-life: 10-100 minutes

Use in Specific Populations:
Testosterone: Effects of long-term use in geriatric populations on cardiovascular disease and prostate cancer are unknown.[25,26]
Estrogen: Use of estrogen by nursing mothers may decrease the quality and quantity of breast milk. Increased risk of dementia in women over 65 years of age has been seen in clinical studies.[21]
Histrelin/Leuprolide– Use in children under 2 is not recommended. Not to be used in pregnant women.[17-18]
Triptorelin: Not studied in pediatric patients and should not be used in pregnant women.[19]
Goserelin: Not studied in pediatric patients and not recommended in women who are nursing. [20]

Drug Safety:
Black Boxed Warnings:
Testosterone: Children should avoid contact with testosterone topical formulations on unwashed clothes or unclothed application sites in men using topical testosterone formulations due to virilization risk from secondary exposure. [25,26]
Estrogen (oral): Endometrial cancer is increased in individuals using unopposed estrogen. Estrogen use has been associated with increased risk of MI, stroke, VTE, invasive breast cancer, and probable dementia.[21]

Contraindications:
Testosterone: Patients should not take testosterone if they are men with breast cancer or suspected carcinoma of the prostate, women who are pregnant or breastfeeding, or known hypersensitivity to testosterone. [25,26]
Estrogen: Women should not take estrogen if they have undiagnosed abnormal genital bleeding, breast cancer unless being treated for metastatic disease in selected patients, known or suspected estrogen-dependent neoplasia, active DVT, PE or a history of these conditions, active arterial thromboembolic disease, liver impairment, thrombophilic disorders, pregnancy or hypersensitivity to estrogen.[21]
Histrelin/Leuprolide/Triptorelin: Pregnant patients or those with a GnRH analog hypersensitivity should not use.[17-19]
Goserelin: Pregnant patients, unless used for the treatment of advanced breast cancer, or those with a GnRH analog hypersensitivity.[20]

Table 9. Summary of Warnings and Precautions.[17-28]

Warning/Precaution	Histrelin	Leuprolide	Triptorelin	Goserelin	Estrogen (oral)	Estrogen (patch)	Estrogen (IM)	Testosterone (oral)	Testosterone (patch/gel/nasal)	Testosterone (IM)
Anaphylactic reaction	-		X							
Prolonged QT interval	-		X	X						
Decreased bone density	X	X	X	X						
Increased blood glucose	X	X	X	X						
Tumor flare			X	X						
VTE					X	X	X	X	X	X
Worsening BPH								X	X	X
Cardiovascular Risk	X	X	X	X	X	X	X	X	X	X
Edema								X	X	X
Hepatic injury								X	X	X
Prostate Cancer	X	X	X	X				X	X	X
Gynecomastia								X	X	X
Polycythemia								X	X	X
Reduced spermatogenesis								X	X	X
Lipid changes								X	X	X
Dementia					X	X	X			
Endometrial cancer					X	X	X			
Breast cancer					X	X	X			

Appendix 2: Medline Search Strategy

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

Search Strategy:

#	Searches	Results
1	transgender.mp. or Transgendered Persons/	1245
2	gender dysphoria.mp.	194
3	cross-sex hormone therapy.mp.	30
4	gender identity disorder.mp.	292
5	1 or 2 or 3 or 4	1620
6	limit 5 to (english language and humans)	1528
7	limit 6 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)	161
8	from 7 keep 9, 15, 24, 49, 74-75, 104...	13
9	transgender.mp. or Transgendered Persons/	1245
10	gender dysphoria.mp.	194
11	cross-sex hormone therapy.mp.	30
12	gender identity disorder.mp.	292
13	9 or 10 or 11 or 12	1620
14	limit 13 to (english language and humans)	1528
15	limit 14 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)	161

Gonadotropin-Releasing Hormone (GnRH) Analogs

Goal:

- Restrict pediatric use to medically appropriate conditions funded under the Oregon Health Plan (eg, central precocious puberty or gender dysphoria)

Length of Authorization:

- Up to 6 months

Requires PA:

- GnRH analogs (i.e., goserelin, histrelin, leuprolide, nafarelin, triptorelin) prescribed for pediatric patients less than 18 years of age.

Approval Criteria		
1. What diagnosis is being treated and what is the age and gender of the patient assigned at birth?	Record ICD10 code Record age and gender assigned at birth	
2. Is the prescriber a pediatric endocrinologist?	Yes: Go to #3	No: Pass to RPh; deny for medical appropriateness
3. Is the diagnosis central precocious puberty (ICD10 E301, E308)?	Yes: Approve for up to 6 months	No: Go to #4
4. Is the diagnosis gender dysphoria (ICD10 F642, F641)?	Yes: Go to #5	No: Pass to RPh; go to #6
5. Does the request meet **all** of the following criteria? • Diagnosis of gender dysphoria made by a mental health professional with experience in gender dysphoria. • Onset of puberty confirmed by physical changes and hormone levels, but no earlier than Tanner Stages 2. • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	Yes: Approve for up to 6 months	No: Pass to RPh; deny for medical appropriateness

Approval Criteria
6. RPh only: All other indications need to be evaluated as to whether it is funded under the OHP. Refer unique situations to Medical Director of DMAP.

P&T / DUR Review: *11/15 (KS), 7/15; 5/15; 9/07*
Implementation: *7/1/15; 11/07; 7/09*

Testosterone

Goal:

- Restrict use to medically appropriate conditions funded under the Oregon Health Plan (use for sexual dysfunction or body-building is not covered)

Length of Authorization:

- Up to 12 months

Requires PA:

- All topical testosterone products and non-preferred injectable testosterone products in adults
- All testosterone products in pediatric patients <18 years of age

Covered Alternatives:

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

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

Approval Criteria		
2. Does the diagnosis for the medication requested include any of the following? • Testicular Hypofunction; or • Hypopituitarism and related disorders; or • AIDS-related cachexia?	**Yes:** Go to #5	**No:** Go to #3
3. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #4	**No:** Go to #6
4. Have **all** of the following criteria been met? • Patient age ≥16 years with capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in the Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Go to #5	**No**: Pass to RPh; deny for medical appropriateness
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products to not require a co-pay. • 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 up to 12 months.	**No:** Approve for up to 12 months.
6. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny (not funded by the OHP)

P&T / DUR Review: *11/15 (KS); 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*

Estrogen Derivatives

Goal:
- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the estrogen requested for a patient ≥18 years of age?	**Yes:** Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. 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 up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Have **all** of the following criteria been met? • Patient age ≥16 years with capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Approve for up to 6 months	**No**: Pass to RPh; deny for medical appropriateness
6. Is the medication requested for hypogonadism?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny (not covered by the OHP)

P&T / DUR Review: *11/15 (KS); 2/12; 9/10; 2/06; 2/01; 9/00*
Implementation: *7/31/14; 5/14/12, 1/24/12, 1/1/11, 9/1/06*

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Drug Effectiveness Review Project Summary Report – PCSK9 Inhibitors

Date of Review: November 2015

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

DERP Research Questions:

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with familial hypercholesterolemia?
2. What are the comparative benefits and harms of PCSK9 inhibitors in patients with familial or non-familial hypercholesterolemia who are unable to take an HMG-CoA reductase inhibitor ('statin') due to intolerance?
3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with non-familial hypercholesterolemia who cannot achieve adequate low-density lipoprotein cholesterol (LDL-C) reduction with their current lipid-lowering regimen (eg, statin, with or without ezetimibe, etc.)?
4. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups based on demographics, socioeconomic status, other medications, or comorbidities?

Conclusions:

- In patients with familial hypercholesterolemia, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In patients with heterozygous familial hypercholesterolemia already on a statin and ezetimibe, there is low quality evidence from short-term data that alirocumab can improve LDL-C by a difference of -57% compared to placebo; however, there is high quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -61% compared to placebo.
    - In patients with homozygous familial hypercholesterolemia already on a statin and ezetimibe, there is insufficient evidence to use alirocumab; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -32% compared to placebo.
- In patients with non-familial hypercholesterolemia intolerant to statins, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - In addition, there is insufficient evidence for use of alirocumab in this population; however, there is low quality evidence from short-term data that evolocumab can improve LDL-C by a difference of -47% compared to ezetimibe alone.
- In patients with non-familial hypercholesterolemia who cannot achieve adequate LDL-C reduction with their current lipid-lowering regimen, there is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
    - However, there is high quality evidence from short-term data that use of alirocumab can result in a significantly higher proportion of patients at high risk for cardiovascular (CV) events to achieve an LDL-C of less than 70 mg/dL versus placebo, with as much as a -62% greater reduction in LDL-C.
    - However, there is low quality evidence of no difference in CV events between alirocumab and placebo at 52- and 78-week follow-up when alirocumab and placebo were continued long-term with concomitant statin therapy. In addition, there is moderate quality evidence of no difference

in CV events between alirocumab and ezetimibe at 52-week follow-up when both treatments were continued long-term with concomitant statin therapy.
    - There is high quality evidence from short-term data that use of evolocumab can result in a significantly higher proportion of patients at high risk for cardiovascular (CV) events to achieve an LDL-C of less than 70 mg/dL versus placebo. When compared to the addition of ezetimibe, there is low quality evidence that the addition of evolocumab can also result in higher achievement rates of target LDL-C of less than 70 mg/dL.
- In a mix of all populations studied above, there is insufficient evidence to draw conclusions on the effect of evolocumab on CV outcomes.
- There is insufficient evidence to differentiate between differences in harms between PCSK9 inhibitors. It is unknown if significantly lowering LDL-C will adversely affect gastrointestinal, metabolic and neurocognitive functions.

Recommendations:
- Designate alirocumab and evolucmab as non-preferred in the "Other Dyslipidemia Drugs" class. Preferred status cannot be made at this time due to limited evidence of long-term CV benefit and harms.
- 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. See **Appendix 3** for the proposed prior authorization criteria.

Methods:
The July 2015 Drug Class Review on Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available 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.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturers, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Summary Findings:
PCSK9 inhibitors are human monoclonal antibodies that inhibit the PCSK9 enzyme. Inhibition of PCSK9 reduces degradation of the LDL receptor, consequently lowering LDL-C levels in the bloodstream. Two PCSK9 inhibitors, alirocumab and evolocumab, were recently approved by the U.S. Food and Drug Administration (FDA) (Table 1). A third agent, bococizumab, is still in phase 3 testing.

Table 1. PCSK9 Inhibitors Included in DERP Report.

Generic Name	Brand Name	Drug Sponsor	FDA Approval Date
Alirocumab	Praluent®	Sanofi Aventis	July 24, 2015
Evolocumab	Repatha™	Amgen	August 27, 2015
Bococizumab	NA	Pfizer	*Anticipated 2016*

Evidence for use of these drugs is based on 17 clinical trials, of which 14 are placebo-controlled. No completed trials have evaluated health outcomes (morbidity or mortality) as primary endpoints. Two ongoing studies, one for evolocumab and one for bococizumab, will evaluate health outcomes as a primary endpoint but are not expected to be completed until 2018. None of the 5 completed trials of bococizumab have been published. In addition, no completed or ongoing studies directly compare different PCSK9 inhibitors.

Both alirocumab and evolocumab demonstrate evidence for significant LDL-C reduction. The strongest evidence for alirocumab is in patients at high risk for CV risk who are unable to achieve LDL-C (either <100 mg/dL or <70 mg/dL) on statin therapy. In contrast, the strongest evidence for evolocumab is in patients with heterozygous familial hypercholesterolemia and patients at average CV risk who are unable to achieve LDL-C of <100 mg/dL or <70 mg/dL on statin therapy.

<u>HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (ON HIGH-INTENSITY STATIN AND EZETIMIBE)</u>

- There is low quality evidence (n=98; 2 RCTs) alirocumab 150 mg, 200 mg, or 300 mg every 4 weeks, or 150 mg every 2 weeks for 12 weeks (baseline LDL-C: 151-170 mg/dL) can achieve greater LDL-C reduction compared to placebo (difference in LDL-C change: -8% to -57%), but have similar effect on high-density lipoprotein cholesterol (HDL-C).
- There is high quality evidence (n=499; 2 RCTs) that evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks for 12 weeks (baseline LDL-C: 150-155 mg/dL) can achieve greater LDL-C reduction compared to placebo (difference in LDL-C change: -44% to -61%), with greater improvement in HDL-C (difference in HDL-C change: +6.8% to +9.2%).

<u>HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (ON HIGH-INTENSITY STATIN AND EZETIMIBE)</u>

- There is low quality evidence (n=50; 1 RCT) that evolocumab 420 mg every 4 weeks for 12 weeks (baseline LDL-C: 348 mg/dL) can reduce LDL-C significantly more than placebo (difference in LDL-C change: -32.1%) without comparative improvement in HDL-C. There is insufficient evidence for the use of alirocumab in this population.

STATIN INTOLERANCE

- There is low quality evidence (n=496; 2 RCTs) that 12 weeks of evolocumab 140 mg every 2 weeks, 280 mg every 4 weeks, or 420 mg every 4 weeks (baseline LDL-C: 192-195 mg/dL) can reduce LDL-C significantly more than ezetimibe 10 mg daily (-38%, -26% and -47%, respectively) without comparative improvement in HDL-C. There is insufficient evidence for the use of alirocumab in patients intolerant to statins.

UNABLE TO ACHIEVE TARGET LDL-C* (<70 mg/dL or <100 mg/dL) STABILIZED ON STATIN THERAPY

- There is low quality evidence (n=124; 2 RCTs) that the addition of alirocumab 150 mg every 2 weeks for 8-10 weeks (baseline LDL-C: 123-124 mg/dL) can result in significantly more patients at average risk for CV events to achieve goal LDL-C of <100 mg/dL compared to placebo (100% vs. 16%-52%, respectively), with -49% to -67% greater reduction in LDL-C.
- There is moderate quality evidence (n=720; 1 RCT) that alirocumab 75-100 mg every 2 weeks for 24 weeks (baseline LDL-C: 106 mg/dL) can result in a significantly higher proportion of patients at high risk for CV events to achieve a goal LDL-C <70 mg/dL versus ezetimibe 10 mg daily (RR 1.70; 95% CI, 1.46 to 1.95), with a -29.8% greater reduction in LDL-C (p<0.0001) and a HDL-C increase of +8.1% (p<0.0001).
- There is high quality evidence (n=2656; 2 RCTs) that alirocumab 75-150 mg every 2 weeks for 24 weeks (baseline LDL-C: 100-123 mg/dL) can result in a significantly higher proportion of patients at high risk for CV events to achieve a goal LDL-C <70 mg/dL versus placebo (pooled RR 9.65; 95% CI, 7.7 to 12.0), with a -45.9% to -61.9% greater reduction in LDL-C (p<0.001) and a HDL-C increase of +7.3% to +7.6% (p<0.001) compared to placebo.
- There is low quality evidence of no difference in CV events between alirocumab and placebo at 52- and 78-week follow-up when alirocumab and placebo were continued long-term with concomitant statin therapy. In addition, there is moderate quality evidence of no difference in CV events between alirocumab and ezetimibe at 52-week follow-up when both treatments were continued long-term with concomitant statin therapy. In these studies, a variety of CV outcomes were reported as secondary outcomes and listed as harms, rather than as potential benefits. As such, neither of the alirocumab studies that reported CV events had statistical power calculations for these outcomes. A pooled analysis of the studies indicated no statistically significant benefit with alirocumab on the incidence of combined CV events over 52 to 78 weeks. The pooled relative risk (RR) for a combined outcome of any CV event was 0.91 (95% Confidence Interval [CI], 0.63 to 1.31).
- There is high quality evidence (n=1375; 2 RCTs) that the addition of evolocumab 420 mg every 4 weeks for 12 weeks (baseline LDL-C: 104 mg/dL) can result in higher achievement rates of target LDL-C <70 mg/dL in patients at varying risk for CV events versus placebo (71.8%-94.5% vs. 0%-9.3%, respectively) with a modest increase in HDL-C (difference in HDL-C change: 4.5%-9.1%). There is moderate quality evidence that these benefits are similarly maintained with continued use of evolocumab over 52 weeks. When compared to the addition of ezetimibe 10 mg daily, there is low quality evidence that the addition of evolocumab can result in higher achievement rates of target LDL-C <70 mg/dL in this population (LDL-C goal <70 mg/dL: 86%-95% vs. 6%-62%, respectively).

**PCSK9 inhibitor study protocols were developed before the 2013 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines were published. The new guidelines stress intensity of statin therapy based on patient risk to achieve ≥50% LDL-C reduction (high intensity statin) or 30% to <50% LDL-C reduction (moderate-intensity statin). The guidelines essentially replace the NCEP-ATP III guidelines, which supported treatment to targeted LDL-C or non-HDL levels, because evidence is insufficient to support specific LDL-C and non-HDL target levels.*

MIXED POPULATIONS (HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA, STATIN-INTOLERANCE, AND UNABLE TO ACHIEVE TARGET LDL-C)

- In open-label extension studies (n=4465; 2 RCTs) of evolocumab in mixed populations maintained on standard therapy (ie, statins), there is low quality evidence evolocumab 420 mg every 4 weeks can reduce LDL-C by 58.4% more than standard care alone at 48 weeks (p<0.001). A reduction in CV events was also observed in secondary or post-hoc analyses (hazard ratio for any event: 0.47; 95% CI, 0.28 to 0.78), but evidence is insufficient to draw conclusions.

- The evidence is insufficient to draw conclusions on the effect of evolocumab on CV outcomes in mixed populations in part due to methodologic limitations of the open-label extension studies that reported CV events, lack of information to assess consistency of findings across the studies, and the imprecision of the estimates. Although all CV events were pre-specified, the analyses were secondary and exploratory, and consequently, were likely inadequately powered to identify differences on these outcomes. Thus, the meaningfulness of the statistical differences that were found is unclear. For incidence of any CV event the hazard ratio [HR] was 0.47 (95% CI, 0.28 to 0.78; rates 0.95% vs. 2.18%) with evolocumab (plus standard care) compared with standard care alone. In a post-hoc analysis, the composite of death, major coronary events and major cerebrovascular events (MACE) were 0.95% compared with 2.11% (HR, 0.47; 95% CI, 0.28 to 0.78). No differences were found on a variety of individual CV events.

SAFETY

- There is moderate quality evidence of no differences in harms between alirocumab and ezetimibe, and low quality evidence of no differences in harms between alirocumab and placebo, with the exception of more frequent injection site reactions with alirocumab. There is low quality evidence that use of evolocumab can result in more adverse events than statins alone but no differences were observed in withdrawals or serious adverse events compared to placebo. Long-term studies will more clearly differentiate harms (ie, neurocognitive effects) associated with use of PCSK9 Inhibitors.

Appendix 1: Current Status of PDL Class.

Other Dyslipidemia Drugs

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	POWD PACK	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWD PACK	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWD PACK	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	CHOLESTYRAMINE LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	PREVALITE	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	POWDER	QUESTRAN	CHOLESTYRAMINE (WITH SUGAR)	Y
ORAL	POWDER	QUESTRAN LIGHT	CHOLESTYRAMINE/ASPARTAME	Y
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	Y
ORAL	TABLET	LOFIBRA	FENOFIBRATE	Y
ORAL	TABLET	GEMFIBROZIL	GEMFIBROZIL	Y
ORAL	TABLET	LOPID	GEMFIBROZIL	Y

ORAL	GRANULES	COLESTID	COLESTIPOL HCL	N
ORAL	GRANULES	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	PACKET	COLESTID	COLESTIPOL HCL	N
ORAL	PACKET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	POWD PACK	WELCHOL	COLESEVELAM HCL	N
ORAL	TABLET	COLESTID	COLESTIPOL HCL	N
ORAL	TABLET	COLESTIPOL HCL	COLESTIPOL HCL	N
ORAL	TABLET	WELCHOL	COLESEVELAM HCL	N
ORAL	TABLET	ZETIA	EZETIMIBE	N
ORAL	CAPSULE	ANTARA	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE	N
ORAL	CAPSULE	FENOFIBRATE	FENOFIBRATE,MICRONIZED	N
ORAL	CAPSULE	LIPOFEN	FENOFIBRATE	N
ORAL	CAPSULE	LOFIBRA	FENOFIBRATE,MICRONIZED	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE	N
ORAL	TABLET	FENOFIBRATE	FENOFIBRATE NANOCRYSTALLIZED	N
ORAL	TABLET	FENOFIBRIC ACID	FENOFIBRIC ACID	N
ORAL	TABLET	FENOGLIDE	FENOFIBRATE	N
ORAL	TABLET	FIBRICOR	FENOFIBRIC ACID	N
ORAL	TABLET	TRICOR	FENOFIBRATE NANOCRYSTALLIZED	N
ORAL	TABLET	TRIGLIDE	FENOFIBRATE NANOCRYSTALLIZED	N
ORAL	CAPSULE DR	FENOFIBRIC ACID	FENOFIBRIC ACID (CHOLINE)	N
ORAL	CAPSULE DR	TRILIPIX	FENOFIBRIC ACID (CHOLINE)	N
ORAL	CAPSULE	JUXTAPID	LOMITAPIDE MESYLATE	N
SUB-Q	SYRINGE	KYNAMRO	MIPOMERSEN SODIUM	N
ORAL	CAPSULE ER	NIACIN	NIACIN	N
ORAL	TAB ER 24H	NIACIN ER	NIACIN	N
ORAL	TAB ER 24H	NIASPAN	NIACIN	N
ORAL	TABLET	NIACOR	NIACIN	N
ORAL	CAPSULE	VASCEPA	ICOSAPENT ETHYL	N
ORAL	CAPSULE	LOVAZA	OMEGA-3 ACID ETHYL ESTERS	N
ORAL	CAPSULE	OMEGA-3 ACID ETHYL ESTERS	OMEGA-3 ACID ETHYL ESTERS	N

Appendix 2: Highlights of Prescribing Information.

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

PRALUENT™ (alirocumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
PRALUENT is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C). (1.1)

Limitations of Use
- The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined. (1.2)

----------DOSAGE AND ADMINISTRATION----------
The recommended starting dose for PRALUENT is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. (2.1)

Measure LDL-C levels within 4 to 8 weeks of initiating or titrating PRALUENT, to assess response and adjust the dose, if needed. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled pen (3)
- Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled syringe (3)

----------CONTRAINDICATIONS----------
History of a serious hypersensitivity reaction to PRALUENT. (4)

----------WARNINGS AND PRECAUTIONS----------
- Allergic Reactions: Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve. (5.1)

----------ADVERSE REACTIONS----------
The most commonly occurring adverse reactions (≥5% of patients treated with PRALUENT and occurring more frequently than with placebo) are nasopharyngitis, injection site reactions, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Revised: 7/2015

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

REPATHA (evolocumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
REPATHA is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). (1.1)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (1.2)

Limitations of Use

- The effect of REPATHA on cardiovascular morbidity and mortality has not been determined. (1.3)

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

- Administer by subcutaneous injection (2.1)
- Primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH: 140 mg every 2 weeks or 420 mg once monthly in abdomen, thigh, or upper arm. (2.1)
- HoFH: 420 mg once monthly. (2.1)
- To administer 420 mg, give 3 REPATHA injections consecutively within 30 minutes. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

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

- Injection: 140 mg/mL in a single-use prefilled syringe (3)
- Injection: 140 mg/mL in a single-use prefilled SureClick® autoinjector (3)

----------CONTRAINDICATIONS----------
Patients with a history of a serious hypersensitivity reaction to REPATHA. (4)

----------WARNINGS AND PRECAUTIONS----------
Allergic Reactions: Rash and urticaria have occurred. If signs or symptoms of serious allergic reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve. (5.1)

----------ADVERSE REACTIONS----------
Common adverse reactions in clinical trials (>5% of patients treated with REPATHA and occurring more frequently than placebo): nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Revised: 8/2015

PCSK9 Inhibitors

Goal:

- Restrict use of PCSK9 inhibitors to populations in which the drugs have demonstrated efficacy.

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 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 to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have clinical atherosclerotic cardiovascular disease, defined as documented history of ≥1 of the following: • Myocardial infarction • Unstable angina • Coronary revascularization procedure (PCI or CABG) • Diagnosis of clinically significant coronary heart disease by coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging Or a coronary heart disease (CHD) risk-equivalent, defined as documented history of ≥1 of the following: • Peripheral arterial disease • Ischemic stroke of atherothrombotic origin • Chronic kidney disease (CrCl 30-60 mL/min) • Diabetes mellitus PLUS ≥2 additional risk factors: o Hypertension; ankle-brachial index ≤0.90; micro- or macro-albuminuria; retinopathy; or family history of early coronary heart disease?	Yes: Go to #4	No: Go to #8
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 12 months with <50% LDL-C reduction? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C (within last 12 weeks).	Yes: Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ mg/dL Date:_____ Recent LDL-C _____ mg/dL Date:_____	No: Go to #6

Approval Criteria		
5. Is the patient adherent with a high-intensity statin and ezetimibe?	Yes: Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	No: Pass to RPh; deny for medical appropriateness
6. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	Yes: Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	No: Go to #7

Approval Criteria		
7. Is there chart documentation the patient experienced persistent myalgia or myopathy on 3 separate trials (each trial ≥8 weeks' duration) of moderate- or high-intensity statin (see table below), separated by an adequate washout period of ≥2 weeks? Note: Prescriber must provide chart documentation of myalgia/myopathy from each statin trial and provide chart documentation of recent LDL-C (within last 12 weeks).	Yes: Document statin trials and approve for up to 12 months 1. Statin: Dose: Date Initiated: Date D/C: Cause of D/C: 2. Statin: Dose: Date Initiated: Date D/C: Cause of D/C: 3. Statin: Dose: Date Initiated: Date D/C: Cause of D/C Recent LDL-C _____ mg/dL Date:_____	No: Pass to RPh; deny for medical appropriateness.
8. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia and already takes a maximally tolerated statin and/or ezetimibe? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	Yes: Document diagnosis and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	No: Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Is the patient adherent with PCSK9 inhibitor therapy?	Yes: Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 12 months)	No: Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

High-intensity Statins (≥50% LDL-C Reduction)		**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40 mg	Pitavastatin 2-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

References:
1. NICE Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available at: guidance.nice.org.uk/cg181. Accessed 18 September 2015.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.

P&T / DUR Review: *11/15 (AG)*
Implementation: ***TBD***

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Drug Effectiveness Review Project Summary Report – Long-acting Insulins

Date of Review: November 2015

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

DERP Research Questions:

1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with Type 1 or Type 2 diabetes mellitus (T1DM, T2DM)?
2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with T1DM or T2DM?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions [eg, obesity]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

Conclusions:

- There is insufficient comparative evidence that evaluates long-term health outcomes (ie, macrovascular outcomes, microvascular outcomes, mortality or cancer) between insulin detemir and glargine products.
- There is insufficient comparative evidence between insulin detemir and glargine products in children.
- There is insufficient comparative evidence between insulin glargine pens and vials.
- In adults with T1DM or T2DM, there is no difference between insulin detemir and glargine in absolute reduction of hemoglobin A1c (HbA1c) or proportion with HbA1c of 7.0% or less between 12 to 52 weeks based on low quality evidence.
- In adults with T1DM or T2DM, there is no difference between insulin glargine U100 and U300 in absolute reduction in HbA1c or proportion with HbA1c of 7.0% or less between 4 to 6 months based on low to moderate quality evidence.
- There is insufficient evidence to determine if there are differences in nocturnal hypoglycemia rates between insulin detemir and glargine in adults with T1DM; however, there does not appear to be any differences in nocturnal hypoglycemia rates between these insulins in adults with T2DM based on low quality evidence.
- There is low quality evidence that there are no differences in rates of severe hypoglycemia or serious adverse events between insulin determir and glargine in adults enrolled in studies up to 1 year in length; however, there may be increased risk of drug discontinuation with insulin detemir due to adverse events (pooled RR 2.1; 95% CI, 1.4 to 3.3).
- In adults with T1DM or T2DM, glargine concentration (U100 vs. U300) did not affect rates of severe hypoglycemia or serious adverse events based on low quality evidence in studies up to 6 months in length. However, there is moderate quality evidence that rates of nocturnal hypoglycemia may be less with U300 in adults with T2DM, but not T1DM, over 6 months (38% vs. 51%; pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%).
- Rates of severe hypoglycemia may be lower with insulin glargine administered in a pen than via a vial, based on low quality evidence from observational studies in adults with T2DM that were observed over 12 months (RR 0.72; 95% CI, 0.65 to 0.79).

- There is insufficient evidence for differences in long-acting insulin products in specific subgroups based on demographics. One small, observational study observed neonates born to mothers on insulin detemir were at higher risk for being large for gestational age versus neonates born to mothers who took insulin glargine. However, the study was not able to adjust for potential confounding.

Recommendations:

- Make insulin glargine U300 non-preferred and subject to current PA criteria for insulin pens (**appendix 3**). Further research is needed to confirm place-in-therapy with other long-acting insulin products.
- Maintain at least one preferred long-acting insulin product on the PDL. Review comparative long-acting insulin costs in the executive session.
- Review insulin degludec (Tresiba®) and insulin degludec/aspart (Ryzodeg® 70/30) as separate new drug evaluations at a later time.

Previous Conclusions and Recommendations:

- There is low quality evidence of no significant differences in change in HbA1C or overall and severe hypoglycemia between insulin detemir and insulin glargine and high quality evidence that insulin detemir is associated with less weight gain and low quality evidence of more injection site reactions compared to insulin glargine. With no clinically relevant difference in efficacy or safety of the two long acting agents, evaluate comparative costs.
- There is no significant new comparative evidence on the efficacy and safety of other agents on the PDL.
- Bring back full review of inhaled human recombinant insulin (Afrezza®) once available.
- Continue to include at least one agent from each subgroup (short-acting, rapid-acting, etc.) as preferred on the PDL and evaluate comparative costs in executive session.

Methods:

The September 2015 Drug Class Review on long-acting insulins by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available 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.

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

Summary Findings:
Eligible studies for inclusion into the systematic review were studies of adults or children with T1DM or T2DM that compared one long-acting insulin with another or compared the same insulin in a different formulation or device. Outcomes of interest were macrovascular disease (ie, cardiovascular events, cardiovascular-related mortality, stroke, extremity amputation, etc.), microvascular disease (diabetic neuropathy, nephropathy, or retinopathy), all-cause mortality, glycemic control (fasting, A1c, goal A1c), and harms (nocturnal hypoglycemia, severe hypoglycemia, withdrawals due to adverse events, serious adverse events, or malignancy). Studies had to be other systematic reviews or randomized controlled trials with head-to-head comparisons; however, for harms data, comparative observational studies were considered.

A total of 771 records were identified and screened for inclusion in the review. The DERP received dossiers from 3 pharmaceutical manufacturers: Eli Lilly (Basaglar; Peglispro), Novo Nordisk (Levemir®; Insulin Degludec), and Sanofi (Lantus®; Toujeo®, Insulin Glargine U300). Twenty-five studies (13 fair-quality head-to-head trials and 1 good-quality systematic review) of adults with T1DM or T2DM were included. There were no studies in children, and no studies reported long-term effectiveness outcome (eg, macro- or microvascular events). The insulin products included in the review are in table 1.

Table 1. FDA-approved Long-acting Insulin Products.

Drug	Trade Name	Formulation	FDA Approval
Insulin glargine	Lantus® (U100) Toujeo® (U300)	Pen or vial	4/20/2000; 2/25/2015
Insulin detemir	Levemir® (U100)	Pen or vial	6/16/2005

Key Question 1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with diabetes mellitus?

T1DM OR T2DM

- There was no evidence directly comparing long-term health outcomes (eg, macro- or microvascular events) between included insulins or devices.

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: There was low-strength evidence, based on 2 fair-quality open-label trials (N=763), that there was no difference between insulin detemir and insulin glargine in glycemic control measured by achieving HbA1c goals or mean plasma glucose levels at 26 or 52 weeks.
- T2DM: There was low-strength evidence based on a good quality systematic review of 4 trials and 2 more recent fair quality trials (total N=2,750) that there was no difference between insulin detemir and insulin glargine in glycemic control measured by achieving HbA1c goals and the reduction in HbA1c at 12 to 52 weeks. There was statistical heterogeneity in these findings, with inconsistency in individual study results such that future studies are needed to strengthen the conclusion.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- T1DM: Two fair-quality trials including a total of 602 patients provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between patients given insulin glargine U300 and insulin glargine U100 for 4 to 6 months.
- T2DM: Three fair-quality Phase 3 trials in a total of 2,474 patients provided moderate-strength evidence that glycemic control measured by hemoglobin A1C did not differ between patients treated for 6 months with insulin glargine U300 and insulin glargine U100. Two of these Phase 3 trials have

completed 6-month treatment extension periods. Glycemic control was improved with insulin glargine U300 in 1 of the trials, but did not differ between insulin glargine concentrations in the other.

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- T1DM or T2DM: No evidence comparing insulin glargine delivered via pen versus vial met inclusion criteria.

Key Question 2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with diabetes mellitus?

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: Low-strength evidence from 2 fair-quality randomized controlled trials (RCTs) and 2 observational studies suggested no difference in the risk of severe hypoglycemic events between insulin detemir and insulin glargine. Evidence on nocturnal hypoglycemia was insufficient due to sparse reporting (only 2 studies) and inconsistent findings. Future studies are needed to inform evidence on both outcomes. Low-strength evidence from 2 fair-quality RCTs suggested no differences in withdrawals due to adverse events or serious adverse events thought to be related to study insulin.
- T2DM: Low-strength evidence based on 1 systematic review (of 4 RCTs), 1 additional RCT, and 4 observational studies suggested that there was no difference in the incidence of either severe or nocturnal hypoglycemia between insulin detemir and insulin glargine. Low-strength evidence from a systematic review of 4 RCTs and 2 additional RCTs suggested no difference in serious adverse events. Analysis of all trials indicates that withdrawals due to adverse events occurred significantly more frequently for patients assigned to insulin detemir compared with insulin glargine over 12 to 52 weeks (RR 2.1; 95% CI, 1.4 to 3.3; I2=0%).

OTHER HARMS

- Evidence was inadequate to evaluate the comparative risk for cancer in either population.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- T1DM: Two fair-quality trials in 608 patients showed no difference between insulin glargine U300 and insulin glargine U100 in severe hypoglycemia, withdrawals due to adverse events, serious adverse events (all low strength of evidence for no difference), or nocturnal hypoglycemia (moderate-strength) after 4 to 6 months' treatment.
- T2DM: Three fair-quality trials in 2,488 patients provided moderate- strength evidence that rates of nocturnal hypoglycemia were lower with insulin glargine U300 than with insulin glargine U100 (38% vs. 51%; EPC pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%). The 3 trials did not show differences between insulin glargine concentrations in rates of severe hypoglycemia, withdrawals due to adverse events, or serious adverse events (all low strength of evidence for no difference).

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- T1DM: No RCTs or observational studies comparing insulin glargine delivered via pen versus vial in patients with met inclusion criteria.
- T2DM: Seven observational studies in 24,564 patients provided low-strength evidence that rates of severe hypoglycemia were lower with insulin glargine via pen than with insulin glargine via vial and syringe (EPC pooled RR 0.72; 95% CI, 0.65 to 0.79; I^2=0%).

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions [e.g., obesity]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: Two small, fair-quality observational studies (N=203) found inconsistent results with respect to perinatal mortality, neonatal birth weight outcomes, insulin dose, and neonatal hypoglycemia in neonates of women using insulin detemir or insulin glargine throughout pregnancy. Given these differences in findings, concerns over methodology, and the small size of the studies, the results are not sufficient to draw conclusions, and more study is needed.
- T2DM: No comparative evidence found.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- Included studies did not report outcomes by subgroup.

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- Included studies did not report outcomes by subgroup.

Therefore, the strength of evidence for all outcomes across key questions and comparisons was primarily low, with few exceptions. In adults with T1DM, differences in efficacy or harms were not found between insulin detemir and insulin glargine, or insulin glargine U300 and insulin glargine U100. In patients with T2DM, no differences were found in efficacy outcomes. The few differences found in harms were that insulin glargine may result in fewer patients who discontinue due to adverse events than insulin detemir; in addition, nocturnal hypoglycemia may occur in fewer patients with insulin glargine U300 than with insulin glargine U100; lastly, insulin glargine given via pen may result in lower incidence of severe hypoglycemia than when given by vial and syringe. There was inadequate evidence to assess comparative effects on long-term health outcomes, in subgroups, or risk of cancer. Current evidence in pregnant women with T1DM suggests more research is needed to determine comparative effects of long-acting insulins on the neonate.

Appendix 1: Current Status of PDL Class.

Insulins (long-acting insulins bolded)

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

Appendix 2: Highlights of Prescribing Information.

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

TOUJEO (insulin glargine injection) U-300, for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
TOUJEO is a long- acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1)

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

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

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 300 units/mL insulin glargine in 1.5 mL SoloStar® disposable prefilled pen (3)

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

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

----------ADVERSE REACTIONS----------
Adverse reactions commonly associated with TOUJEO (≥5%) are:
- Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema and weight gain. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose. (7.1, 7.2, 7.3)
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent (7.3, 7.4)

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

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

Revised: February 2015

Insulins

Goal:

- Restrict certain insulin products to specified patients populations to ensure appropriate and safe use.

Length of Authorization:

Up to 12 months

Requires PA:

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

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 covered diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is on 40 units or less of insulin per day • The patient is a child less than 18 years of age	Yes: Go to #5	No: Pass to RPh; ~~go to #6~~deny for medical appropriateness

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require 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. Approve insulin pens/cartridges for up to 12 months (other preferred products do not require PA)	No: Approve for up to 12 months
~~6. RPh only~~ ~~• Requests for insulin pens and cartridges on a patient-specific basis.~~ ~~• Refer to the PDL for the preferred pens.~~ ~~AND/OR~~ ~~• Approve for up to 12 months if the above criteria are met and the request is NOT for convenience alone.~~		

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

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Class Update with New Drug Evaluation: Antiemetics

Date of Review: November 2015
Generic Name: netupitant/palonosetron
rolapitant

End Date of Literature Search:
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 for updated evidence to incorporate 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 (ie, 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 one antiemetic treatment would be more effective or associated with less harm?

Conclusions:
- There is insufficient new comparative effectiveness evidence or comparative harms 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 receiving chemotherapy.[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 300mg/palonosetron 0.5 mg) (Akynzeo®) is superior to palonosetron for complete response (ie, no rescue treatment required and no emesis) during the delayed phase (25-120h) in patients who received moderate emetogenic chemotherapy (MEC) (p=0.001).[4]

- There is insufficient data on the comparative effectiveness of the NK1 RA rolapitant (VARUBI™). Currently, only prescribing information is available for analysis.[5]

Recommendations:
- No changes are recommended to the PDL based on review of the clinical data. Evaluate drug costs in executive session.
- Recommend that patients receiving chemotherapy or radiation, who meet PA criteria, 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:
- 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.
- 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.
- 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.

Previous Recommendations:
- 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.

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).[12] The combination of pyridoxine with doxylamine, a first-generation antihistamine, is recommended for pregnant patients who fail pyridoxine alone. 5HT3 RAs are frequently prescribed for pregnancy-related n/v, despite limited evidence to support its use.[12]

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 (eg, 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.[10,11,13]

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 1).[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 1. 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.[14] 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.[14]

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.[15] 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.[16] 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	1. 5HT3 RA	- Continue daily

Chemotherapy		
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 route • Palonosetron • NK 1 RA for 2 days after chemotherapy	- Give antiemetic to cover both acute and delayed n/v

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, 4 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 4 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	Quality*
Oliveira, et al[12]	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 visual analog scale (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)	Fair
Roila, et al[17]	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 cyclo-phosphamide	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%.	Fair
Kang H, et al[18]	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.	Good
Schmitt T, et al[19]	Aprepitant regimen vs. placebo <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: Aprepitant 80 mg + granisetron 2mg + 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)	Fair

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

NEW DRUG EVALUATION:

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.

Netupitant and Palonosetron (Akynzeo®)

Clinical Efficacy:
The combination product netupitant/palonosetron (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.[20] Palonosetron was previously approved in 2008 and netupitant is a new molecular entity.[21] The oral palonosetron component helps to prevent CINV during the acute phase and netupitant is effective in both the acute and delayed phase after chemotherapy. NEPA is administered as a single dose 1 hour before chemotherapy.[4] FDA approval was based primarily one phase III study, which will be discussed below.[4] Earlier phase II studies were also performed but do not meet our inclusion crieteria.[22,23]

Netupitant 300 mg and palonosetron 0.5 mg, both as single oral doses, were compared to a single oral dose of palonosetron 0.5 mg alone (n=1449).[4] On day 1, both treatment arms also received a dose of oral dexamethasone, 12 mg for NEPA and 20 mg for palonosetron. All patients received MEC consisting of an anthracycline and cyclophosphamide. 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 during acute and delayed phases. The impact of CINV was assessed via the Functional Living Index-Emesis (FLIE).[4]

Results showed NEPA was superior to palonosetron alone for complete response during the delayed phase (p=0.001). NEPA was also significantly better for complete response in the acute phase (0-24 hours) and overall (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.

Clinical Safety:
NEPA was well tolerated in short-term clinical studies (Table 2).[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 2. 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.[5] No studies have been published and no trial results are available on Clinicaltrials.gov.

Prescribing information for rolapitant provides data from 2 RCTs.[5] 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).[5] 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 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).[5]

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 2. Adverse Reactions Occurring in ≥3% of Patients Receiving Rolapitant on HEC Regimens[5]

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 III, 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% 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 No emesis overall: NEPA 578 (79.8%) P 523 (87.3%) P<0.001 No significant nausea overall: NEPA 540 (74.6%) P 501 (69.1%) P=0.020	7.4/14 3.4/29 7.5/13 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	**Quality Rating**: POOR **Internal Validity (Risk of Bias)**: Selection: No details on randomization provided. Performance: Blinding maintained by double-dummy design. No details on patient or provider blinding. Detection: No details provided on outcome assessment blinding. Attrition: 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. **Analysis**: In female patients with predominately breast cancer, the combination of netupitant and palonosetron was more effective for the delayed phase than palonosetron alone prior to a MEC regimen. Acute phase results were also positive but need to be further studied.

AC= Anthracycline-cyclophosphamide; AE= adverse event; CINV= chemotherapy-induced nausea and vomiting; D/C = discontinuation; ECOG=Eastern Cooperative Oncology Group; FAS= full analysis set; HEC=high emetogenic chemotherapy; MEC= moderately emetogenic chemotherapy; number needed to harm; NNT = number needed to treat; NR= not reported; PP = per protocol

References:

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: antiemesis. Version 2.2015. Available at: http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.
2. Basch E, Prestrud Ann, Hesketh P, et al. Antiemetics: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 2011;29: 4189-4198.
3. Liu M, Zhang H, Du B, et al. Neurokinin-1 receptor antagonists in preventing postoperative nausea and vomiting. *Medicine* 2015;94:1-15.
4. Aapro M, Rugo H, Rossi G, et al. A randomized phase IIII study evaluating the efficacy ad 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.
5. Tesaro, Inc. Varubi Label. US Food and Drug Administration 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206500s000lbl.pdf. Accessed September 2, 2015.
6. Meeker, A. Newer Antiemetic Class Update. *Drug Use Research and management group* 2013. Available at: http://www.orpdl.org/durm/meetings/meetingdocs/2013_11_21/finals/2013_11_21_PT_Minutes.pdf. Accessed September 26, 2015.
7. Drug Effectiveness Review Project. Newer Antiemetics. Oregon Evidence Based Practice Center 2009.
8. Duchesnay USA, Inc. Diglegis Label. US Food and Drug Administration 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021876s002lbl.pdf. Accessed on September 26, 2015.
9. Anderson W, Strayer S. Evaluation of nausea and vomiting in adults: a case-based approach. *Am Fam Physician* 2013;88: 371-379.
10. Kovac, A. Update on the management of postoperative nausea and vomiting. *Drugs* 2013; 73: 1525-1547.
11. Gan T, Diemunsch P, Habib A, et al. Consensus guidelines on the management of postoperative nausea and vomiting. *Anesth Analg* 2014;118:85-113.
12. 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.
13. Carlisle J, Stevenson CA. Drugs fro preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006;3:CD004125.
14. Matthews A, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 9. Art. No.: CD007575. DOI: 10.1002/14651858.CD007575.pub4.
15. Canadian Agency for Drugs and Technologies in Health. Long-term use of ondansetron, dolasetron and granisetron for the prevention of nausea and vomiting: a review of the clinical effectiveness and safety. 2014. Available at: https://www.cadth.ca/long-term-use-ondansetron-dolasetron-and-granisetron-prevention-nausea-and-vomiting-review-clinical.
16. Canadian Agency for Drugs and Technologies in Health. Antiemetics for opioid-induced nausea: a review. 2014. Available at: https://www.cadth.ca/sites/default/files/pdf/htis/nov-2014/RC0529_RR_RiB_AntiEmetics_e.pdf
17. 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.
18. 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.
19. 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.
20. Eisai Inc. Akynzeo Label. US Food and Drug Administration 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205718s002lbl.pdf. Accessed September 2, 2015.

21. FDA Summary Review for Akynzeo. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205718Orig1s000SumR.pdf. Accessed September 22, 2015.
22. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Annals of Oncology 2014;25 :1333-1339.
23. Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. *Ann Oncol* 2014; 25:1340-1346.

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 ad 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

Appendix 5: Prior Authorization Criteria

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 doxylamine/pyridoxine (Diclegis) 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: *11/15 (KS); 11/14 (MH); 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) was approved by the United States (U.S.) Food and Drug Administration (FDA) to treat uncomplicated influenza in adults.

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 (about a 10% reduction) 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 does not reduce hospitalizations.[2,3] There is insufficient evidence to determine if treatment with zanamivir or peramivir can improve 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 by 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 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.
- There is insufficient evidence to support the use of amantadine and rimantadine for the prevention or treatment of influenza A. Safety concerns with amantadine, both drug's inactivity 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.
- 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. **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/Alaska Natives
    - Morbidly obese (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:

1. Heneghan C, Onakpoya I, Thompson M, Spencer E, Jones M, Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2547. doi:10.1136/bmj.g2547.

2. Jefferson T, Jones M, Doshi P, Spencer E, Onakpoya I, Heneghan C. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2545. doi:10.1136/bmj.g2545.

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.

4. Michiels B, Van Puyenbroeck K, Verhoeven V, Vermeire E, Coenen S. The Value of Neuraminidase Inhibitors for the Prevention and Treatment of Seasonal Influenza: A Systematic Review of Systematic Reviews. *PLoS ONE*. 2013;8(4):e60348. doi:10.1371/journal.pone.0060348.

5. Center for Drug Evaluation and Research. U.S. Food and Drug Administration. Peramivir Summary Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206426Orig1s000SumR.pdf. Accessed June 2, 2015.

6. Alves Galvao M, Rocha Crispino Santos M, Alves da Cunha A. Amantadine and rimantadine for influenza A in children and elderly. *Cochrane Database of Systematic Reviews*. 2014;(Issue 11. Art. No.: CD002745). doi:10.1002/14651858.CD002745.pub4.

7. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf. Accessed June 2, 2015.

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

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.

Approval Criteria		
5. Is the antiviral prescribed oseltamivir or zanamivir?	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness.
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:
1. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinician.pdf. Accessed June 2, 2015.
2. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2009; 48:1003-32.

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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 Jadenu™ (deferasirox) 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 at the end of treatment.
  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,	Ratio of the geometric mean Gmean T2* after 1 year of treatment with DFS divided by the ratio of Gmean for DFO	1.055 (0.999 to 1.129) P=0.054

		low/intermediate 1 myelodysplastic syndromes, or sideroblastic anemia with myocardial T2* 6 to 20 milliseconds without clinical symptoms of cardiac dysfunction	(95% CI)	

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
5 limit 4 to (english language and yr="2012 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv 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)) 118

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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.

References:

1. Penninga L, Penninga EI, Møller CH, Iversen M, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. *Cochrane Database Syst Rev*. 2013;5:CD008817. doi:10.1002/14651858.CD008817.pub2.

2. Saldanha IJ, Akinyede O, McKoy NA, Robinson KA. Immunosuppressive drug therapy for preventing rejection following lung transplantation in cystic fibrosis. *Cochrane Database Syst Rev*. 2013;12:CD009421. doi:10.1002/14651858.CD009421.pub2.

3. Kharfan-Dabaja M, Mhaskar R, Reljic T, et al. Mycophenolate mofetil versus methotrexate for prevention of graft-versus-host disease in people receiving allogeneic hematopoietic stem cell transplantation. *Cochrane Database Syst Rev*. 2014;7:CD010280. doi:10.1002/14651858.CD010280.pub2.

4. Su L, Tam N, Deng R, Chen P, Li H, Wu L. Everolimus-based calcineurin-inhibitor sparing regimens for kidney transplant recipients: a systematic review and meta-analysis. *Int Urol Nephrol*. 2014;46(10):2035-2044. doi:10.1007/s11255-014-0783-1.

5. Kelly DA, Bucuvalas JC, Alonso EM, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19(8):798-825. doi:10.1002/lt.23697.

6. Astagraf XL. Prescribing Information. Astellas Pharmaceuticals. Northbrook, IL 6/2015.

7. Alloway R, Steinberg S, Khalil K, et al. Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37(2):867-870. doi:10.1016/j.transproceed.2004.12.222.

8. Florman S, Alloway R, Kalayoglu M, et al. Conversion of stable liver transplant recipients from a twice-daily Prograf-based regimen to a once-daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37(2):1211-1213. doi:10.1016/j.transproceed.2004.11.086.

9. Marin-Gomez LM, Gomez-Bravo MA, Alamo-Martinez JA, et al. Evaluation of clinical safety of conversion to Advagraf therapy in liver transplant recipients: observational study. *Transplant Proc*. 2009;41(6):2184-2186. doi:10.1016/j.transproceed.2009.06.085.

10. Budde K, Bunnapradist S, Grinyo JM, et al. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. *Am J Transplant*. 2014;14(12):2796-2806. doi:10.1111/ajt.12955.

11. Heffron TG, Pescovitz MD, Florman S, et al. Once-daily tacrolimus extended-release formulation: 1-year post-conversion in stable pediatric liver transplant recipients. *Am J Transplant*. 2007;7(6):1609-1615. doi:10.1111/j.1600-6143.2007.01803.x.

12. Cabello M, García P, González-Molina M, et al. Pharmacokinetics of once- versus twice-daily tacrolimus formulations in kidney transplant patients receiving expanded criteria deceased donor organs: a single-center, randomized study. *Transplant Proc*. 2010;42(8):3038-3040. doi:10.1016/j.transproceed.2010.08.008.

13. de Jonge H, Kuypers DR, Verbeke K, Vanrenterghem Y. Reduced C0 concentrations and increased dose requirements in renal allograft recipients converted to the novel once-daily tacrolimus formulation. *Transplantation*. 2010;90(5):523-529. doi:10.1097/TP.0b013e3181e9feda.

14. Diez Ojea B, Alonso Alvarez M, Aguado Fernández S, Baños Gallardo M, García Melendreras S, Gómez Huertas E. Three-month experience with tacrolimus once-daily regimen in stable renal allografts. *Transplant Proc*. 2009;41(6):2323-2325. doi:10.1016/j.transproceed.2009.06.048.

15. Ho ETL, Wong G, Craig JC, Chapman JR. Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. *Transplantation*. 2013;95(9):1120-1128. doi:10.1097/TP.0b013e318284c15b.

16. Urbanowicz T, Baszyńska-Wachowiak H, Ligowski M, Straburzyńska-Migaj E, Misterski M, Jemielity M. Comparison of conventional tacrolimus versus prolong release formula as initial therapy in heart transplantation. *Ann Transplant*. 2014;19:295-299. doi:10.12659/AOT.890268.

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*