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, May 26, 2016 1:00 - 5:00 PM
Barbara Roberts Human Services Building, Room 137 A-D
500 Summer St. SE
Salem, OR 97301

MEETING AGENDA

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

I. CALL TO ORDER

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 (HPE)
C. RetroDUR Report	T. Williams (OSU)
D. Oregon State Drug Reviews	K. Sentena (OSU)

1. "2015 in Review: Relevant Safety Updates and Ongoing Safety Concerns"
2. "Antidiabetic Treatments and Cardiovascular Implications"

III. DUR NEW BUSINESS

A. Abbreviated Clinical Prior Authorization Reviews — D. Moretz (OSU)

1. Ampyra® (dalfampridine)
2. Kynamro® (mipomersen) and Juxtapid® (lomitapide)
3. Kuvan® (saproterin)
4. Public Comment
5. Discussion of Clinical Recommendations to OHA

IV. PREFERRED DRUG LIST NEW BUSINESS

A. New Drug Evaluations for COPD — K. Sentena (OSU)

1. Utibron™ Neohaler® (indacaterol/glycopyrrolate) New Drug Evaluation
2. Seebri™ Neohaler® (glycopyrrolate) New Drug Evaluation
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

B. Antipsychotics Drug Class Update — A. Gibler (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

C. Long-acting Opioids Drug Class Update — A. Gibler/C. Strouse (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

D. Smoking Cessation Drug Class Update — M. Herink (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

E. Cough and Cold Drug Class Update — K. Ketchum (OSU)
1. Class Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

F. Vyvanse™ (lisdexamfetamine) New Indication Evaluation — K. Ketchum (OSU)
1. New Indication Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

G. Veltassa® (patiromer) New Drug Evaluation — M. Herink/E. Le (OSU)
1. New Drug Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

H. Zurampic® (lesinurad) New Drug Evaluation — D. Engen (OSU)
1. New Drug Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

I. Briviact® (brivaracetam) New Drug Evaluation — D. Moretz (OSU)
1. New Drug Evaluation
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

J. Drug Class Literature Scans — D. Moretz/K. Sentena (OSU)
1. Erythropoiesis Stimulating Agents
2. Antivirals for Herpes Simplex Virus
3. Public Comment
4. Discussion of Clinical Recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

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

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
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	Corvallis	December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018

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, March 31, 2016 1:00-5:00 PM
DHS Barbara Roberts Building
500 Summer St. NE
Salem, OR 97301

MEETING MINUTES

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

Members Present: Cathy Zehrung, RPh; Bill Origer, MD; Rich Clark, MD, MPH; James Slater, PharmD; Walter Hardin, D.O., MBA;

Members Present by Phone: Stacy Ramirez, PharmD; Caryn Mickelson, PharmD; Dave Pass, MD

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

Staff Present by Phone:

Audience: Jennifer Srec (Med Impact), Rick Frees (Vertex), Bruce Wallace (Silvergate), Deanna Moretz (OSU), Bobbi Jo Drum (BMS), Tony Locke (Upsher-Smith), Venus Holder (Elli Lilly), George Yasutake (Actelion)*, John Hartney (Actelion), Lori Howerth (Bayer), Barry Benson (Merck), Hiral Patel (AstraZeneca)*, Merrie Kay Alzova (Novo Nordisk), Shawn Hansen (Novo Nordisk)*, Michelle Bice (Gilead Sciences), Mary Kemhus (Novartis), Mindy Schimpf (UCB), Samantha Min (Otsuka), Mark Galgshu (Pacific U), Margaret Olmon (AbbVie), Don Stecher (Novartis), Sylvia Churchill, PharmD (Amgen), Richard McLeod (Pfizer), Steven Fuchs (Pfizer)*, Marc Jansen (Pfizer)*, Jenny Morrison (Boehringer Ingelheim), Mike Willett (Pfizer), Jennifer Croft (WVCH), Lisa Boyle (WVCH), Kristel Jordan (IHN), Aaron Nichols (OSU), Stuart O'Brochta (Gilead)*, Dr. McCale (Baxalta),

(*) 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 - 8)

Dr. Clark said the draft minutes did not reflect the concerns he voiced regarding the lack of disclosure of conflicts of interest from the CF Foundation and CF specialists and stated he would like to bring the Orkambi review back to the Committee again (using the same established review) to discuss whether this information would change the recommendations. Mr. Citron discussed then changes that have been made to the conflict of interest form.

ACTION: Motion, 2nd, All in Favor. Approved minutes as amended.

d. Department updates for OHA.

II. DUR NEW BUISNESS

a. Compound Drugs Drug Use Evaluation (pages 9 - 16)
Ms. Ketchum presented the following drug use evaluation.

1. Produce and publish educational documents.
2. Approve proposed edits and quantity limits
3. Approve cap upon paid amounts to require PA
4. Perform and present policy evaluation in 2 years.

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

b. Multi-vitamins Policy Evaluation (pages 17 - 35)
Ms. Ketchum presented the multi-vitamin policy evaluation.

Maintain current PA policy.

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

c. Biologics Policy Evaluation (pages 36 - 58)
Dr. Herink presented the Biologic policy evaluation.

1. Continue to require PA for non-preferred biologics.
2. Require PA for medical claims and auto-approve for cancer and MS diagnoses.
3. Require PA on preferred biologics to promote step through appropriate DMARD therapy.

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

III. PREFERRED DRUG LIST NEW BUSINESS

a. Pulmonary Arterial Hypertension Drug Class Update (pages 59 - 84)
Dr. Gibler presented the following drug class update.

1. Continue current PA criteria for oral/inhaled agents and parenteral agents.
2. Add epoprostenol to the PMPDP and do not require PA.
3. Evaluate comparative costs in executive session.

Public Comment:

George Yasutake, PharmD from Actelion gave public comment.
Stuart O'Brochta from Gilead gave public comment.

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

b. Phosphate Binders Class Update (pages 85 – 100)
Dr. Gibler presented the following class update.

1. Maintain ferric citrate as non-preferred at this time and incorporate into current PA.
2. Continue to prefer at lease one calcium-based phosphate binder and one non-calcium-based phosphate binder on the PMPDP.
3. Evaluate comparative costs in the executive session.

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

c. ADHD Drug Class Update (pages 101 – 114)
Dr. Gibler presented the following class update.

1. Maintain QuilliChew ER and Adzenys XR-ODT as non-preferred on PMPDP based on limited evidence for safety and efficacy.
2. Approved proposed updates to the Safety Edit.
3. Evaluate comparative costs in executive session.

Public Comment:
Steven Fuchs, PharmD from Pfizer gave public comment.

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

d. Sodium-glucose Co-transporter 2 Inhibitor Class Update (pages 115 – 125)
Dr. Sentena presented the following class update.

1. Modify current PA criteria to allow use of SGLT2 inhibitors as a third-line option with metformin and sulfonylureas.

Public Comment:
Hiral Patel from AstraZeneca gave public comment.

ACTION: Motion to approve, 2nd, 1 in favor, 6 opposed, proposal rejected.

e. Calcium and Vitamin D Class Update (pages 126 – 143)
Dr. Sentena presented the following class update.

1. Approve proposed PA criteria to restrict non-preferred vitamin D and calcium supplements to patients who are: pregnant; have a nutrient deficiency; have a diagnosis of osteopenia or osteoporosis; and patients 65 years of age or older who are at risk for falls
2. Allow dispensing of 90 day supply for pharmacy claims
3. Evaluate comparative costs in executive session

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

f. Opioid Reversal Agents Class Review (pages 144 – 154)
Dr. Gibler presented the following class review.

1. Limit the quantity of naloxone to 2 units every 12 months without PA.

2. Refer clients who require naloxone more frequently for case management.
3. Evaluate comparative costs in executive session.

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

g. Insulin Degludec New Drug Evaluations (pages 155 – 182)
Dr. Sentena presented the following drug evaluation.

1. Maintain insulin degludec as non-preferred and subject to current PA criteria for insulin pens.
2. Make insulin degludec / aspart non-preferred and subject to current PA criteria when it comes to market.

Public Comment:
Shawn Hansen from Novo Nordisk gave public comment.

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

h. Drug Class Literature Scans

1. Triptans (pages 183 – 195)
Dr. Herink presented the following drug class scan.

a. No further research is needed at this time.
b. Continue to include at lease one agent available for each route of administration (oral, nasal, subcutaneous) and maintain current PA criteria.
c. Evaluate comparative cost in executive session.

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

2. NSAIDs (pages 196 -205)
Dr. Herink presented the following drug class scan.

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

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

3. Topical Antibiotics (pages 206 – 209)
Dr. Engen presented the following drug class scan.

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

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

4. Topical Antiparasitics (pages 210 – 215)
Dr. Engen presented the following drug class scan.

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

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

I. Abbreviated Drug Reviews
Dr. Engen presented the following abbreviated drug reviews.

1. Eluxadoline (page 216)

   Require PA to restrict use to OHP-funded conditions.

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

2. Flibanserin (page 217)

   Require PA to restrict use to OHP-funded conditions.

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

3. Liraglutide (page 218)

   Require PA to restrict use to OHP-funded conditions.

Public Comment:
Shawn Hansen from Novo Nordisk gave public comment.

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

4. Azelaic Acid (page 219)

   Require PA to restrict use to OHP-funded conditions.

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

IV. EXECUTIVE SESSION

V. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

a. Pulmonary Arterial Hypertension Class Update (pages 59 – 84)
   ***ACTION:** recommend no changes to the PMPDP
   Motion, 2nd, All Favor. Approved.

b. Phosphate Binder Class Update and New Drug Evaluation (pages 85 – 100)
   ***ACTION:** recommend no changes to the PMPDP
   Motion, 2nd, All Favor. Approved.

c. ADHD Class Update (pages 101 – 114)
   ***ACTION:** recommend no changes to the PMPDP
   Motion, 2nd, All Favor. Approved.

d. Calcium & Vitamin D Class Update (pages 126 – 143)
   ***ACTION:** recommend removing calcitriol and derivatives from the class and designate all other calcium and vitamin D products non-preferred on the PMPDP
   Motion, 2nd, All Favor. Approved.

e. Opioid Reversal Agent Class Review (pages 144 – 154)
   ***ACTION:** recommend Naloxone auto-injector PDL – N, other formulations PDL – Y. Add class to the PMPDP

Motion, 2nd, All Favor. Approved.

f. Triptans Drug Class Scan (pages 183 – 195)
***ACTION:** recommend no changes to the PMPDP
Motion, 2nd, All Favor. Approved.

g. NSAIDs Drug Class Scan (pages 196 – 205)
***ACTION:** recommend no changes to the PMPDP
Motion, 2nd, All Favor. Approved.

h. Topical Antibiotics Drug Class Scan (pages 206 – 209)
***ACTION:** recommend no changes to the PMPDP
Motion, 2nd, All Favor. Approved.

i. Topical Antiparasitics Drug Class Scan (pages 210 – 215)
***ACTION:** recommend no changes to the PMPDP, investigate a RetroDUR proposal
Motion, 2nd, All Favor. Approved.

VI. ADJOURN

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

Pharmacy Utilization Summary Report: October 2014 - September 2015

Eligibility	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Total Members (FFS & Encounter)	1,021,045	977,740	998,873	1,027,655	1,043,479	1,059,499	1,081,244	1,078,839	1,049,644	1,030,099	1,053,977	1,051,180	1,039,440
FFS Members	132,913	140,236	139,950	157,174	140,889	134,463	130,455	132,476	126,047	135,197	145,013	138,135	137,746
OHP Basic with Medicare	29,015	29,111	29,136	29,283	29,328	29,255	29,480	29,794	29,983	30,262	30,466	30,646	29,647
OHP Basic without Medicare	23,833	21,350	18,720	18,429	17,581	16,680	16,978	16,784	16,112	15,354	14,992	14,714	17,627
ACA	80,065	89,775	92,094	109,462	93,980	88,528	83,997	85,898	79,952	89,581	99,555	92,775	90,472
Encounter Members	888,132	837,504	858,923	870,481	902,590	925,036	950,789	946,363	923,597	894,902	908,964	913,045	901,694
OHP Basic with Medicare	38,810	38,812	38,946	39,105	39,244	39,267	39,566	39,496	39,527	39,574	39,754	39,815	39,326
OHP Basic without Medicare	205,287	164,063	131,637	120,645	116,957	116,321	116,337	113,941	97,164	92,850	90,593	85,877	120,973
ACA	644,035	634,629	688,340	710,731	746,389	769,448	794,886	792,926	786,906	762,478	778,617	787,353	741,395

Gross Cost Figures for Drugs	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	YTD Sum
Total Amount Paid (FFS & Encounter)	$60,482,401	$53,630,206	$61,065,112	$62,876,159	$59,131,164	$67,269,872	$64,587,071	$64,450,814	$66,678,117	$66,100,962	$65,000,405	$65,498,852	$756,771,135
Mental Health Carve-Out Drugs	$11,545,755	$10,221,071	$11,014,645	$10,868,347	$10,363,183	$11,630,315	$11,305,867	$10,691,717	$10,932,113	$10,821,027	$10,677,035	$10,763,436	$130,834,511
OHP Basic with Medicare	$5,630	$6,949	$10,422	$10,229	$10,140	$10,995	$12,864	$11,878	$13,598	$11,082	$8,812	$3,611	$116,209
OHP Basic without Medicare	$6,274,154	$5,353,484	$5,460,993	$5,353,856	$4,997,610	$5,533,693	$5,339,094	$5,037,774	$5,094,841	$5,067,438	$4,866,542	$4,830,935	$63,210,413
ACA	$5,184,075	$4,795,522	$5,499,239	$5,471,811	$5,324,416	$6,054,539	$5,921,780	$5,614,465	$5,800,431	$5,723,225	$5,779,473	$5,899,623	$67,068,598
FFS Physical Health Drugs	$3,470,963	$3,326,293	$3,822,872	$3,883,355	$3,274,971	$3,125,962	$3,070,159	$2,856,996	$3,223,458	$3,479,545	$3,033,957	$3,217,262	$39,785,794
OHP Basic with Medicare	$246,761	$228,680	$252,356	$249,872	$227,174	$239,842	$228,025	$230,736	$232,816	$263,038	$225,706	$218,199	$2,843,205
OHP Basic without Medicare	$1,370,587	$1,209,086	$1,290,861	$1,294,806	$1,152,932	$1,167,338	$1,049,568	$949,612	$1,008,770	$991,645	$989,033	$953,819	$13,428,056
ACA	$1,770,733	$1,815,314	$2,199,305	$2,266,834	$1,819,727	$1,648,672	$1,720,461	$1,608,489	$1,911,696	$2,163,064	$1,757,647	$1,966,526	$22,648,467
FFS Physician Administered Drugs	$1,689,820	$1,398,569	$1,475,769	$1,861,608	$1,515,699	$1,781,417	$1,618,468	$1,572,741	$1,640,828	$1,599,208	$1,584,890	$1,470,317	$19,209,333
OHP Basic with Medicare	$182,016	$151,968	$230,576	$284,529	$245,748	$227,308	$291,911	$253,746	$267,061	$282,746	$273,243	$276,877	$2,967,728
OHP Basic without Medicare	$429,306	$503,693	$286,757	$368,768	$303,421	$344,732	$406,258	$247,313	$385,423	$244,257	$312,171	$280,485	$4,112,585
ACA	$877,464	$575,178	$779,804	$964,378	$819,761	$1,002,613	$697,970	$874,688	$728,455	$865,415	$776,570	$699,925	$9,662,220
Encounter Physical Health Drugs	$36,288,955	$32,526,268	$37,352,253	$39,197,231	$37,478,922	$42,816,109	$40,855,025	$41,872,850	$43,024,423	$42,238,192	$42,169,417	$42,600,239	$478,419,884
OHP Basic with Medicare	$200,505	$200,808	$197,179	$256,990	$242,596	$247,628	$275,801	$267,863	$280,483	$202,208	$212,016	$145,132	$2,729,210
OHP Basic without Medicare	$14,263,349	$11,829,606	$12,703,631	$12,479,051	$11,507,016	$12,776,306	$12,308,401	$12,410,496	$12,476,123	$12,298,160	$12,032,897	$11,814,537	$148,899,573
ACA	$21,507,378	$20,198,267	$24,252,793	$26,199,565	$25,554,934	$29,598,380	$28,103,963	$29,017,400	$30,139,083	$29,602,270	$29,790,616	$30,477,074	$324,441,724
Encounter Physician Administered Drugs	$7,486,907	$6,158,006	$7,399,573	$7,065,619	$6,498,389	$7,916,069	$7,737,551	$7,456,511	$7,857,294	$7,962,990	$7,535,107	$7,447,597	$88,521,613
OHP Basic with Medicare	$207,725	$152,372	$166,921	$232,150	$195,919	$180,188	$186,892	$169,577	$164,069	$162,748	$124,937	$169,114	$2,112,611
OHP Basic without Medicare	$2,636,122	$2,224,458	$2,325,155	$2,275,085	$2,008,867	$2,503,768	$2,326,781	$2,106,517	$2,325,095	$2,349,169	$1,972,732	$1,870,932	$26,924,681
ACA	$4,382,050	$3,614,102	$4,722,891	$4,382,401	$4,169,418	$5,043,586	$5,091,927	$5,065,874	$5,179,821	$5,321,143	$5,358,223	$5,312,919	$57,644,356

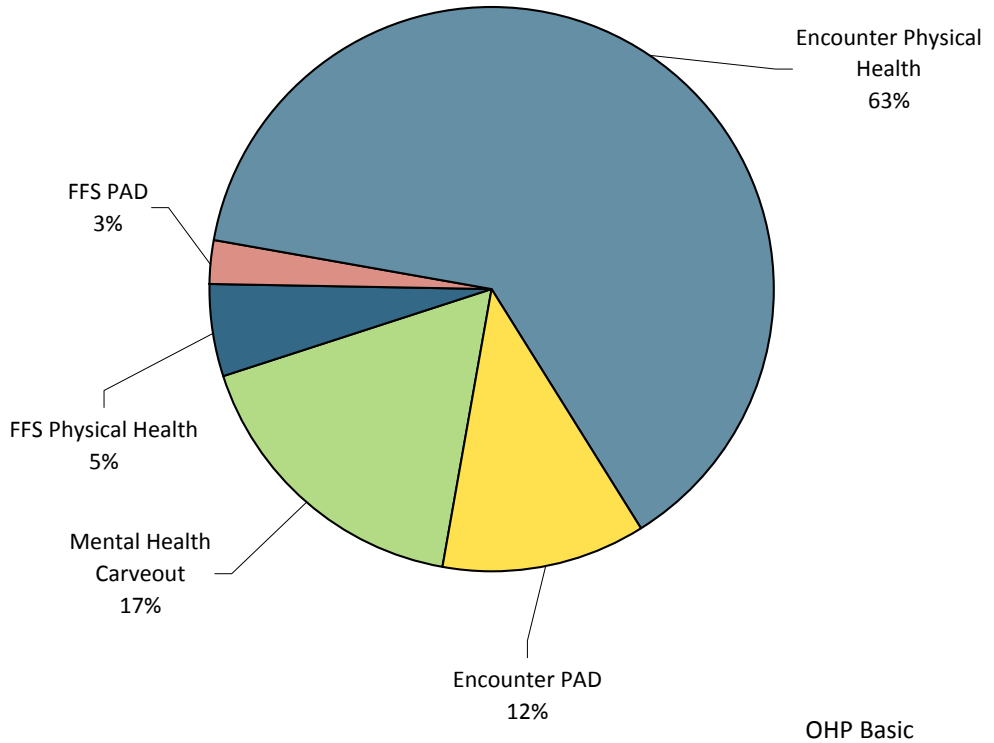
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

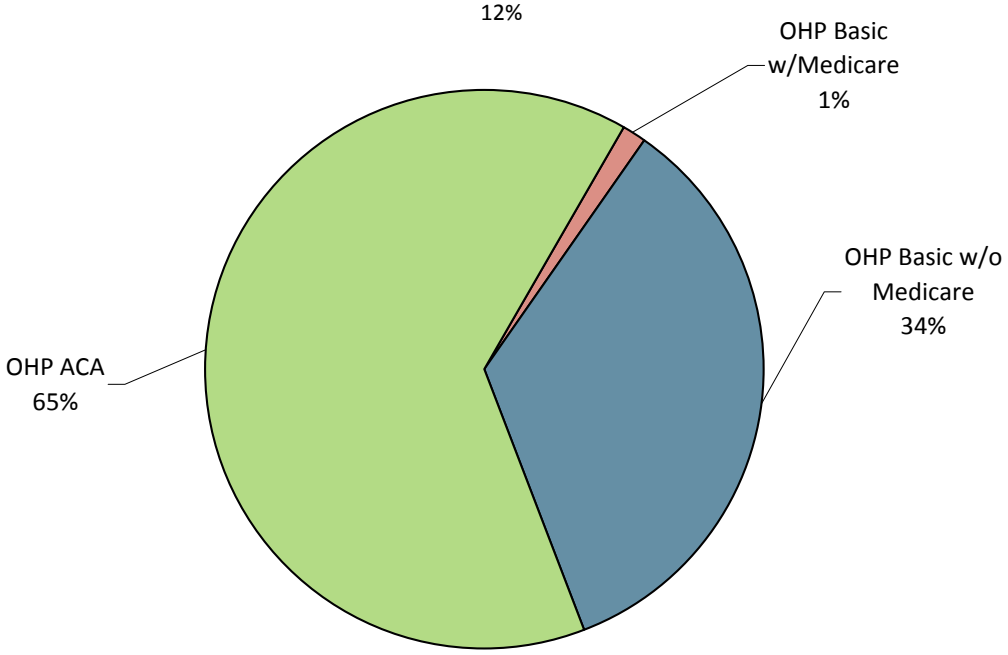
Last Updated: April 28, 2016

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

Pharmacy Utilization Summary Report: October 2014 - September 2015

YTD Percent Paid Amounts





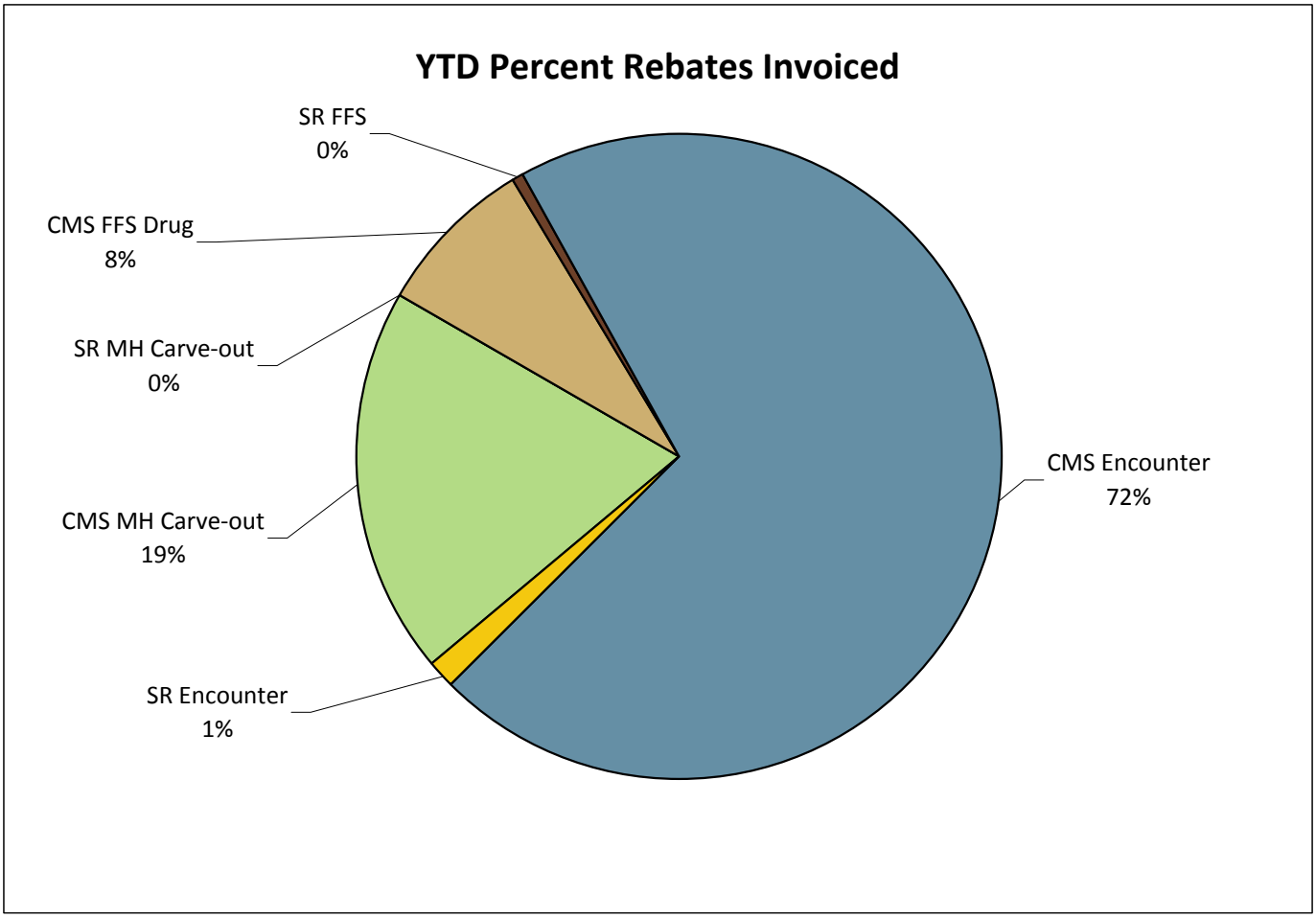
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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

Pharmacy Utilization Summary Report: October 2014 - September 2015

Quarterly Rebates Invoiced	2014-Q4	2015-Q1	2015-Q2	2015-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$75,559,371	$90,317,848	$96,965,410	$96,702,587	$359,545,216
CMS MH Carve-out	$15,183,164	$18,443,216	$18,968,489	$17,383,620	$69,978,488
SR MH Carve-out	$64,652				$64,652
CMS FFS Drug	$6,545,185	$7,218,763	$6,124,949	$9,439,245	$29,328,141
SR FFS	$257,781	$254,210	$222,397	$292,108	$1,026,496
CMS Encounter	$52,440,657	$63,520,362	$70,366,887	$68,016,528	$254,344,435
SR Encounter	$1,067,932	$881,296	$1,282,688	$1,571,086	$4,803,003

Quaterly Net Drug Costs	2014-Q4	2015-Q1	2015-Q2	2015-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$99,618,349	$98,959,348	$98,750,591	$99,897,632	$397,225,919
Mental Health Carve-Out Drugs	$17,533,656	$14,418,629	$13,961,208	$14,877,878	$60,791,371
FFS Phys Health + PAD	$8,381,320	$7,970,038	$7,635,304	$4,653,827	$28,640,489
Encounter Phys Health + PAD	$73,703,372	$76,570,680	$77,154,079	$80,365,927	$307,794,059



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

Last Updated: April 28, 2016

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

Pharmacy Utilization Summary Report: October 2014 - September 2015

PMPM Drug Costs (Rebates not Included)	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$59.24	$54.85	$61.13	$61.18	$56.67	$63.49	$59.73	$59.74	$63.52	$64.17	$61.67	$62.31	$60.64
Mental Health Carve-Out Drugs	$11.31	$10.45	$11.03	$10.58	$9.93	$10.98	$10.46	$9.91	$10.42	$10.50	$10.13	$10.24	$10.49
FFS Physical Health Drugs	$26.11	$23.72	$27.32	$24.71	$23.25	$23.25	$23.53	$21.57	$25.57	$25.74	$20.92	$23.29	$24.08
FFS Physician Administered Drugs	$12.71	$9.97	$10.54	$11.84	$10.76	$13.25	$12.41	$11.87	$13.02	$11.83	$10.93	$10.64	$11.65
Encounter Physical Health Drugs	$40.86	$38.84	$43.49	$45.03	$41.52	$46.29	$42.97	$44.25	$46.58	$47.20	$46.39	$46.66	$44.17
Encounter Physician Administered Drugs	$8.43	$7.35	$8.61	$8.12	$7.20	$8.56	$8.14	$7.88	$8.51	$8.90	$8.29	$8.16	$8.18

Claim Counts	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Total Claim Count (FFS & Encounter)	1,011,568	892,993	1,017,681	1,029,208	963,502	1,069,046	1,063,007	1,032,003	1,038,242	1,015,449	1,003,237	1,015,858	1,012,650
Mental Health Carve-Out Drugs	148,376	132,273	151,760	148,733	139,073	154,438	154,149	148,814	152,199	152,180	150,978	151,853	148,736
FFS Physical Health Drugs	80,323	76,044	81,276	83,918	70,340	72,809	70,967	68,496	72,311	73,666	67,651	69,915	73,976
FFS Physician Administered Drugs	13,738	12,627	13,362	16,134	13,266	13,957	14,451	14,173	15,144	15,582	14,583	14,617	14,303
Encounter Physical Health Drugs	687,848	602,618	694,955	703,071	668,393	743,803	737,507	716,143	713,608	692,850	690,397	700,265	695,955
Encounter Physician Administered Drugs	81,283	69,431	76,328	77,352	72,430	84,039	85,933	84,377	84,980	81,171	79,628	79,208	79,680

Amount Paid per Claim (Rebates not Included)	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$59.79	$60.06	$60.00	$61.09	$61.37	$62.93	$60.76	$62.45	$64.22	$65.10	$64.79	$64.48	$62.25
Mental Health Carve-Out Drugs	$77.81	$77.27	$72.58	$73.07	$74.52	$75.31	$73.34	$71.85	$71.83	$71.11	$70.72	$70.88	$73.36
FFS Physical Health Drugs	$43.21	$43.74	$47.04	$46.28	$46.56	$42.93	$43.26	$41.71	$44.58	$47.23	$44.85	$46.02	$44.78
FFS Physician Administered Drugs	$123.00	$110.76	$110.45	$115.38	$114.25	$127.64	$112.00	$110.97	$108.35	$102.63	$108.68	$100.59	$112.06
Encounter Physical Health Drugs	$52.76	$53.97	$53.75	$55.75	$56.07	$57.56	$55.40	$58.47	$60.29	$60.96	$61.08	$60.83	$57.24
Encounter Physician Administered Drugs	$92.11	$88.69	$96.94	$91.34	$89.72	$94.20	$90.04	$88.37	$92.46	$98.10	$94.63	$94.03	$92.55

Amount Paid per Claim - Multi Source Drugs (Rebates not Included)	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$29.63	$29.71	$27.97	$28.51	$28.93	$28.97	$27.64	$28.11	$28.15	$27.85	$27.59	$27.72	$28.40
Mental Health Carve-Out Drugs	$63.41	$62.65	$56.54	$56.12	$57.38	$57.78	$55.49	$54.13	$53.49	$51.87	$51.26	$50.98	$55.92
FFS Physical Health Drugs	$22.17	$22.44	$22.98	$23.42	$22.62	$22.37	$21.54	$21.57	$21.00	$22.13	$21.41	$21.74	$22.12
Encounter Physical Health Drugs	$22.90	$23.11	$22.10	$23.07	$23.49	$23.45	$22.22	$23.16	$23.30	$23.01	$22.84	$23.07	$22.98

Amount Paid per Claim - Single Source Drugs (Rebates not Included)	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$392.82	$419.70	$444.19	$448.07	$466.02	$481.63	$476.20	$498.99	$517.15	$530.56	$524.35	$484.53	$473.68
Mental Health Carve-Out Drugs	$430.40	$435.72	$450.76	$470.29	$470.76	$478.63	$480.88	$478.31	$493.52	$510.14	$514.25	$522.36	$478.00
FFS Physical Health Drugs	$300.21	$311.23	$349.42	$319.72	$349.28	$307.30	$324.16	$302.02	$349.17	$375.40	$353.06	$354.74	$332.98
Encounter Physical Health Drugs	$399.12	$431.22	$454.55	$461.33	$478.00	$499.16	$490.44	$520.58	$537.05	$549.43	$541.70	$491.96	$487.88

Multi-Source Drug Use Percentage	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Multi-Source Drug Use Percentage	92.7%	93.0%	93.2%	93.1%	93.3%	93.3%	93.4%	93.4%	93.3%	93.3%	93.2%	92.6%	93.1%
Mental Health Carve-Out Drugs	96.1%	96.1%	95.9%	95.9%	95.9%	95.8%	95.8%	95.8%	95.8%	95.8%	95.8%	95.8%	95.9%
FFS Physical Health Drugs	92.4%	92.6%	92.6%	92.3%	92.7%	92.8%	92.8%	92.8%	92.8%	92.9%	92.9%	92.7%	92.7%
Encounter Physical Health Drugs	92.1%	92.4%	92.7%	92.5%	92.8%	92.8%	92.9%	92.9%	92.8%	92.8%	92.6%	91.9%	92.6%

Preferred Drug Use Percentage	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Avg Monthly
Preferred Drug Use Percentage	86.48%	86.44%	86.49%	86.72%	86.60%	86.56%	86.52%	86.45%	86.48%	86.33%	86.45%	86.45%	86.5%
Mental Health Carve-Out Drugs	77.04%	77.12%	76.83%	76.97%	76.76%	76.94%	76.81%	76.71%	76.57%	76.24%	76.38%	76.26%	76.7%
FFS Physical Health Drugs	94.58%	94.83%	94.60%	94.99%	94.80%	94.60%	94.61%	94.59%	94.89%	95.23%	95.40%	95.42%	94.9%
Encounter Physical Health Drugs	87.74%	87.56%	87.74%	87.88%	87.87%	87.83%	87.82%	87.74%	87.79%	87.54%	87.71%	87.72%	87.7%

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

Last Updated: April 28, 2016

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

Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2016

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ABILIFY	Antipsychotics, 2nd Gen	$7,895,493	17.3%	8,106	$974	V
2	LATUDA	Antipsychotics, 2nd Gen	$3,184,201	7.0%	3,379	$942	V
3	ABILIFY	Antipsychotics, 2nd Gen	$2,018,902	4.4%	2,181	$926	Y
4	SEROQUEL XR	Antipsychotics, 2nd Gen	$1,913,134	4.2%	3,022	$633	V
5	STRATTERA	ADHD Drugs	$1,846,734	4.0%	4,950	$373	Y
6	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,252,207	2.7%	801	$1,563	V
7	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$788,620	1.7%	2,884	$273	V
8	INVEGA	Antipsychotics, 2nd Gen	$661,487	1.4%	629	$1,052	V
9	DULOXETINE HCL	Antidepressants	$627,071	1.4%	25,246	$25	V
10	FLUOXETINE HCL	Antidepressants	$598,893	1.3%	32,073	$19	Y
11	ABILIFY MAINTENA	Antipsychotics, Parenteral	$546,054	1.2%	342	$1,597	V
12	SAPHRIS	Antipsychotics, 2nd Gen	$484,969	1.1%	881	$550	V
13	BUPROPION XL	Antidepressants	$474,584	1.0%	17,448	$27	V
14	SERTRALINE HCL	Antidepressants	$460,991	1.0%	39,746	$12	Y
15	HARVONI	Hepatitis C - Direct Acting Antivirals	$453,631	1.0%	16	$28,352	Y
16	PRISTIQ ER	Antidepressants	$448,051	1.0%	1,566	$286	V
17	RISPERDAL CONSTA	Antipsychotics, Parenteral	$446,238	1.0%	621	$719	Y
18	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$419,971	0.9%	1,216	$345	V
19	TRAZODONE HCL	Antidepressants	$385,455	0.8%	38,527	$10	
20	DIVALPROEX SODIUM ER	Antiepileptics (oral & rectal)	$361,019	0.8%	4,299	$84	Y
21	VENLAFAXINE HCL ER	Antidepressants	$345,527	0.8%	1,948	$177	V
22	AMITRIPTYLINE HCL	Antidepressants	$339,509	0.7%	17,867	$19	Y
23	Factor Viii Recombinant Nos	Physican Administered Drug	$303,890	0.7%	10	$30,389	
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	$297,971	0.7%	20,810	$14	Y
25	VIIBRYD	Antidepressants	$281,509	0.6%	1,295	$217	V
26	CITALOPRAM HBR	Antidepressants	$278,516	0.6%	30,787	$9	Y
27	ESCITALOPRAM OXALATE	Antidepressants	$260,253	0.6%	19,745	$13	Y
28	ENBREL	Biologics for RA, Psoriasis and Crohn's Disease	$255,654	0.6%	82	$3,118	Y
29	LANTUS	Diabetes, Insulins	$246,636	0.5%	797	$309	Y
30	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$244,616	0.5%	629	$389	Y
31	Infliximab Injection	Physican Administered Drug	$244,376	0.5%	127	$1,924	
32	VENLAFAXINE HCL ER	Antidepressants	$236,332	0.5%	14,932	$16	Y
33	BUPROPION HCL SR	Antidepressants	$229,759	0.5%	11,608	$20	Y
34	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$223,787	0.5%	13,379	$17	
35	NUVIGIL	Other Stimulants	$221,722	0.5%	372	$596	V
36	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$220,087	0.5%	2,142	$103	
37	QUETIAPINE FUMARATE	Antipsychotics, 2nd Gen	$216,888	0.5%	11,999	$18	Y
38	INVEGA TRINZA	Antipsychotics, Parenteral	$215,418	0.5%	46	$4,683	V
39	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$209,010	0.5%	3,848	$54	Y
40	METHYLPHENIDATE ER	ADHD Drugs	$204,592	0.4%	1,650	$124	N
		Top 40 Aggregate:	**$30,343,755**		**342,006**	**$2,024**	
		All FFS Drugs Totals:	**$45,761,878**		**708,134**	**$372**	

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

Last updated: April 28, 2016

ProDUR Report for January through March 2016

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	46	14	0	32	0.05%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,888	389	1	1,498	1.63%
DD (Drug/Drug Interaction)	Set alert/Pay claim	196	58	0	138	0.10%
ER (Early Refill)	Set alert/Deny claim	79,148	13,927	180	65,017	69.60%
ID (Ingredient Duplication)	Set alert/Pay claim	21,298	5,358	13	15,905	18.63%
LD (Low Dose)	Set alert/Pay claim	854	142	0	707	0.73%
LR (Late Refill/Underutilization)	Set alert/Pay claim	70	37	0	33	0.05%
MC (Drug/Disease Interaction)	Set alert/Pay claim	153	40	1	112	0.09%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	1,122	277	8	836	0.93%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	1,479	835	2	642	1.23%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,464	2,126	4	5,330	6.53%
	Totals	**113,718**	**23,203**	**209**	**90,250**	**99.59%**

ProDUR Report for January through March 2016

Top Drugs in Early Refill

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
DC	Diazepam	131	29	102	11,826	1.1%	22.1%
	Haloperidol	259	57	202	2,692	9.6%	22.0%
	Wellbutrin (Bupropion)	903	130	773	41,233	2.2%	14.4%
DD	Geodon (Ziprasidone)	68	23	45	4,915	1.4%	33.8%
ER	Remeron (Mirtazapine)	1,130	155	975	9,756	11.6%	13.7%
	Hydrocodone/APAP	183	67	116	7,501	2.4%	36.6%
	Oxycodone	304	121	183	6,341	4.8%	39.8%
	Lorazepam	1,698	354	1,344	26,588	6.4%	20.8%
	Alprazolam	1,279	222	1,057	20,006	6.4%	17.4%
	Lamictal (Lamotrigine)	3,993	714	3,279	30,976	12.9%	17.9%
	Abilify (Aripiprazole)	2,383	397	1,986	22,524	10.6%	16.7%
	Seroquel (Quetiapine)	2,982	532	2,449	21,567	13.8%	17.8%
	Risperdal (Risperidone)	2,099	405	1,694	15,234	13.8%	19.3%
	Wellbutrin (Bupropion)	3,735	466	3,269	41,233	9.1%	12.5%
	Zoloft (Sertraline)	5,250	931	4,319	50,139	10.5%	17.7%
	Prozac (Fluoxetine)	3,771	541	3,230	40,443	9.3%	14.3%
	Celexa (Citalopram)	3,376	456	2,920	37,611	9.0%	13.5%
	Trazodone	5,285	819	4,466	48,502	10.9%	15.5%
	Cymbalta (Duloxetine)	3,317	502	2,815	32,810	10.1%	15.1%
ID	Lamictal (Lamotrigine)	1,339	308	1,031	30,976	4.3%	23.0%
	Seroquel (Quetiapine)	1,390	324	1,060	21,567	6.4%	23.3%
	Risperdal (Risperidone)	895	250	645	15,234	5.9%	27.9%
	Zoloft (Sertraline)	1,187	302	883	50,139	2.4%	25.4%
	Prozac (Fluoxetine)	944	193	751	40,443	2.3%	20.4%
PG	Lorazepam	233	167	66	26,588	0.9%	71.7%
	Alprazolam	151	112	38	20,006	0.8%	74.2%
TD	Lamictal (Lamotrigine)	556	133	423	30,976	1.8%	23.9%
	Depakote (Divalproex Sodium)	401	129	272	13,973	2.9%	32.2%
	Seroquel (Quetiapine)	674	153	518	21,567	3.1%	22.7%
	Zyprexa (Olanzapine)	509	129	380	13,609	3.7%	25.3%
	Risperdal (Risperidone)	404	129	275	15,234	2.7%	31.9%

ProDUR Report for January through March 2016

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	1,130	155	9,756	2	10	56	6	81	0
	Hydrocodone/APAP	183	67	7,501	1	1	42	0	23	0
	Oxycodone	304	121	6,341	0	5	72	0	44	0
	Lorazepam	1,698	354	26,588	5	7	174	2	166	0
	Alprazolam	1,279	222	20,006	6	11	110	2	93	0
	Lamictal (Lamotrigine)	3,993	714	30,976	27	33	327	3	324	0
	Abilify (Aripiprazole)	2,383	397	22,524	7	22	141	6	221	0
	Seroquel (Quetiapine)	2,982	532	21,567	10	40	192	5	285	0
	Risperdal (Risperidone)	2,099	405	15,234	5	13	145	5	237	0
	Wellbutrin (Bupropion)	3,735	466	41,233	16	39	170	5	236	0
	Zoloft (Sertraline)	5,250	931	50,139	32	43	468	13	375	0
	Prozac (Fluoxetine)	3,771	541	40,443	18	31	231	9	252	0
	Celexa (Citalopram)	3,376	456	37,611	19	29	140	6	232	1
	Trazodone	5,285	819	48,502	17	57	338	16	390	1
	Cymbalta (Duloxetine)	3,317	502	32,810	13	30	211	7	241	0

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

Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	26	42	12	0
		Profiles Sent	10	18	3	0
		Responses Received	4	10	2	0
		Response Rate	40%	56%	67%	0
		Information Useful or Will Change Practice	4	6	2	0
		Patient Not With Office	0	0	0	0
		Already Scheduled	3	7	2	0
		Will Not Schedule	0	0	0	0
		Requested No Future Notifications	0	1	0	0
	Antipsychotic Metabolic Monitoring	Members Identified	61	728	0	0
		Profiles Sent	60	727	0	0
		Members With Response	1	176	0	0
		Response Rate	2%	24%	0	0
		Newly Scheduled	0	92	0	0
		Provider Contacted	55	274	0	0
		Provider Responses	1	58	0	0
		Provider Agreed with Recommendation	1	25	0	0
		Patient Not With Office	0	26	0	0

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

Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Profile Review	Children under age 12 antipsychotic	Profiles Reviewed	87	131	61	0
	Children under age 18 on 3 or more psychotropics	Profiles Reviewed	14	27	6	0
	Children under age 18 on any psychotropic	Profiles Reviewed	99	155	48	0
	Children under age 6 on any psychotropic	Profiles Reviewed	14	15	10	0
	Lock-In	Profiles Reviewed	89	57	7	0
		Letters Sent To Providers	0	1	1	0
		Provider Responses	0	0	0	0
		Provider Agreed / Found Info Useful	0	0	0	0
		Locked In	15	23	1	0

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

Retro-DUR Intervention History by Quarter FFY 2015 - 2016

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul-Sep
Safety Net	ICS/LABA	Disqualified	13	2	3	0
		Disqualified - TPL coordination issue	5	0	0	0
		Disqualified - Other	1	0	0	0
		Disqualified - No Provider Info	3	0	0	0
		Disqualified - Erroneous denial	4	2	3	0
		Faxes Sent	7	5	3	0
		Fax Sent - SABA	0	2	1	0
		Fax Sent - Controller	2	0	2	0
		Fax Sent - Combination Inhaler	4	2	0	0
		No Subsequent Pulmonary Claims	1	1	0	0

Oregon State University
College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

Pediatric Psychotropic Quarterly Report

All OHP

Fiscal Year 2015 - 2016

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	1,076	2,402	45%									
Five or more concurrent psychotropics	188	10,624	2%									
Three or more concurrent psychotropics	1,985	10,624	19%									
Two or More Concurrent Antipsychotics	97	10,624	1%									
Under 18 years old on any antipsychotic	2,419	10,624	23%									
Youth five years and younger on psychotropics	143	10,624	1%									

5/16/2016

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.

Oregon State University
College of Pharmacy

Drug Use Research & Management Program

OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-107
Phone 503-947-5220 | Fax 503-947-1119

Pediatric Psychotropic Quarterly Report

Fee For Service

Fiscal Year 2015 - 2016

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	271	452	60%									
Five or more concurrent psychotropics	31	2,138	1%									
Three or more concurrent psychotropics	332	2,138	16%									
Two or More Concurrent Antipsychotics	17	2,138	1%									
Under 18 years old on any antipsychotic	442	2,138	21%									
Youth five years and younger on psychotropics	35	2,138	2%									

5/16/2016

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.

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
February 2016 Volume 6, Issue 1

2015 in Review: Relevant Safety Updates and Ongoing Safety Concerns

By Megan Herink, Pharm.D, BCPS, Oregon State University College of Pharmacy, Drug Use Research and Management

The U.S. Food and Drug Administration (FDA) issues drug alerts and drug safety communications to help patients and practitioners stay abreast of rapidly changing medical knowledge. These communications may or may not have serious consequences as to how patients, caretakers, and prescribers respond. However, these alerts are important to increase safety awareness and initiate a dialogue between patients and providers.

Typically, drugs are FDA approved based on relatively short-term trials that are not designed to evaluate safety end points. Furthermore, for some drugs, assessing a postmarketing safety signal can be challenging due to lack of robust evidence, leaving a potentially harmful drug on the market. Over the past 9 years, the FDA has taken a more proactive approach to the reporting of potential adverse effects, readily disseminating preliminary information regarding drug safety issues as the information becomes available. With this increased transparency, however, it is important to place these safety alerts in context and to consider them not as conclusive mandates. This article will review some of the more relevant FDA drug safety alerts and ongoing safety concerns of 2015.

2015 New Drug Safety Alerts Resulting In Drug Labeling Changes

In May 2015, the FDA warned that the sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin) used in the treatment of type 2 diabetes (T2D), may cause ketoacidosis requiring hospitalization.[1] The concern originated from 20 reported cases of reported diabetic ketoacidosis (DKA), ketoacidosis, or ketosis that resulted in emergency room or hospital visits. SGLT2 inhibition causes a rapid increase in urinary glucose excretion including losses from daily carbohydrate availability.[5] This results in an increased use of fat oxidation for energy production and eventually ketosis. Unlike the more typical presentation of DKA, many of these were accompanied by only mild to moderately elevated blood sugar levels (euglycemic DKA). The European Medicines Agency (EMA) further corroborated this risk.[2]

After a further safety review, the FDA added a warning to the label about the risks of ketoacidosis and of serious urinary tract infections.[3] From March 2013 to May 2015, 73 cases of ketoacidosis were reported in the FDA Adverse Event Reporting System (FAERS) database with the use of the SGLT2 inhibitors. In all of these cases, patients were hospitalized or treated in the emergency room. The median time from drug initiation or dose change to symptoms was 43 days. Although these agents are currently only approved for T2D, fifteen cases were reported in patients with type 1 diabetes (T1D). The FDA also warned about serious urinary tract infections or urosepsis resulting in hospitalization that was reported in 19 cases from March 2013 through October 2014. [3]

Overall, the absolute risk of DKA in T2D associated with the use of SGLT2 inhibitors is relatively low.[4] However, patients and practitioners should be aware of the risk as well as patient specific risk factors. The cause of ketoacidosis is usually multifactorial and potential contributing factors are concurrent illness, reduced food and fluid intake, reduced insulin doses, discontinuation of an oral insulin secretagogue, T1D or patients with long-standing T2D with marked B-cell insufficiency, and history of alcohol intake.[5] In addition, because of the lack of accompanying severe hyperglycemia, euglycemic DKA can easily go unrecognizable by patients and providers.[6] Any patients with diabetes who experiences nausea, vomiting, shortness of breath or malaise on a SGLT2 inhibitor should be evaluated for ketosis, despite a normal glucose level. All patients taking SGLT2 inhibitors should be advised to check their ketone levels whenever they feel unwell, regardless of their glucose level. If ketones are detected, patients should be directed to seek immediate medical care, as it can be difficult to reverse at home. There are currently ongoing, long-term randomized controlled trials evaluating the use of SGLT2 inhibitors in T1D and insulin-treated T2D to help quantify the risk in these populations. Furthermore, in September 2015, the FDA also released a safety communication strengthening the warning for the SGLT2 inhibitor canagliflozin and the increased risk of bone fractures and decreased bone mineral density.[7] SGLT2 inhibitors increase concentrations of phosphate through increased tubular reabsorption, which can adversely affect the bone.[8] Confirmatory data from nine pooled clinical trials resulted in incidence rates of bone fractures of 1.4 and 1.5 per 100 patient-years of exposure for canagliflozin 100 mg and 300 mg, respectively. This is compared to a rate of 1.1 per 100 patient-years seen in the comparator group including placebo and active comparators. Fractures occurred as early as 12 weeks after initiation of therapy and were more likely to be from low trauma and affect the upper extremities. The FDA is continuing to assess the risk of fractures with the other SGLT2 inhibitors, including dapagliflozin and empagliflozin to determine if this is a class effect. The FDA also added new information about decreased bone mineral density at the hip and lower spine based on data from a postmarketing double blind placebo controlled trial in elderly patients with T2D (n=714). [7]

The FDA added a new Warning and Precaution that the dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin and alogliptin) may cause joint pain that can be severe and disabling.[9] Cases have been reported in the literature as well as the FAERS database that have started anywhere from 1 day to years after starting a DPP-4 inhibitor.[9,10,11] Symptoms resolve after discontinuation of the medication.

NSAIDs have been pivotal drugs for the treatment of pain management and are available by prescription and over the counter. However, ever since refocoxib was withdrawn from the market in 2004, the cardiovascular (CV) safety of the class has been uncertain.[12] After a recent review of the current safety data, the FDA opted to strengthen the label warning that non-aspirin NSAIDs do in fact increase the chance of a heart attack and stroke.[13] A review of a meta-analysis of RCTs[14] and observational trials were reviewed by the FDA Advisory Committee in 2014.[15] Based on this review, the following conclusions were made: 1) A multitude of studies support the finding that NSAIDs can cause serious CV thrombotic events (relative risk [RR] 10% - 50%) and this risk is also evident in healthy individuals; 2) It appears there could be a significant risk within days to weeks of initiation and there may be a higher risk with longer NSAID use; 3) Some observational data suggests that naproxen may have a lower CV risk compared to other NSAIDs. However, this is based on limited data from studies not designed to compare the safety of one NSAID to another. The ongoing randomized safety trial comparing CV events with celecoxib, naproxen and ibuprofen among high CV risk patients[16] will help determine if there are differences between individual agents; and 4) There is an approximately two-fold increase in hospitalizations due to heart failure with use of both COX-2 selective and nonselective NSAIDs.

Other notable FDA warnings that resulted in label changes include the safety caution of possible increased risk of heart attack and stroke with use of testosterone products.[17] Further definitive high quality studies are needed to confirm this risk as the current data is conflicting and has many limitations.[18]
There were also two new concerns regarding treatments for hepatitis C. In March, the FDA warned of an increased risk of symptomatic bradycardia when sofosbuvir, with or without another direct acting antiviral, is used in combination with amiodarone.[19] In October 2015, the FDA released a drug safety communication warning that hepatitis C treatments ombitasvir, paritaprevir and ritonavir +/- dasabuvir (Viekira Pak® and Technivie®) can cause serious liver injury, mostly in patients with underlying advanced liver disease.[20] As a result, drug labeling was updated to include this risk.
Lastly, the FDA made changes to the varenicline drug label warning that the prescription smoking cessation medication may react with alcohol, resulting in decreased tolerance or aggressive behavior. Rate reports of seizures were also reported.[21] None of the cases involved excessive amounts of alcohol.

2015 Ongoing Safety Investigations

Tramadol and codeine in children

The FDA is investigating the use of tramadol and codeine cough and cold medicines in children <18 y/o because of the risk of respiratory depression in children.[22,23] Although tramadol is not FDA-approved for use in children, it can be used off-label in this population. The FDA warns of a concern with both agents post-operatively after tonsillectomy and/or adenoidectomy. The risk with is thought to be increased as a result of some children being ultra-rapid metabolizers and subsequently having higher levels of the active form of the opioid than usual. Codeine is converted to morphine and tramadol to its active form (O-desmethyltramadol) in the liver by the cytochrome P450 CYP2D6 enzyme. Higher levels of the active opioid can lead to respiratory depression and possibly death. Fifteen deaths or overdoses of children who received standard doses of codeine have been reported in the U.S; all of which were found to have very elevated levels of morphine in their blood.[23,24] Since routine genotype testing is not recommended to assess for ultra-rapid metabolizers, tramadol and codeine should be avoided in children (particularly those under 12 years of age) and only used if the benefits clearly outweigh the risks.

Rosiglitazone

After continued monitoring of rosiglitazone for the treatment of T2D, the FDA has eliminated the Risk Evaluation and Mitigation Strategy (REMS) which put prescribing restrictions in place due to the suggested increased risk of myocardial infarction (MI) with rosiglitazone.[25] In 2013, the FDA determined that the readjudicated results from the RECORD trial did not show an increased risk of MI with rosiglitazone compared to metformin and sulfonylureas.[26] Since 2013, no new pertinent safety information was identified and as a result, the FDA has deemed the REMS is no longer necessary.

Risk of cancer or death from cancer with clopidogrel

In 2014, results from the Dual Antiplatelet (DAPT) trial suggested a reduction in cardiovascular and cerebrovascular events, but also a possible increased risk of cancer or death from cancer from the long-term use (30 months) of clopidogrel following placement of a drug-eluting stent compared to 12 months.[27] The increased risk of death was seen in patients given clopidogrel, but not those given prasugrel. However, in November 2015, the FDA determined that the long-term use of clopidogrel does not increase the overall risk of death in patients with high CV risk.[28] A meta-analysis of other long term clinical trials did not result in a change in the overall risk of death with long-term DAPT (12 months or longer) with clopidogrel and aspirin compared to short-term (6 months or less) or aspirin alone (6.7% vs. 6.6%; respectively). There was also no apparent increase in the risk of cancer-related adverse events (4.2% vs. 4.0%) or cancer-related deaths (0.9% vs. 1.1%) with long term DAPT compared to short term DAPT, respectively. The American College of Cardiology/American Heart Association currently recommends DAPT for at least 12 months after drug eluting stent implantation.

Peer Reviewed By: Jonathan White, Pharm D, BCPS, Clinical Pharmacy Specialist, Primary Care, Providence Medical Group and Andrew Gibler, Pharm.D., Oregon State University College of Pharmacy Drug Use Research and Management

References

1. US Food and Drug Administration: Drug Safety and Availability - FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm.
2. European Medicines Agency. Review of diabetes medicines called SGLT2 inhibitors started: risk of diabetic ketoacidosis to be examined [Internet],12 June 2015.
3. US Food and Drug Administration: Drug Safety and Availability: FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm.
4. Erondu N, Desai M, Ways K, et al. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Dia Care. July 2015:dc151251.
5. Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care. 2015;38(9):1638-1642.
6. Peters AL, Buschur EO, Buse JB, et al. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015;38(9):1687-1693.
7. US Food and Drug Administration. Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density. September 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm.
8. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol. 2015;3(1):8-10.
9. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. August 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm.
10. Sasaki T, Hiki Y, Nagumo S, et al. Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP-4) inhibitor to patients with diabetes mellitus. Diabetol Int. 2010;1(2):90-92.
11. Crickx E, Marroun I, Veyrie C, et al. DPP4 inhibitor-induced polyarthritis: a report of three cases. Rheumatol Int. 2014;34(2):291-292.
12. Trelle S, Reichenbach S, Wandel S, Hildebrand P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342(7789), p. 154
13. US Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. July 2015. Available at http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.
14. Bhala N, Emberson J, et al Coxib and traditional NSAID Trialists' (CNT) Collaboration, Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382(9894):769-779.
15. Food and Drug Administration [Internet]. Silver Spring, MD. FDA Briefing Information for the February 10-11, 2014 Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM383180.pdf.
16. Becker MC, Wang TH, Wisniewski L, et al. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. Am Heart J. 2009;157(4):606-612.
17. US Food and Drug Administration: FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm.
18. Goodman N, Guay A, Dandona P, et al. American Association Of Clinical Endocrinologists And American College Of Endocrinology Position Statement On The Association Of Testosterone And Cardiovascular Risk. Endocr Pract. 2015;21(9):1066-1073.
19. US Food and Drug Administration: FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm.
20. FDA Drug Safety Communication. FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. 10/22/15. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm.
21. US Food and Drug Administration: FDA Drug Safety Communication: FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm.
22. US Food and Drug Administration: FDA Drug Safety Communication: FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger. September 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm462991.htm.
23. US Food and Drug Administration: FDA Drug Safety Communication: FDA evaluating the potential risks of using codeine cough-and-cold medicines in children. July 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm453125.htm.
24. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361(8):827-828..
25. US Food and Drug Administration: Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS). December 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm477601.htm. 26. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-2135.
27. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine. 2014;371(23):2155-2166.
28. US Food and Drug Administration: FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death. November 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm471286.htm.

THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE
http://pharmacy.oregonstate.edu/drug-policy/newsletter
March 2016 Volume 6, Issue 2

Antidiabetic Treatments and Cardiovascular Implications

By Megan Herink, Pharm.D, BCPS and Kathy Sentena, Pharm.D., both from Oregon State University College of Pharmacy, Drug Use Research and Management

The incidence of diabetes among Oregon Health Plan (OHP) members is approximately 19%, costing $106 million dollars on an annual basis.[1] A major contributor to the morbidity of these patients is the high incidence of cardiovascular disease (CVD).[2] Improving glycemic control has been shown to have microvascular benefits, but evidence of macrovascular benefits (e.g., cardiovascular [CV] outcomes) remain scarce. This newsletter will review the potential CV effects associated with the most common diabetes medications.

Metformin

The beneficial CV effects of metformin have been debated in the literature. The original data suggesting positive CV outcomes with metformin came from the United Kingdom Prospective Diabetes Study (UKPDS) in 1998.[3] The UKPDS trial showed a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance.[3] After 10 years of follow-up, those originally randomly assigned to intensive glycemic control with metformin had significant long term reductions in myocardial infarction (MI) (Risk Ratio [RR] 0.67; 95% CI 0.51-0.89; ARR 6.3%; number needed to treat [NNT] 16) and a 7% absolute reduction in all-cause mortality (NNT 14) compared to the conventional glycemic control group.[4] Conversely, a systematic review evaluated the non-UKPDS metformin monotherapy trials and showed no significant benefit on mortality (RR 2.94; 95% CI 0.31-28.16) or ischemic heart outcomes (RR 3.02; 95% CI 0.62-14.75).[5] Additionally, the ACCORD trial suggested a possibility of increased all-cause mortality in the intensive arm, in which approximately 94% of patients were on metformin therapy.[6] In conclusion, the positive CV effects associated with metformin comes from the UKPDS trial; these results have not been replicated and were likely, in part, a product of trial design. UKPDS included patients with newly-diagnosed diabetes who were largely free of vascular events, whereas the major trials that have not found a reduction in CVD outcomes with intensive glycemic control (ACCORD[6], ADVANCE[7], VADT[8]) included participants who had more advanced type 2 diabetes (T2DM). Regardless, metformin is a suitable first choice for hyperglycemic therapy based on its efficacy in lowering hemoglobin A1C (A1C), positive effect on weight, and low cost, in addition to the potential to decrease CV events when initiated early on in the disease.

Sulfonylureas

There is conflicting data suggesting that the use of sulfonylureas may be associated with an increase in CV events and mortality.[9] However, this finding is most consistent with first generation sulfonylureas that are no longer used. Overall, it is unlikely that sulfonylureas directly cause CVD, but some hypothesize that they may worsen outcomes due to the effect of sulfonylureas on mitochondrial ATP-sensitive potassium channels in cardiac myocytes.[10] In addition, sulfonylureas have a relatively high risk of hypoglycemia, which can precipitate adverse CV outcomes such as myocardial ischemia and cardiac arrhythmia.[11] There is also data supporting the relative CV safety of sulfonylureas from a systematic review comparing sulfonylurea monotherapy to placebo and other agents for the treatment of T2DM.[12] In this review, there were no significant differences in CV mortality or overall mortality between sulfonylurea monotherapy and any other class of agents. This was similar to the BARI 2D study which demonstrated no difference in CV events or mortality between those on an insulin-sensitizing regimen versus insulin-provision therapy (insulin and/or sulfonylurea) over 5 years of follow up.[13] In conclusion, there is no reason to prefer or to avoid sulfonylurea therapy based on CVD considerations but patients and providers should be aware of the potential CV risks of hypoglycemia in patients with underlying CVD.

Insulin

The use of insulin is known to be a potent glucose lowering agent but the CV effects have been inconclusive. Recently, the ORGIN trial compared glargine to standard of care (predominately metformin and sulfonylureas) and found glargine to have a neutral effect on CV outcomes (hazard ratio [HR] 1.02; 95% CI, 0.94 to 1.11).[14] A CV study comparing degludec to glargine will have results in September of 2015, which will help to further define the relationship between insulin and CVD.[15]

Thiazolidinediones

Historically, the thiazolidinediones (TZDs), especially rosiglitazone, have been viewed as having a potentially negative CV effect. A meta-analysis of rosiglitazone demonstrated an increased risk of MI (OR 1.43; 95% CI 1.03 to 1.98; P=0.03).[16] However, a review of the re-adjudicated results of the evidence found that rosiglitazone wasn't associated with an increased risk of MI compared to metformin or sulfonylureas.[17] A RCT specifically designed to assess the CV impact of pioglitazone included 5,238 patients with T2DM and macrovascular disease.[18] The primary endpoint was the composite of all-cause mortality, MI, stroke, acute coronary syndrome, coronary or leg revascularization or leg amputation. No significant difference was found between pioglitazone and placebo (HR 0.90; 95% CI, 0.8-1.02; P=0.095).[18] Other studies have shown an increased risk of heart failure (HF) with rosiglitazone and pioglitazone, supported by findings from a meta-analysis showing a hazard ratio for pioglitazone of 1.32 (95% CI, 1.04 to 1.68) and for rosiglitazone 2.18 (95% CI, 1.44 to 3.32).[19] Lack of conclusive CV benefit and side effects such as weight gain, HF and edema limit routine use of TZDs in patients with CV disease.

DPP-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors have CV results for three of the four approved therapies. In the EXAMINE trial, 5,380 patients with T2DM and a recent acute coronary syndrome (ACS) were randomized to alogliptin or placebo.[20] The primary endpoint was the composite of death from CV causes, nonfatal MI, or nonfatal stroke. A neutral effect was seen on CV endpoints with the primary outcome experienced by 11.3% in the alogliptin group compared to 11.8% in the placebo group (HR 0.96; P<0.001 for noninferiority).[15] Observational studies have shown CV benefit with glucose lowering, however, the lower A1C levels associated with alogliptin compared to placebo, -0.33% vs. 0.03%, did not translate into CV benefit.[20] Sitagliptin was also compared to placebo in the TECOS trial.[21] The primary composite outcome was CV death, non-fatal MI, and non-fatal stroke or hospitalization for unstable angina. After a median follow up of 3 years, sitagliptin was not associated with any CV harm or benefit compared to placebo, 11.4% vs, 11.6% (HR 0.98; 95% CI, 0.88 to 1.09; P=0.001 for noninferiority).[21] Heart failure-related hospital admissions was a secondary outcome that was also found to be the same in both groups, 3.1% (HR 1.00; 95% CI, 0.83 to 1.20; P = 0.98).[21] The CV effects of saxagliptin were studied in patients with T2DM and CVD.[22] The primary outcome was a composite of CV death, nonfatal MI, or nonfatal ischemic stroke. The incidence of the primary endpoint was 7.3% for saxagliptin vs. 7.2% for placebo after a follow-up of 2.1 years (HR 1.00; 95% CI, 0.89 to 1.12; P<0.001 for noninferiority).[22] There was an increased risk of hospitalization for HF in the saxagliptin group compared to placebo, 3.5% and 2.8%, respectively (HR 1.27; 95% CI, 1.07 to 1.51; P=0.007).[22] The mechanism for the elevated hospital admissions with saxagliptin is unknown. DPP-4 inhibitors appear to exhibit neutral CV effects, except for an increased risk of hospitalization for HF with saxagliptin, which warrants continued monitoring.

GLP-1 Receptor Agonists

Prospective, randomized trials evaluating the CV effects of glucagon-like peptide-1 (GLP-1) receptor agonists are ongoing and have not been published. In a meta-analysis of 37 trials, GLP-1 receptor agonists were compared to various treatments from other therapeutic classes in T2DM

patients.[19] GLP-1 receptor agonists were not found to be associated with an increased risk of major CV events (MACE) compared to active or placebo treatments (OR 0.78; 95% CI, 0.54 to 1.13; p=0.18).[19]

SGLT-2 Inhibitors

Recently, trial results for the CV safety of empagliflozin, 10 mg and 25 mg, were compared to placebo over a median observation time of 3.1 years in patients with T2DM and preexisting CV disease. [23] The primary composite outcome was CV death, nonfatal MI or nonfatal stroke. Pooled empagliflozin doses were shown to decrease the primary composite outcome more than placebo, 10.5% vs. 12.1% (HR 0.86; 95.02% CI, 0.74 to 0.99; P<0.001 for noninferiority and P=0.04 for superiority).[23] The difference in the primary endpoint was driven by a significantly lower incidence of CV death in the empagliflozin group: 5.9% vs. 3.7% (p<0.001). All-cause mortality was also significantly lower, 8.3% vs. 5.7% (p<0.001).[23] It has been theorized that the CV benefits could be related to diuresis caused by empagliflozin, which is supported by the decreased incidence of hospitalizations related to HF found with empagliflozin compared to placebo, 4.1% vs. 2.7% (HR 0.65, 95% CI, 0.50 to 0.85; P=0.002).[23]

Empagliflozin trial results are significant because it is the first diabetes drug to demonstrate a reduction in CV events in an adequately powered randomized controlled trial. Limitations to CV benefits seen with empagliflozin are that all included patients had preexisting CV disease and there is no evidence that these findings would apply to patients without preexisting disease. Empagliflozin should not be used in patients who have reduced kidney function and the rate of genital mycotic infections are more common with empagliflozin than in placebo treated patients.[24] Additionally, canagliflozin, another SGLT-2 inhibitor, has been shown to increase the risk of bone fractures and it is not known if this is a class effect.[25] Two CV safety and efficacy trials with canagliflozin and dapagliflozin are ongoing and will clarify effects of SGLT-2 inhibitors on CV outcomes.[26, 27]

High quality, prospective trials will provide valuable evidence to direct prescribing of antidiabetic agents. In addition to CV implications, consideration of adverse event profiles and patient characteristics should be considered so that benefits can be maximized and risks minimized.

Peer Reviewed By: Tracy Klein, PhD, FNP, Assistant Professor, College of Nursing, Washington State University Vancouver and Abby Frye, Pharm D, BCACP, Clinical Pharmacy Specialists, Primary Care, Providence Medical Group

References:

1. Oregon Health Authority. Oregon diabetes report. January 2015. Available at:https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf. Accessed on February 18, 2016.
2. Avalrez, CA, Lingvay I, Vuylsteke V, et al. Cardiovascular risk in diabetes mellitus: complication of the disease or of antihyperglycemic medications. *Clin Pharm and Ther* 2015;98:145-161. Doi: 10.1002/cpt.143.
3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854-865.
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589. doi:10.1056/NEJMoa0806470.
5. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2005.http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002966.pub3/abstract. Accessed March 15, 2016.
6. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559. doi:10.1056/NEJMoa0802743.
7. Group TAC. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2008;358(24):2560-2572. doi:10.1056/NEJMoa0802987.
8. Duckworth WC, McCarren M, Abraira C. Glucose Control and Cardiovascular Complications: The VA Diabetes Trial. *Dia Care*. 2001;24(5):942-945. doi:10.2337/diacare.24.5.942.
9. Bell DSH. Do sulfonylurea drugs increase the risk of cardiac events? *CMAJ*. 2006;174(2):185-186. doi:10.1503/cmaj.051237.
10. Sato T, Nishida H, Miyazaki M, Nakaya H. Effects of sulfonylureas on mitochondrial ATP-sensitive K+ channels in cardiac myocytes: implications for sulfonylurea controversy. *Diabetes Metab Res Rev*. 2006;22(5):341-347. doi:10.1002/dmrr.621.
11. Bell DSH, Bakris GL, McGill JB. Comparison of carvedilol and metoprolol on serum lipid concentration in diabetic hypertensive patients. *Diabetes Obes Metab*. 2009;11(3):234-238. doi:10.1111/j.1463-1326.2008.00927.x.
12. Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2013;4:CD009008. doi:10.1002/14651858.CD009008.pub2.
13. Group TB 2D S. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. *N Engl J Med* .2009;360(24):2503-2515.doi:10.1056/NEJMoa0805796.
14. Gerstein HC, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med.* 2012;367:319-328.
15. Novo Nordisk A/S. A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events. Clinical Trials.gov. Accessed March 25, 2016.
16. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular disease. *N Engl J Med* 2007;356:2457-2471.
17. US Food and Drug Administration: Rosiglitazone-containing Diabetes Medicines: Drug Safety Communication - FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS). December 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm477601.htm.
18. Dormandy, JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial in macrovascular Events): a randomised controlled trial. *Lancet.* 2005:1279-1289.
19. Lago RM, Singh PP and Nesto RW. Congestive heart failure and cardiovascular death in patients with pre-diabetes and type 2 diabetes given thiazolindinediones: a meta-analysis of randomised clinical trials. *Lancet*. 2007; 370:1129-1136.
20. White W, Cannon C, Heller S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-35. Doi: 10.1056/NEJMoal305889.
21. Green J, Bethel A, Armstrong P, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232-42. Doi:10.1056/NEJMoal1501352.
22. Scirica B, Bhatt D, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1317-26.
23. Zinman B, Wanner C, Lachin J, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-28. Doi: 10.1056/NEJMoal504720.
24. Empagliflozin Prescribing Information. *Boehringer Ingelheim Pharmaceuticals, Inc*. Ridgefield, CT; 2016.
25. US Food and Drug Administration. Invokana and Invokamet (canagliflozin): FDA drug safety communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. *FDA Drug Safety Communication.* 2015. Available at: http://www.fda.gov/drugs/drugsafety/ucm461449.htm. Accessed March 3, 2016.
26. Janssen Research & Development, LLC. A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus. *ClinicalTrials.gov*. Available at: https://clinicaltrials.gov/ct2/show/NCT01032629?term=CANVAS&rank=1. Accessed March 4, 2016.
27. Astra Zeneca. Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes. *ClinicalTrials.gov*. Available at: https://clinicaltrials.gov/ct2/show/NCT01730534?term=DECLARE+TIMI58&rank=1. Accessed March 4, 2016.

Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy Sentena
sentenak@ohsu.edu

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

Prior Authorization Review: dalfampridine

Background:
Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system.[1] Patients with MS may experience cognitive dysfunction, mental and physical fatigue. Dalfampridine (Ampyra®) is a potassium channel blocker used to improving walking in patients with multiple sclerosis.[2] It was approved by the U.S. Food and Drug Administration (FDA) in 2010 to improve mobility in MS patients. The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The efficacy of dalfampridine to improve walking speed in MS patients was established in clinical trials and confirmed in post-marketing experience. The largest Phase 3 trial compared oral dalfampridine 10 mg twice daily to placebo in 283 adults.[3] The primary outcome was defined as patients who achieved faster walking speeds after 14 weeks of treatment compared to baseline values. The improvement in walking speed was greater in the treatment group compared to placebo (35% vs. 8%, respectively; $p<0.0001$).[3] An open-label extension of the initial Phase 3 trial evaluated long-term safety and efficacy of dalfampridine in 269 patients over 5 years.[4] Throughout the study period mean improvement in walking speed declined but remained improved compared to baseline. Medication related adverse effects were reported in 98.1% of study participants. The most common effects were urinary tract infections, falls, MS relapse, arthralgia and edema. Discontinuation due to adverse effects occurred in 13.8% of patients. Three patients experienced seizures and 3 patients experienced myocardial infarction. No other indications have been approved by the FDA.

The efficacy of dalfampridine has not been established for the treatment of cognitive dysfunction, depression, fatigue or mood swings associated with MS. No other off label uses of oral dalfampridine have been evaluated. Five prior authorization requests were received for dalfampridine in 2015. Three requests were approved and two were denied.

Recommendations:
No changes to the current PA criteria are recommended. No further review or research needed at this time.

References:
1. Harrison DM. Multiple Sclerosis. *Ann Intern Med*. 2014;160(7):ITC4-1. doi:10.7326/0003-4819-160-7-201404010-01004.
2. Ampyra (dalfampridine) [Prescribing Information]. Ardsley, NY: Acorda Therapeutics, Inc., December 2014.
3. Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*. 2009;373(9665):732-738. doi:10.1016/S0140-6736(09)60442-6.
4. Goodman AD, Bethoux F, Brown TR, et al. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: Results of open-label extensions of two Phase 3 clinical trials. *Mult Scler*. 2015;21(10):1322-1331. doi:10.1177/1352458514563591.

Dalfampridine (Ampyra®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Multiple Sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the patient have moderate or severe renal impairment (est. GFR <50 mL/min)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7

Approval Criteria		
7. Is the patient ambulatory with a walking disability requiring use of a walking aid **OR;** have moderate ambulatory dysfunction and does not require a walking aid AND able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	**Yes:** Approve initial fill for 2-month trial.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking dalfampridine for ≥2 months with documented improvement in walking speed while on dalfampridine (≥20% improvement in timed 25-foot walk test)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

P&T Review: *5/16 (DM); 3/12*
Implementation: *9/1/13*

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

Prior Authorization Review: mipomersen and lomitapide

Background:
Familial hypercholesterolemia is a genetic disorder which results in extremely high levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature cardiovascular disease. [1] Homozygous familial hypercholesterolemia (HoFH) is caused by mutations in the low density lipoprotein receptor (LDLR) gene. Patients with HoFH present with severe hypercholesterolemia and accelerated atherosclerosis within the first two decades of life. [2] Clinical diagnosis includes appearance of xanthomas at an early age, untreated LDL >500 mg/dL, treated LDL ≥300 mg/dL, or non high-density lipoprotein cholesterol (HDL-C) ≥330 mg/dL. [2] Available treatments to lower LDL include high-intensity statin therapy, ezetimibe, PCSK-9 inhibitors, bile acid sequestrants, niacin, and lomitapide, mipomersen, and LDL apheresis.[3]

Mipomersen (Kynamro®) is an oligonucleotide inhibitor of apolipoprotein B synthesis. Apo B is the principal precursor of LDL-C and VLDL-C. Mipomersen is indicated as an adjunct to lipid lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non HDL-C in patients with HoFH.[4] It was approved by the U.S. Food and Drug Administration (FDA) in 2013 to reduce hypercholesterolemia only for HoFH patients. The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The safety and effectiveness of mipomersen was evaluated in a randomized, double blind, placebo-controlled Phase 3 trial conducted in 51 adult HoFH patients. Mipomersen was administered as 200 mcg subcutaneously once a week for 26 weeks. The primary efficacy endpoint was percent change in LDL-C from baseline. At week 26 the mean percent reduction in LDL-C from baseline was 25% ($p<0.001$) in the mipomersen arm.[5] Four patients (12%) in the mipomersen group had increases in ALT 3-times the upper limit of normal (ULN). The drug carries a "black box" warning regarding the risk of hepatotoxicity and is only available through a restricted risk evaluation and mitigation strategies (REMS) program. The efficacy and safety of mipomersen was evaluated in a post marketing open-label extension trial. [6] Thirty eight patients with HoFH and 103 patients with heterozygous familial hypercholesterolemia (HeFH) were recruited for the study. At 104 weeks, a 28% decrease in mean LDL-C was noted from baseline in the 53 patients that were still actively participating in the study. Almost all patients experienced one adverse event including injection site reactions (98%) or flu-like symptoms (65%). Changes in ALT greater than 3-times ULN were noted in 18 (13%) of patients. The transaminase elevations were reversible upon drug discontinuation.

Lomitapide (Juxtapid®) is an oral microsomal triglyceride transfer (MTP) protein inhibitor indicated as an adjunct to a low-fat diet and other lipid lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol, apolipoprotein B and non-HDL-C in patients with HoFH. [7] It was approved by the FDA in 2012 to reduce hypercholesterolemia only for HoFH patients. The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The Phase 3 trial that led to FDA approval was conducted in 29 adults HoFH patients in an international, multicenter, open-label, and 26-week study sponsored by the manufacturer.[8] The primary endpoint was reduction in LDL-C from baseline to week 26. The study was continued for an additional 52 weeks to assess safety. At the week 26, researchers noted a 50% mean reduction in LDL-C. By the end of the 78 weeks, a mean LDL-C reduction of 38% was noted in the 23 patients that completed the trial. Ten patients in the study (34%) had increased ALT or AST levels greater than 3-times ULN. Four patients (14%) experienced ALT or AST elevations greater than 5-times ULN. Due to the incidence of elevated LFTs, lomitapide received a "black box" warning regarding the incidence of hepatotoxicity. Because of this risk, lomitapide is only available through a restricted REMS program.

The effect of both of these agents on cardiovascular morbidity and mortality has not been evaluated. There was no utilization for either one of these drugs in the Oregon Health Plan fee-for-service population in 2015.

Recommendations:
No changes to the current PA criteria are recommended. No further review or research needed at this time. A discussion of whether the PA is still needed for these agents may be appropriate.

References:

1. Bouhairie VE, Goldberg AC. Familial Hypercholesterolemia. *Endocrinol Metab Clin North Am*. 2016;45(1):1-16. doi:10.1016/j.ecl.2015.09.001.
2. Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. *Atherosclerosis*. 2012;223(2):262-268. doi:10.1016/j.atherosclerosis.2012.02.019.
3. Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation*. 2015;132(22):2167-2192. doi:10.1161/CIR.0000000000000297.
4. Kynamro (Mipomersen) [Prescribing Information]. Cambridge, MA: Genzyme Corporation. March, 2015.
5. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375(9719):998-1006. doi:10.1016/S0140-6736(10)60284-X.
6. Santos RD, Duell PB, East C, et al. Long-term efficacy and safety of mipomersen in patients with familial hypercholesterolaemia: 2-year interim results of an open-label extension. *Eur Heart J*. 2015;36(9):566-575. doi:10.1093/eurheartj/eht549.
7. Juxtapid (Lomitapide). [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals. March 2016.
8. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381(9860):40-46. doi:10.1016/S0140-6736(12)61731-0.

Appendix 1: Current Prior Authorization Criteria.

Mipomersen (Kynamro®) and Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen or lomitapide has been shown to be effective and safe.

Length of Authorization:

Up to 6 months

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs (high-intensity statin with ezetimibe; see Table 1)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient failed or are they not appropriate for LDL-C apheresis **OR** Is LDL-C apheresis not available to them?	**Yes:** Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. High-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)
Atorvastatin 40-80 mg
Rosuvastatin 20-40 mg

Ref. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

P&T Review: *5/16 (DM); 9/13; 7/13; 5/13*
Implementation: *1/1/14; 11/21/2013*

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

Prior Authorization Review: sapropterin

Background:
Phenylketonuria (PKU) is the most common inherited genetic defect in amino acid metabolism. It is caused by mutations in the phenylalanine hydroxylase (PAH) gene which result in decreased phenylalanine hydroxylase activity and consequent hyperphenylalaninemia (HPA).[1] Untreated PKU can cause irreversible mental disability, behavioral abnormalities and motor impairment. Restriction of dietary phenylalanine (Phe) is the primary component of PKU management.[1] Some mutations are associated with a BH-4 phenotype and can be managed by administering exogenous tetrahydrobiopterin (BH4).[2] Approximately 2 percent of patients with elevated phenylalanine levels will have the BH4 phenotype.[2] Sapropterin (Kuvan®) is a phenylalanine hydroxylase activator indicated to reduce blood phenylalanine levels in patients with HPA due to BH4 responsive PKU.[3] It was approved by the U.S. Food and Drug Administration (FDA) in 2007 to manage BH4 responsive PKU patients along with Phe diet restrictions. The Pharmacy & Therapeutics Committee reviewed this drug previously and approved Prior Authorization (PA) for its use (see **Appendix 1**). The efficacy of sapropterin in PKU patients was established in clinical trials and confirmed in post-marketing experience. The Phenylketonuria Demographics, Outcomes, and Safety (PKUDOS) registry was established to evaluate long term safety and efficacy data on patients treated with sapropterin. To date, 504 patients have been continuously treated with sapropterin and have seen a significant decrease in blood Phe (34%, p= 0.0009) levels after 5 years of therapy.[4] Very few drug related adverse effects were reported (6%) and they included diarrhea, rhinorrhea, and headaches. Less than 1% of patients experienced serious adverse effects including cardiac arrhythmia, cholecystitis, diabetes and premature labor. No deaths have been reported for any patients maintained on sapropterin.

No other indications for sapropterin have been approved by the FDA. The efficacy of sapropterin has not been established for other types of PKU. No other off label uses of sapropterin have been evaluated. Not all patients will respond to sapropterin therapy and a 2 month therapeutic trial is necessary to assess patient response.[3] During 2015, one Prior Authorization was received and it was approved. In general, utilization of this drug is very low, which is not surprising given the small percentage of PKU patients that will benefit from exogenous tetrahydrobiopterin therapy. The American College of Medical Genetics and Genomics developed guidelines to assist in PKU diagnosis and treatment. One of the key recommendations was to recommend target blood levels of Phe in the range of 120 to 360 µmol/l for patients in all age ranges.[5]

Recommendations:
Update target Phe goals to 120 – 360 µmol/L for patients in all age ranges. No further review or research needed at this time.

References:
1. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *The Lancet*. 2010;376(9750):1417-1427. doi:10.1016/S0140-6736(10)60961-0.

2. Shintaku H. Disorders of tetrahydrobiopterin metabolism and their treatment. *Curr Drug Metab*. 2002;3(2):123-131.

3. 'HIGHLIGHTS OF PRESCRIBING INFORMATION - KUVAN_Prescribing_Information1.pdf. http://www.kuvan.com/hcp/wp-content/file/KUVAN_Prescribing_Information1.pdf. Accessed April 6, 2016.

4. Longo N, Arnold GL, Pridjian G, et al. Long-term safety and efficacy of sapropterin: the PKUDOS registry experience. *Mol Genet Metab*. 2015;114(4):557-563. doi:10.1016/j.ymgme.2015.02.003.

5. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. *Genet Med*. 2014;16(2):188-200. doi:10.1038/gim.2013.157.

Appendix 1: Current Prior Authorization Criteria.

Sapropterin (Kuvan®)

Goal(s):

- Promote safe and cost effective therapy for the treatment of phenylketonuria.

Length of Authorization:

- Initial: 1 to 2 months; Renewal: 1 year

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the drug prescribed by or in consultation with a specialist in metabolic disorders?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient currently compliant with a Phe-restricted diet and unable to achieve target blood phenylalanine level?	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.

Approval Criteria		
5. Is the patient's baseline blood phenylalanine level provided in the request and above the target range (see Clinical Notes)?	**Yes:** Approve for 2 months if initial dose is 5-10 mg/kg/day (to allow for titration to 20 mg/kg/day). Approve for 1 month if initial dose is 20 mg/kg/day (adults and children).	**No:** Request information from provider.
Renewal Criteria		
1. Did the patient meet the target phenylalanine level set by the specialist (see Clinical Notes)?	**Yes:** Go to #2	**No:** Pass to RPh; Deny for lack of treatment response.
2. Is the patient remaining compliant with the Phe-restricted diet?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.

Target blood phenylalanine levels in the range of 120-360 µmol/l for patients in all age ranges.[1]
In addition to the recommended Phe concentrations, a 30% or more reduction in blood Phe is often considered a clinically significant change from baseline and should occur after the initial trial.[2] If not, the patient is a nonresponder and will not benefit from sapropterin therapy.

Doses above 20 mg/kg/day have not been studied in clinical trials.

References:
1.Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16(2):188-200. doi:10.1038/gim.2013.157

2.Blau N., Belanger-Quintana A., Demirkol M. Optimizing the use of sapropterin (BH_4) in the management of phenylketonuria. *Molecular Genetics and Metabolism* 2009;96:158-163.

P&T Review: *5/16 (DM); 11/13; 9/13; 7/13*
Implementation: *1/1/14*

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

New Drug Evaluation: **indacaterol/glycopyrrolate** and **glycopyrrolate** inhalation powder, oral

Date of Review:	May 2016	**End Date of Literature Search:**	February 1, 2016
Generic Name:	indacaterol/glycopyrrolate inhalation powder glycopyrrolate inhalation powder	**Brand Name (Manufacturer):**	Utibron™ Neohaler® (Novartis) Seebri™ Neohaler® (Novartis)
PDL Class:	LAMA/LABA Inhalers; Anticholinergics, Inhaled	**Dossier Received**:	Utibron™ Neohaler® - yes Seebri™ Neohaler® - no

Research Questions:

- Is there any evidence that glycopyrrolate (GLY) or the fixed dose combination indacaterol (IND)/GLY are more effective than other long-acting muscarinic antagonists (LAMAs) or LAMA/long-acting beta-2 agonists (LABAs) when important outcomes such as mortality, hospitalizations, and quality of life are compared?
- Is there any evidence that GLY or IND/GLY are associated with less harms than other LAMAs or combination LAMA/LABA products?
- Is there any evidence that GLY is more effective or more harmful in certain subpopulations?

Conclusions:

- There is insufficient evidence that GLY or IND/GLY decreases risk for hospitalizations, decreases mortality or improves functionality in patients with COPD. There is insufficient comparative evidence between GLY and other LAMA products and between IND/GLY and other LAMA/LABA products.
- There is insufficient evidence for the efficacy of GLY due to the lack of published trials that can be critically assessed for risk of bias and applicability. Labeled prescribing information reports GLY to be superior to placebo with an improvement in Forced Expiratory Volume in 1 second (FEV1) area-under-the-curve (AUC) 0-12 hours at day 85 based on 2 industry-sponsored, 12-week randomized controlled trials.[1]
- There is low quality of evidence from 2 international, industry-sponsored, 12-week trials that IND/GLY increases FEV1 AUC 0-12 hours more than GLY or IND alone. The first trial found a change of 0.171 L for IND/GLY and 0.083 L for IND (mean difference [MD] 0.094 L; 95% CI 0.055 to 0.133; p<0.001) and a change of 0.128 L for GLY (TD 0.098 L; 95% CI 0.059 to 0.137; p<0.001).[2] The magnitude of change for FEV1 values are at the lower end of a clinically relevant difference of 0.100 L to 0.140 L. In the second trial, FEV1 AUC 0-12 changes were higher for the IND/GLY group compared to IND alone (0.184 L vs. 0.080 L, respectively; MD 0.112 L; 95% CI, 0.075 to 0.149; p<0.001) and to GLY alone (0.184 vs. 0.135 L, respectively; MD 0.079 L; 95% CI, 0.042 to 0.116 L; p<0.001).[2] Demographic data was pooled for both studies; therefore, it is unknown if patient characteristics account for a larger treatment effect of IND/GLY seen in the second study.
- There is low quality evidence that IND/GLY does not improve quality of life compared to IND or GLY on St. George's Respiratory Questionnaire (SGRQ) scores; however, IND/GLY may be statistically superior to placebo by -3.8 and -6.4 units, respectively (P < 0.001).[2] A difference of 4 points is considered the minimally clinical important difference.

- There is moderate quality data that adverse reactions occurring in ≥ 1% of patients treated with GLY are upper respiratory infections and nasopharyngitis.[1] In placebo-controlled comparisons the most clinically relevant adverse reaction was a 2.3% greater incidence of nasopharyngitis with IND/GLY.[8] Discontinuations due to adverse reactions were slightly higher for placebo compared to both GLY and IND/GLY.[1,8]
- There is insufficient evidence to suggest greater efficacy or harm in any subpopulation.

Recommendations:
- Recommend GLY be non-preferred on the preferred drug list (PDL) due to insufficient evidence for review.
- Recommend IND/GLY be non-preferred on the PDL and subject to prior authorization criteria for LAMA/LABA fixed-dose combination treatments.
- Evaluate costs in executive session. Consider preferring a fixed-dose combination LAMA/LABA product if more cost-effective than single entity products.

Background:
Chronic cough, sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of FEV1/FVC < 0.70), symptom severity, risk of exacerbations and comorbidities.[3] COPD is classified into 4 stages based on spirometric measurements of FEV1/FVC; grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (very severe) (Table 1).[3] The GOLD guidelines recommend therapeutic approaches based on disease burden as well as FEV1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations).[3] This type of classification system shifts the focus from including just FEV1 measurements, as these are not always indicative of COPD status.

Table 1. Classification of COPD Based on GOLD Guidelines*[3]

Classification	Severity	Post-Bronchodilator FEV_1
GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV_1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV_1 < 50% predicted
GOLD 4	Very severe	FEV_1 < 30% predicted

* For patients with a FEV1/FVC < 0.70

Mortality, hospitalizations, functional capacity, quality of life (QoL), dyspnea, and exacerbation rates are all important outcomes in the management of COPD patients.[3] FEV1 is the most common surrogate outcome used in studies to determine therapy effectiveness. Minimally important FEV1 values for COPD changes have not been clearly defined but are suggested to range from 100-140 mL.[4] The SGRQ is a validated quality of life assessment used to quantify the health and well-being of patients with COPD.[5] The scores range from 0-100 units, with higher scores indicative of worse health.[5] A change of 4 points has been determined as the minimally clinical important difference.[5] The COPD Assessment Test (CAT) is another validated instrument used to measure health status.[6] It is less complex than the SGRQ but scores correlate well with SGRQ results. CAT scores range from 0-40 points with higher scores representing worse disease severity.[6]

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management. Treatment often starts with monotherapy and progress to combination regimens. Currently available treatments are the following: short-acting beta-2 agonists (SABA), LABAs, short-acting muscarinic antagonists, LAMAs and inhaled corticosteroids (ICS).[3] Short-acting beta-2 agonists SABA are recommended for acute management. Bronchodilator therapy (LABAs and LAMAs) is recommended for patients with symptoms despite SABA treatment and are used as monotherapy or in combination for maintenance treatment for chronic, stable COPD.[3] Inhaled corticosteroids are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA use. Glycopyrrolate is one of four LAMAs used to treat COPD. Other available treatment options are: aclidinium bromide, tiotropium and umeclidinium.[3] No treatment has been shown

to alter the long-term progression and decline in lung function associated with COPD.[3] The 2016 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that tiotropium has the most evidence for reducing exacerbations and hospitalizations. Indirect evidence suggests outcomes of lung function and breathlessness are similar for tiotropium, aclidinium and GLY.(GOLD) A systematic review and meta-analysis found no significant difference between the LABA/LAMA combinations of umeclidinium/vilanterol, GLY/IND, tiotropium/olodaterol and aclidinium/formoterol.[7]

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:
Glycopyrrolate is a long-acting anticholinergic inhaler approved in 2015 for the long-term maintenance treatment of airflow obstruction in patients with COPD.[1] Glycopyrrolate is provided in a powder form, administered as a 15.6 mcg dose by the Neohaler® twice daily. Approval of GLY was based on two unpublished efficacy trials and one unpublished safety trial.[1] Risk of bias and applicability could not be assessed.

Data from the labeled prescribing information describe that GLY 15.6 mcg twice daily was compared to placebo twice daily in two, 12-week, double-blind randomized controlled trials.[1] Patients had a COPD diagnosis, were a mean age of 63 years, 58% were male, 57% were current smokers and baseline post-bronchodilator FEV1 was 55%. The primary endpoint was change from baseline in FEV1 AUC 0-12 hours at day 85. In the first trial, GLY produced a greater change in FEV1 AUC 0-12 hours compared to placebo (0.125 L vs. -0.014 L; MD 0.139 L; 95% CI 0.095 to 0.184 L). The second trial produced similar results with change in FEV1 AUC 0-12 hours of 0.115 L for GLY and -0.008 L for placebo (MD 0.123 L; 95% CI 0.081 to 0.165 L).[1] The percent of patients who experienced a clinically significant change of 4 points in their SGRQ score was not statistically significantly different between GLY and placebo arms (49% vs. 41%, respectively; OR 1.43; 95% CI, 0.95 to 2.15) in the first trial but was statistically significant in the second trial (55% vs. 42%, respectively; OR 1.78; 95% CI, 1.17 to 2.71).[1] Besides quality of life, no other clinically relevant health outcomes were assessed.

Clinical Safety:
In placebo controlled trials, the most common adverse reaction associated with the use of GLY 15.6 mcg where upper respiratory tract infection and nasopharyngitis (Table 2). Discontinuations due to adverse events were lower in GLY 15.6 mcg treated patients compared to placebo (2.4% and 3.8%, respectively).[1]

Table 2. Adverse Reactions of Glycopyrrolate in ≥ 1% incidence and higher than placebo[1]

Adverse Reaction	Glycopyrrolate (N=951)	Placebo (N=938)
Upper respiratory tract infection	3.4%	2.3%
Nasopharyngitis	2.1%	1.9%
Urinary tract infection	1.4%	1.3%
Sinusitis	1.4%	0.7%
Oropharyngeal pain	1.8%	1.2%

Indacaterol/glycopyrrolate

Clinical Efficacy:
The fixed dose combination of IND/GLY is a LABA/LAMA product approved for the long-term maintenance treatment of airflow obstruction in patients with COPD.[8] Glycopyrrolate is provided in a powder form, administered as a 27.5 mcg dose of indacaterol and a 15.6 mcg dose of glycopyrrolate via the Neohaler® device twice daily.[8]

Evidence for efficacy of IND/GLY was provided by 2 identical double-blind, industry-sponsored, international, phase 3, 12-week studies that compared IND/GLY to IND and GLY monotherapy components and placebo in 2,038 patients.[2] The patients were predominately white males (63%) and females (37%) with moderate to severe COPD and a baseline post-bronchodilater FEV1% of 55%. The primary endpoint for both studies was comparison of FEV1 AUC 0-12 hours at 12 weeks. A key pre-specified secondary endpoint was change in SGRQ total score.[2]

In the first study (FLIGHT1) there was greater improvement in the primary endpoint with combination IND/GLY compared to IND (0.171 L vs. 0.083 L, respectively; MD 0.094 L; 95% CI, 0.055 to 0.133 L; p<0.001) and GLY (0.171 L vs. 0.128 L, respectively; MD 0.098 L; 95% CI, 0.059 to 0.137 L; p<0.001).[2] Results were similar in the second study (FLIGHT2) with more improvement in the IND/GLY group compared to IND (0.184 L vs. 0.080 L, respectively; MD 0.112 L; 95% CI, 0.075 to 0.149 L; p<0.001) and GLY (0.184 L vs. 0.135 L; MD 0.262 L; 95% CI, 0.224 to 0.300 L; p<0.001). FEV1 changes with IND/GLY were modest compared to its monotherapy components and are at the low end of what is considered a clinically relevant change. SGRQ total scores were improved with IND/GLY compared to placebo in FLIGHT1 and FLIGHT2 (-3.8 and -6.4, respectively; p <0.001 for both) and compared to GLY in the FLIGHT1 (MD -1.7; 95% CI, -3.6 to 0.2; p<0.05).[2] However, all other SGRQ comparisons were not statistically different between groups. A minimum clinically relevant change in the total SGRQ score of 4 units or more was only demonstrated in the FLIGHT 2 comparison between IND/GLY and placebo.

Longer trial durations are needed to determine the impact of IND/GLY on clinically relevant health outcomes as well as long-term safety. The only clinically relevant health outcome studied was quality of life by SGRQ, which demonstrated a lack of clinically meaningful difference between all treatment arms studied except for one comparison in one of the trials: IND/GLY versus placebo. There is a potential for high risk of detection and attrition bias. Overall, evidence is insufficient to determine if what the clinical impact of IND/GLY may have on disease progression for COPD.

Clinical Safety:
Safety data from the 2 short-term clinical trials not designed to evaluate differences in harms or long-term safety outcomes found nasopharyngitis and hypertension to be the most common adverse reactions experienced with IND/GLY (Table 3).[8] These differences are small and are unlikely to have a meaningful clinical impact. Discontinuations due to adverse reactions were 4.13% for placebo and 2.95% for IND/GLY.

Table 3. Adverse Reactions of Indacaterol/Glycopyrrolate occurring ≥ 1% incidence than placebo[8]

Adverse Reaction	Indacaterol/glycopyrrolate (N=508)	Indacaterol (N=511)	Glycopyrrolate (N=513)	Placebo (N=508)
Hypertension	2.0%	1.0%	0.6%	1.8%
Nasopharyngitis	4.1%	2.5%	2.3%	1.8%
Back Pain	1.8%	1.4%	0.4%	0.6%
Oropharyngeal pain	1.6%	0.8%	1.6%	1.2%

Pharmacology and Pharmacokinetic Properties:

Parameter	**Glycopyrrolate**[1,8]	**Indacaterol***[8]
Mechanism of Action	Bronchodilation due to inhibition of the muscarinic receptor M3	Bronchodilation via beta2-receptors
Inhaled Bioavailability	40%	43-45%
Distribution and Protein Binding	83 L 38-41% protein bound	2,361 to 2,557 L 95.1-96.2%
Elimination	Renal 60-70%, non-renal 30-40%	54% fecal and 23% hydroxylation
Half-Life	33-53 hours (inhaled)	40-56 hours
Metabolism	CYP isoenzymes	CYP3A4

* Only in IND/GLY combination inhaler

Abbreviations: CYP = cytochrome P-450 enzymes; L= liters;

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Mortality
2) Hospitalizations
3) Exacerbations
4) Quality of life

Primary Study Endpoint:

1) Change from baseline FEV1 AUC 0-12 hours

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population (pooled events*)	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes (pooled events*)	ARR/NNH	Risk of Bias/ Applicability
1. Mahler, et al (FLIGHT1)[2] Phase 3, DB, PG, PC, AC, RCT	1.Indacterol/ glycopyrrolate (IND/GLY) 15.6/27.5 mcg twice daily 2. Glycopyrrolate (GLY) 15.6 mcg twice daily 3. Indacaterol (IND) 27.5 mcg twice daily 4. Placebo (P) 1:1:1:1 12 weeks	Demographics: Age: 63 Male: 63% White: 91% Moderate COPD: 61% Severe COPD: 39% Smoker: 52% Post-bronchodilator FEV1%: 55% Key Inclusion Criteria: - Moderate to severe stable COPD - ≥ 40 years - Current or previous smoking history of at least 10 pack years - FEV1 ≥ 30% and < 80% Key Exclusion Criteria: - Diabetes - Cardiac, renal or lab abnormalities - BMI of > 40 kg/m2	mITT: 1. 260 2. 261 3. 260 4. 261 PP: 1. 244 2. 243 3. 244 4. 220 Attrition: 1. 6% 2. 7% 3. 6% 4. 16%	Primary Endpoint: FEV_1 AUC 0-12 hours: IND/GLY 0.211 L GLY 0.112 L IND 0.117 L P -0.021 L IND/GLY vs. IND: LSM 0.094 L (95% CI, 0.055 to 0.133) P < 0.001 IND/GLY vs. GLY: LSM 0.098 L (95% CI, 0.059 to 0.137) P <0.001 IND/GLY vs. P: LSM 0.231 (95% CI, 0.192 to 0.271) P < 0.001 Secondary Endpoint: SGRQ*: IND/GLY vs. IND: LSM -1.9 points (95% CI, -3.8 to 0.0) P=NS IND/GLY vs. GLY: LSM -1.7 points (95% CI, -3.6 to 0.2) P < 0.05 IND/GLY vs. P: LSM -3.8 points (95% CI, -5.7 to -1.8) P < 0.001	NA NA NA NS NA NA	Severe AE: IND/GLY 16 (3.2%) GLY 20 (3.9%) IND 18 (3.5%) P 21 (4.1%) p-values not provided D/C due to AE: IND/GLY 15 (3.0%) GLY 8 (1.6%) IND 10 (2.0%) P 21 (4.1%) p-values not provided Nasopharyngitis: IND/GLY 21 (4.1%) GLY 12 (2.3%) IND 13 (2.5%) P 9 (1.8%) p-values not provided	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized via IRT Performance Bias: (low) double–blinded with masked drug delivery devices Detection Bias: (unclear) no details were provided Attrition Bias: (high) attrition rate higher in placebo arm. mITT used instead of ITT for analysis; LOCF used to impute missing data Reporting Bias: (high) individual study results were only reported for the primary outcome measure and exact p-values are not noted. Study funded by drug sponsor. Seven out of nine authors are employees of sponsor. **Applicability**: Patient: Primarily patients with GOLD Group B or D COPD. GOLD guidelines recommend combination LAMA/LABA therapy as initial therapy for Groups C and D patients and as an alternative therapy for GOLD B patients. Intervention: Doses appropriate, based on phase III clinical program data. Comparator: individual components of IND/GLY were compared to test superiority, which is appropriate. Outcomes: FEV1 is a surrogate endpoint for lung function. Hospitalizations, mortality and long-term safety data are more clinically useful outcomes. Setting: Conducted in 8 countries including the U.S. (percent not provided).

2. Mahler, et al (FLIGHT2)[2] Phase 3, DB, PG, PC, AC, RCT	1. Indacaterol/ glycopyrrolate (GLY/IND) 15.6/27.5 mcg twice daily 2. Glycopyrrolate (GLY) 15.6 mcg twice daily 3. Indacaterol (IND) 27.5 mcg twice daily 4. Placebo (P) 1:1:1 12 weeks	Demographics: Age: 63 Male: 63% White: 91% Moderate COPD: 61% Severe COPD: 39% Smoker: 52% Post-bronchodilator FEV1%: 55% Key Inclusion Criteria: - Moderate to severe stable COPD - ≥ 40 years - Current or previous smoking history of at least 10 pack years - FEV1 ≥ 30% and < 80% Key Exclusion Criteria: - Diabetes - Cardiac, renal or lab abnormalities - Diabetes - BMI of > 40 kg/m2	mITT: 1. 250 2. 251 3. 251 4. 249 PP: 1. 238 2. 236 3. 236 4. 224 Attrition: 1. 5% 2. 6% 3. 6% 4. 10%	Primary Endpoint: FEV_1 AUC 0-12 hours: IND/GLY 0.234 L GLY 0.155 L IND 0.122 L P -0.003 L IND/GLY vs. IND: LSM 0.112 (95% CI, 0.075 to 0.149) P < 0.001 IND/GLY vs. GLY: LSM 0.079 (95% CI, 0.042 to 0.116) P < 0.001 IND/GLY vs. P: LSM 0.262 (95% CI, 0.224 to 0.300) P < 0.001 Secondary Endpoints: SGRQ*: IND/GLY vs. IND: LSM -1.5 points (95% CI, -3.6 to 0.6) NS: P-value not given IND/GLY vs. GLY: LSM -1.4 points (95% CI, -3.5 to 0.7) NS: P-value not given IND/GLY vs. P: LSM -6.4 points (95% CI, -8.5 to -4.2) P < 0.001	 NA NA NA NS NS NA	Severe AE: IND/GLY 16 (3.2%) GLY 20 (3.9%) IND 18 (3.5%) P 21 (4.1%) p-values not provided D/C due to AE: IND/GLY 15 (3.0%) GLY 8 (1.6%) IND 10 (2.0%) P 21 (4.1%) p-values not provided Nasopharyngitis: IND/GLY 21 (4.1%) GLY 12 (2.3%) IND 13 (2.5%) P 9 (1.8%) p-values not provided	 NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) See Maler (FLIGHT1) Performance Bias: (low) See Maler (FLIGHT1) Detection Bias: (unclear) See Maler (FLIGHT1) Attrition Bias: (high) See Maler (FLIGHT1) Reporting Bias: (high) See Maler (FLIGHT1) **Applicability**: Patient: See Maler (FLIGHT1) Intervention: See Maler (FLIGHT1) Comparator: See Maler (FLIGHT1) Outcomes: See Maler (FLIGHT1) Setting: Conducted in 9 countries, including the U.S. (percent not provided).

* Values are from pooled results of FLIGHT1 and FLIGHT2 studies. Individual results not reported.

Abbreviations [alphabetical order]: AC = active control; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; FEV_1 AUC = Forced Expiratory Volume in 1 second (FEV1) area-under-the-curve; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IRT = Interactive Response Technology; ITT = intention to treat; LSM = least-square means; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire.

References:

1. Seebri Neohaler (glycopyrrolate) (product information). East Hanover, NJ: Novartis Pharmaceutical Corporation, January 2016.

2. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Placebo in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2015;192(9):1068-1079. doi:10.1164/rccm.201505-1048OC.

3. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. WatermarkedGlobal Strategy 2016(1).pdf. http://www.goldcopd.org/uploads/users/files/WatermarkedGlobal%20Strategy%202016(1).pdf. Accessed March 15, 2016.

4. Cazzola M, Macknee W, Martinez F, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 31:416-469.

5. Jones P. St.George's Respiratory Questionnaire: MCID. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2015;2:75-79.

6. Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Kline Leidy N. Development and first validation of the COPD Assessment Test. *European Respiratory Journal*. 2009;34(3):648-654. doi:10.1183/09031936.00102509.

7. Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable chronic obstructive pulmonary disease. *Chest*. doi:10.1016/j.chest.2016.02.646.

8. Utibron Neohaler (indacterol/glycopyrrolate) (product Information). East Hanover, NJ: Novartis Pharmaceuticals Corporation, January 201*6.*

Appendix 1: Current Status on Preferred Drug List

Long-Acting Beta-Agonist / Long-Acting Muscarinic, inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	INHAL PWD	UTIBRON NEOHALER	INDACTEROL/GLYCOPYRROLATE	N
INHALATION	BLST W/DEV	ANORO ELLIPTA	UMECLIDINIUM BRM/VILANTEROL TR	N
INHALATION	MIST INHAL	STIOLTO RESPIMAT	TIOTROPIUM BR/OLODATEROL HCL	N

Anticholinergics, Inhaled

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	INHAL PWD	SEEBRI NEOHALER	GLYCOPYRROLATE	N
INHALATION	AMPUL-NEB	DUONEB	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	AMPUL-NEB	IPRATROPIUM-ALBUTEROL	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	CAP W/DEV	SPIRIVA	TIOTROPIUM BROMIDE	Y
INHALATION	HFA AER AD	ATROVENT HFA	IPRATROPIUM BROMIDE	Y
INHALATION	MIST INHAL	COMBIVENT RESPIMAT	IPRATROPIUM/ALBUTEROL SULFATE	Y
INHALATION	SOLUTION	IPRATROPIUM BROMIDE	IPRATROPIUM BROMIDE	Y
INHALATION	AER POW BA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	N
INHALATION	BLST W/DEV	INCRUSE ELLIPTA	UMECLIDINIUM BROMIDE	N
INHALATION	MIST INHAL	SPIRIVA RESPIMAT	TIOTROPIUM BROMIDE	N

Appendix 2: Highlights of Prescribing Information

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

UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate) inhalation powder, for oral inhalation use
Initial U.S. Approval: 2015

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABAs), such as indacaterol, one of the active ingredients in UTIBRON NEOHALER, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of all LABAs, including indacaterol. (5.1)**
- **The safety and efficacy of UTIBRON NEOHALER in patients with asthma have not been established. UTIBRON NEOHALER is not indicated for the treatment of asthma. (5.1)**

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

UTIBRON NEOHALER is a combination of indacaterol, a long-acting beta$_2$-adrenergic agonist (LABA), and glycopyrrolate, an anticholinergic, indicated for the long term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) (1)

Limitations of Use: Not indicated for the relief of acute bronchospasm or for the treatment of asthma. (1, 5.1, 5.2)

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

- **For oral inhalation only. Do not swallow UTIBRON capsules. Only use UTIBRON capsules with the NEOHALER device.** (2)
- Maintenance treatment of COPD: The inhalation of the powder contents of one UTIBRON capsule twice-daily (2)

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

- Inhalation powder: UTIBRON capsules contain 27.5 mcg of indacaterol and 15.6 mcg glycopyrrolate inhalation powder for use with the NEOHALER device (3)

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

- All LABAs are contraindicated in patients with asthma without use of a long-term asthma controller medication. (4) UTIBRON NEOHALER is not indicated for the treatment of asthma. (1)
- History of known hypersensitivity to indacaterol, glycopyrrolate, or to any of the ingredients. (4, 5.5)

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

- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3, 7.1)
- If paradoxical bronchospasm occurs, discontinue UTIBRON NEOHALER immediately and institute alternative therapy. (5.4)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, sensitivity to sympathomimetic drugs, diabetes mellitus, and ketoacidosis. (5.6, 5.7, 7.1)
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur. (5.8, 5.9)
- Be alert to hypokalemia and hyperglycemia. (5.11)

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

Most common adverse reactions (incidence ≥2% and higher than placebo) are nasopharyngitis and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Other adrenergic drugs may potentiate effect: Use with caution (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- Monoamine Oxidase inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness: Use with caution and only when medically necessary. (7.5)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of UTIBRON NEOHALER with other anticholinergic-containing drugs. (7.6)

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

• Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SEEBRI™ NEOHALER® (glycopyrrolate) inhalation powder, for oral inhalation use

Initial U.S. Approval: 1961

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

SEEBRI NEOHALER is an anticholinergic indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) (1)

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

- **For oral inhalation only. Do not swallow SEEBRI capsules. Only use SEEBRI capsules with the NEOHALER device**. (2)
- Maintenance treatment of COPD: The inhalation of the powder contents of one SEEBRI capsule (15.6 mcg) twice-daily (2)

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

- Inhalation powder: SEEBRI capsules contain 15.6 mcg of glycopyrrolate inhalation powder for use with the NEOHALER device (3)

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

- History of known hypersensitivity to glycopyrrolate or to any of the ingredients. (4, 5.3)

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

- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.1)
- If paradoxical bronchospasm occurs, discontinue SEEBRI NEOHALER immediately and institute alternative therapy. (5.2)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder neck obstruction and instruct patients to consult a physician immediately if symptoms occur. (5.5)

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

Most common adverse reactions (incidence greater than or equal to 2% and higher than placebo) are upper respiratory tract infection and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SEEBRI NEOHALER with other anticholinergic-containing drugs. (7.2)

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

- Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.6)

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

Revised: 10/2015

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:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require 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 J4520-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) (i.e., 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.

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

Class Update with New Drug Evaluations: Antipsychotics

Date of Review: May 2016

End Date of Literature Search: February 2016

New Drugs: brexpiprazole
cariprazine

Brand Names (Manufacturer): Rexulti® (Otsuka)
Vraylar™ (Actavis)

Dossiers Received: yes

PDL Classes: Antipsychotics, First generation
Antipsychotics, Second generation
Antipsychotics, Parenteral

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

Purpose for Class Update:
Several new antipsychotic drug products have been approved by the U.S. Food and Drug Administration since these drug classes were last reviewed by the Oregon Health Plan (OHP) Pharmacy and Therapeutics Committee.

Research Questions:
1. Is there new comparative evidence of meaningful difference in efficacy or effectiveness outcomes for schizophrenia, bipolar mania or major depressive disorders (MDD) between oral antipsychotic agents (first- or second-generation) or between parenteral antipsychotic agents (first- or second-generation)?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or between parenteral antipsychotic agents (first- or second-generation)?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics?

Conclusions:
- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if brexpiprazole and cariprazine offer superior efficacy or safety to other antipsychotic agents for schizophrenia.
- There is insufficient evidence to determine if brexpiprazole offers superior efficacy or safety to other antipsychotic agents for MDD.
- There is insufficient evidence to determine if cariprazine offers superior efficacy or safety to other antipsychotic agents for bipolar mania.
- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

Recommendations:

- A recommendation to add brexpiprazole or cariprazine to the voluntary Preferred Drug List (PDL) cannot be made based on the lack of long-term effectiveness and safety data.
- No PDL recommendations can be made for new formulations of aripiprazole and paliperidone based on evidence alone.
- Recommendation to PDL status for first- and second-generation oral or parenteral antipsychotic agents should be informed by comparative drug costs in the executive session.

Previous Conclusions:

- There continues to be no consistent differences in the efficacy between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials. There is moderate quality evidence for aripiprazole, clozapine, olanzapine, quetiapine and risperidone. The comparative evidence is insufficient or very low for aripiprazole long-acting injection, Iloperidone, olanzapine long-acting injection, olanzapine ODT, extended-release paliperidone and lurasidone.
- There is new moderate quality evidence that the risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than with oral risperidone in patients with first-episode schizophrenia.
- There is new moderate quality evidence of no difference in response or remission rates between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes of bipolar disorder.
- There continues to be insufficient comparative evidence of efficacy and effectiveness of second generation antipsychotics in the treatment of Major Depressive Disorder, Bipolar Disorder in children and adolescents, Pervasive Developmental Disorders and Disruptive Behavior Disorders.
- There is moderate quality evidence that the rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months. Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain. Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.
- There is limited comparative effectiveness data available for this class in regards to mortality and serious harms.
- High rates of attrition and small sample sizes in randomized clinical trials make it difficult to draw strong conclusions for this class in systematic review.
- There continues to be insufficient comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in any subgroup population.
- There is low quality evidence that aripiprazole long-acting injection improves time to relapse compared to placebo; there are no head-to-head trials comparing aripiprazole long-acting injection to other second generation antipsychotics.
- There is insufficient evidence to determine the long-term safety and comparative efficacy of aripiprazole long-acting injection.

Previous Recommendations:

- Based on the lack of long-term effectiveness and safety data, recommend listing aripiprazole long-acting injection as non-preferred on the voluntary PDL.
- No changes are recommended for the second generation antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

Background:

Schizophrenia is the ninth most debilitating disease in North America[1] and treatment with second-generation antipsychotics (SGAs) is associated with substantial cost (estimated US $14.5 billion globally in 2014).[2] Schizophrenia not only affects mental health; patients with schizophrenia die 12-15 years earlier than the average population, a trend that appears to be increasing.[3] Persons with schizophrenia experience positive symptoms (hallucinations, delusions, thought disorders) but also typically experience negative symptoms (social withdrawal, loss of motivation, emotional blunting, self-neglect), alterations in cognition (memory, attention, executive functioning), and affective dysregulation giving rise to depressive and manic (bipolar) symptoms.[3,4] Schizophrenia is characterized by long duration, bizarre delusions, negative symptoms, and few affective symptoms (non-affective psychosis).[3] Patients who present with a psychotic disorder with fewer negative symptoms, but whose psychosis is preceded by a high level of affective symptoms (depression and mania) are usually diagnosed with psychotic depression or bipolar disorder (affective psychosis).[3]

Lifetime prevalence of schizophrenia, schizophrenic disorders and schizophreniform disorders are commonly reported as less than 0.5%, with men affected more severely with earlier age of onset and higher rates of negative symptoms than women.[4] Perinatal and early childhood factors might account for a small proportion of incidence of schizophrenia: hypoxia to the fetus, maternal infection, maternal stress, and maternal nutrition have shown to be risk factors.[3] Environmental factors may also play a role. Children who grow up in more urban areas, or children of immigrant ethnic groups, particularly if they live in a low ethnic density area, are more likely to be diagnosed with schizophrenia later in life than children in less urbanized area or native-born children.[3] Cannabis use is also associated with increased risk for psychotic disorder and symptoms (odds ratio [OR] 1.5-2.0). Vulnerability for schizophrenia is partly genetic. Twin studies have demonstrated that schizophrenia has heritability estimates of around 80% (compared to 60% for osteoporosis of the hip and 30-50% for hypertension), though the high heritability may also be partly due to environmental effects that are moderated by genes.[3] Management of negative and cognitive symptoms have

Schizophrenia, in its acute psychotic state, is associated with an increase in dopamine synthesis and dopamine release. Functional MRI results show these abnormal neurochemical compositions lead to abnormal function, with both hyperactivity and hypoactivity in different brain regions compared to healthy control groups. Once the diagnosis is made, antipsychotic drugs, which block dopamine D2 receptors, are used in the context of other psychological and social supports, as the main treatment of schizophrenia. First-generation antipsychotics such as haloperidol and chlorpromazine effectively managed psychotic symptoms of schizophrenia since the 1950s, but often lead to adverse extrapyramidal motor symptoms. The SGAs generally cause less motor effects and remain effective treatment for positive symptoms, but are associated with a high incidence of adverse metabolic effects (weight gain, hyperglycemia, hypercholesterolemia).[3] With a combination of medications and community-case management, remission of about 80% of patients can be achieved if treatment is initiated early during the first episode of the illness.[3] However, during the course of the disease, about one third of patients with schizophrenia remain symptomatic despite medications, psychological and vocational interventions.[3] In such patients, an attempt is often made to use a different antipsychotic, or add an anxiolytic, antidepressant and antiepileptic drug.[3] Other than switching to clozapine, additional treatments are of low proven value and may result in unnecessary polypharmacy.[3] Substance abuse is common in this population: more than half of patients with schizophrenia smoke and a significant higher number abuse cannabis and alcohol relative to the general population.[3]

New SGA drugs such as asenapine, iloperidone, lurasidone and paliperidone continue to be marketed as earlier second-generation drugs come off patent. In addition, several new SGA drugs have been recently approved by the U.S. Food and Drug Administration. Marketing of these new agents focuses not on comparative safety and efficacy but the slightly different pharmacological profiles of these agents with respect to affinity for dopamine or serotonin receptor subtypes, and adrenergic, histamine or muscarinic receptors. Many of these antipsychotics have not been directly compared in clinical trials so it has not been possible to generate clear hierarchies for the efficacy and safety of available regimens. However, drugs for mental health conditions, including SGAs, are by

Oregon rule are exempt from the traditional Preferred Drug List (PDL) and prior authorization (PA) requirements. However, specific clinical PA criteria may be placed to restrict medically inappropriate use or to address specific safety risks.[5]

Trials that assess antipsychotics routinely have high numbers of participant withdrawals (average is 35%). The reasons for patients discontinuing antipsychotic treatment are similar to those in other chronic illnesses except for 2 issues specific to schizophrenia: the stigma of being labeled as psychotic and the fact the dopamine-blocking medications inhibit motivational drive.[3] Unfortunately, high withdrawals in clinical trials frequently lead to poor quality evidence for antipsychotic agents.

Two common scales used to assess the efficacy of antipsychotic agents are the Positive and Negative Syndrome Scale (PANSS) and the Montgomery-Asberg Depression Rating Scale (MADRS). The PANSS is a widely used tool in clinical research to assess symptoms associated with schizophrenia.[6] The PANSS is a 30-item, 7-point rating instrument that uses a positive scale (7 items) to assess positive symptoms, a negative scale (7 items) to assess negative symptoms, and a 16-item General Psychopathology scale.[6] The 7-point rating scale represents increasing levels of psychopathology: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe; and 7 = extreme.[6] Therefore, a minimum score of 30 points to a maximum score of 210 points can be achieved. The instrument was validated in 101 patients with schizophrenia with means scores of 18.20 in the positive scale, 21.01 in the negative scale, and 37.74 in the general psychopathology scale.[6] The minimum clinically important difference (MCID) for PANSS scores is 50%,[7] though lesser differences (34%) have also been deemed relevant.[8] The MADRS is a 10-item diagnostic questionnaire used to measure severity of depressive episodes in patients with mood disorders.[9] Higher MADRS score indications more severe depression, and each item yields a score of 0 to 6 (total score range 0 to 60).[9] The questionnaire addresses the following items: 1) apparent depression; 2) reported depression; 3) inner tension; 4) insomnia; 5) reduced appetite; 6) concentration difficulties; 7) loss of interest; 8) difficulty in activities; 9) pessimism; and 10) suicidal ideation.[9] MCID estimates for MADRS range from 1.6 to 1.9.[10]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence for this review is on high quality systematic reviews and evidence-based guidelines.

Systematic Reviews:
A network meta-analysis (i.e., multiple-treatments meta-analysis) was performed to integrate all the evidence from available antipsychotics in treatment-resistant schizophrenia.[11] This technique was utilized to compare relative effect estimates between all antipsychotics that may or may not have been directly compared in any trial, but are part of a connected network through intermediate comparators (i.e., placebo, other antipsychotics) which allows statistical analyses between the agents and a more precise effect estimate. The analysis included all published and unpublished single- and double-blind RCTs (minimum 3 weeks duration) of adult patients with a treatment-resistant form of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Open-label trials were excluded because they systematically favored SGAs. All antipsychotics, at any dose and in any formulation that were compared with another antipsychotic

or placebo, were included if the antipsychotics were used as monotherapy. The primary outcome was the mean change from baseline to end point in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale, or any other validated scale for the assessment of overall schizophrenia symptoms. A clinically significant response to treatment, defined primarily as at least a 20% reduction of PANSS or Brief Psychiatric Rating Scale score, or at least minimum improvement on the Clinical Global Impressions Scale, was used as a secondary outcome. Forty unique RCTs were identified (n=5172; 71.5% male; mean age 38.8 years). Median trial duration was 11 weeks. The mean dropout rate was 32.0%, and 45% of the studies had evidence of selective reporting. The drug involved with the most comparisons was clozapine (20 of 40 trials), followed by haloperidol (15 of 40 trials), olanzapine (14 of 40 trials), and risperidone (12 of 40 trials). Few trials were available for the other drugs. Aripiprazole, perphenazine and thiothixene were included in the systematic review but were not included in the meta-analysis due to network limitations of the studies. Results from the meta-analysis found severe inconsistency between direct and indirect evidence due to older studies published before 1990 and so these studies had to be removed. Standardized mean differences (SMD) of -0.20 are considered small, -0.50 are considered medium, and -0.80 are considered large. Few statistically significant differences were found. Olanzapine was significantly more effective than quetiapine fumarate (SMD, -0.29, corresponding to -6.08 PANSS points; 95% confidence interval [CI], -0.56 to -0.02) and haloperidol (SMD, -0.29, corresponding to -6.08 PANSS points; 95% CI, -6.08 PANSS points; 95% CI, -0.44 to -0.13); and clozapine was significantly more effective than haloperidol (SMD, -0.22, corresponding to -4.61 PANSS points; 95% CI, -0.38 to -0.07). A pattern of superiority was seen for olanzapine, clozapine and risperidone in other efficacy outcomes, but results were inconsistent and effect sizes were usually small. Overall, there is insufficient evidence to determine whether one antipsychotic is more efficacious than another for patients with treatment-resistant schizophrenia. In addition, there is little evidence to show that clozapine is superior to other SGAs in this population despite its FDA-approved indication for treatment-resistant schizophrenia. Few significant differences were found in terms of adverse effects.[11]

A systematic review of literature was performed to determine the efficacy of antipsychotics for the management of hostility and aggression in patients with schizophrenia spectrum disorders (SSDs).[12] SSDs are associated with an elevated risk of committing violent acts such as assault or other violent crimes, and has been related to premorbid conduct disorders, positive symptoms of schizophrenia, especially paranoia, or concomitant antisocial or psychopathic traits. A total of 186 studies were identified that evaluated improvement in hostility or overt interpersonal aggression as primary or secondary outcomes. The studies showed considerable and problematic differences in quality (i.e., risk of bias) and research study design. Heterogeneity limitations included: diagnoses of the patient populations, which varied between populations confined to schizophrenia and mixed populations; clinical sites (inpatients vs. outpatients); adjunctive treatments (monotherapy with an antipsychotic vs. allowance for adjunctive treatments); and differing definitions for aggression. Given the diversity of research, the investigators sought to determine 1) if there is evidence that any medication will reduce overt aggression in patients with SSDs; 2) if there is evidence that any medication will reduce hostility in patients with SSDs; and 3) if there is evidence that one antipsychotic is more effective than another antipsychotic at reducing overt aggression or hostility in patients with SSDs. Of the original 186 studies, 92 studies provided sufficient methodological information to grade the evidence, which was classified according to the Academy of Neurology's recommendations for levels of evidence. Study durations ranged from 3 weeks to 3 years and included mostly inpatients. For reduction in overt aggression, there was insufficient placebo-controlled evidence. However, low quality evidence was found to suggest clozapine may be significantly superior to haloperidol at reducing over aggression among inpatients with SSDs on concomitant psychotropic medications. The comparative benefit of other antipsychotics is unknown. One observational study found evidence to support the use of SGAs over first-generation antipsychotics for overt aggression; however, the overall evidence was deemed insufficient to determine clinical significance. For reduction in hostility, only paliperidone extended-release (moderate-quality) and quetiapine (low-quality) have placebo-controlled evidence for efficacy among inpatients with SSDs on concomitant psychotropics. There is low-quality evidence clozapine may be more effective than chlorpromazine, chlorpromazine, or haloperidol at reducing hostility among patients with SSDs. There is also low-quality evidence that risperidone may be associated with significantly greater reduction in hostility versus haloperidol. The investigators concluded clozapine is possibly more effective than chlorpromazine, and risperidone is possibly more effective than

haloperidol for the management of hostility among inpatients with SSDs who are receiving other psychotropics. Specific study methods were detailed for each of the 92 studies; however, specific effect estimates were not disclosed.[12]

The comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia were recently assessed by multiple-treatments meta-analysis.[2] The investigators aimed to compare two prototypical first-generation antipsychotics (haloperidol and chlorpromazine) and 13 SGAs used in patients with schizophrenia in order to provide evidence-based hierarchies of comparative efficacy, risk of all-cause discontinuation, and major adverse effects of these agents. Multiple-treatments meta-analysis allows the integration of direct and indirect comparisons of antipsychotic drugs (ie, how 2 or more drugs compare with a common comparator) and provides evidence-based hierarchies when head-to-head comparisons are limited. Eligible studies included published and unpublished single-blinded or double-blinded RCTs of oral antipsychotic monotherapy in patients with schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder). Unblinded studies were excluded because they systematically favor SGAs. Studies in which sequence generation had a high risk of bias or in which allocation was not concealed were also excluded. To maintain homogeneity in the analysis, trials performed in patients with predominant negative symptoms, significant comorbidities, treatment resistance, and trials in patients with stable illness (ie, relapse prevention studies) were excluded. Doses of the antipsychotic could be flexible-dosed to allow titration to an adequate dose, or fixed-dose if doses were at target doses. The primary outcome was the mean overall change in symptoms, which was assessed by change in PANSS (total score from baseline to endpoint); if data from this scale were not available, change in Brief Psychiatric Rates scale from baseline to endpoint was used. Secondary outcomes were all-cause discontinuation, weight gain, use of antiparkinson drugs as a measure of extrapyramidal adverse effects, prolactin increase, QTc prolongation and sedation. A total of 212 studies reported between 1955 and September 2012 (n=43,049) were included in the analysis. The mean duration of illness was 12.4 years and the mean age was 38.4 years. Most studies (n=199, 94%) were double-blinded and the remaining 13 studies were single-blinded, but few details were reported about the methods of allocation concealment or how successful they were. Overall, premature discontinuation rates in the studies were around 35%, which is consistent with expectations of investigators of these studies. Standardized mean differences (SMD) between drugs were assessed. As a general rule, a SMD of -0.2 is small, -0.5 is medium, and -0.8 is larger. All drugs were superior to placebo (range of mean effect sizes -0.33 to -0.88). Clozapine was significantly more effective than all the other drugs (SMD 0.88; 95% CI, 0.73-1.03). After clozapine, olanzapine (SMD 0.59; 95% CI, 0.53-0.65) and risperidone (SMD 0.56; 95% CI, 0.50-0.63) were significantly more effective than the other drugs apart from paliperidone (SMD 0.50; 95% CI, 0.39-0.60) but these effect sizes were small. All-cause discontinuation was used as a measure of acceptability of treatments because it encompasses efficacy and tolerability. All of the U.S. approved drugs were significantly better than placebo. Olanzapine (range of significant mean odds ratios (OR) 0.58-0.76; numbers-needed-to-treat (NNT) 9-17), clozapine (OR 0.57-0.67; NNT 9-12), paliperidone (OR 0.60-0.71; NNT 9-14) and risperidone (OR 0.66-0.78; NNT 11-18) had significantly lower all-cause discontinuation than several other drugs. Haloperidol (OR 0.80; NNT 20) was worse than quetiapine (OR 1.32; NNT 15) and aripiprazole (OR 1.33; NNT 15). Apart from haloperidol, ziprasidone, and lurasidone, all drugs produced more weight gain than placebo, with olanzapine associated with the most weight gain (SMD -0.74). Olanzapine also produced significantly more weight gain than most other drugs. Clozapine, iloperidone, chlorpromazine, quetiapine, risperidone and paliperidone produced significantly more weight gain than haloperidol, ziprasidone, lurasidone, aripiprazole and asenapine. Standardized mean differences for these comparisons ranged from -0.18 to -0.57. Clozapine, olanzapine, quetiapine, aripiprazole, iloperidone and asenapine did not cause significantly more extrapyramidal side-effects than placebo. The range of OR and numbers-needed-to-harm (NNH) for the other drugs were 1.61-4.76 and 3-11, respectively. Clozapine produced fewer extrapyramidal side-effects than all other drugs and placebo (range of mean OR 0.06-0.40; NNT 5-9), and was followed by olanzapine and quetiapine. Haloperidol caused significantly more extrapyramidal side-effects than the other drugs except for chlorpromazine, for which the difference was not significant. Lurasidone, aripiprazole, paliperidone and asenapine were not associated with significant QTc prolongation compared to placebo. Paliperidone and iloperidone were not significantly more sedating than placebo, but mean ORs and NNHs for other drugs ranged from 1.84 and 10 for aripiprazole) to 8.82 and 2 for clozapine, respectively. The authors emphasized that the differences in efficacy between drugs were small (standardized mean differences 0.11-0.55, median 0.24), and smaller overall than for harms outcomes for which there was more robust differences between antipsychotics. The efficacy differences compared to

placebo were of medium size (0.33-0.88, median 0.44), so the differences in efficacy found between the drugs are possibly substantial enough to be clinically important.

The effects of quetiapine were compared with other SGA drugs in a systematic review with meta-analysis published by the Cochrane Collaboration.[7] All RCTs that evaluated oral quetiapine with other oral SGA drugs in patients with schizophrenia or with schizophrenia-like psychosis were included.[7] Extensive literature searches were used without restriction to language or publication status.[7] Authors of manuscripts and drug sponsors were contacted for missing information.[7] Risk ratios (RR) were calculated for dichotomous outcomes based on an intention-to-treat (ITT) analysis and random effects model.[7] Mean differences (MD) were calculated for continuous outcomes and were also analyzed based on a random-effects model.[7] Risk of bias for each included study and used GRADE approach to rate quality of evidence.[7] Overall, efficacy tended to favor other SGA drugs compared to quetiapine but the clinical relevance of these differences remains unclear.[7] There is low quality evidence from 11 RCTs (n=1486) that the total PANSS score was superior with olanzapine compared to quetiapine by a mean score of 3.67 (95% CI, 1.95 to 5.39).[7] There is moderate quality evidence from 13 RCT (n=2155) that the total PANSS score was superior with risperidone compared to quetiapine by a mean score of 1.74 (95% CI, 0.19 to 3.29).[7] There is moderate quality evidence from 1 RCT (n=319) that the total PANSS score was superior with risperidone compared to quetiapine by a mean score of 1.74 (95% CI, 0.19 to 3.29).[7] There is moderate quality evidence from 1 RCT (n=319) that the total PANSS score was superior with paliperidone compared to quetiapine by a mean score of 6.30 (95% CI, 2.77 to 9.83).[7] There were no clear differences in efficacy between quetiapine and clozapine, aripiprazole or ziprasidone.[7] In terms of harms outcomes, moderate quality evidence tended to favor quetiapine over olanzapine.[7] Quetiapine produced fewer movement disorders in the clinical trials (RR for use of antiparkinson drug = 0.51; 95% CI, 0.32 to 0.81; 7 RCTs [n=1127]), led to less weight gain (RR 0.68; 95% CI, 0.51 to 0.92; 8 RCTs [n=1667]), and did not result in as much glucose elevation; however, incidence of QTc prolongation was higher with quetiapine compared to olanzapine (MD 4.81%; 95% CI 0.34 to 0.98; 3 RCTs [n=643]).[7] There is moderate quality evidence that quetiapine induced fewer movement disorders (RR for use of antiparkinson drug = 0.50; 95% CI, 0.36 to 0.69; 8 RCTs [n=2163]) but increased total cholesterol levels compared to risperidone (MD 8.57 mg/dL; 95% CI, 4.85 to 12.29; 6 RCTs [n=1473]).[7] There is also moderate quality evidence, though based on more limited data, that paliperidone induced more movement disorders (RR for use of antiparkinson drug = 0.64; 95% CI, 0.45 to 0.91; 1 RCT [n=319]) and more weight gain compared to quetiapine (RR for total body weight gain ≥7% = 2.52; 95% CI, 0.50 to 12.78; 1 RCT [n=319].[7] Compared to ziprasidone, there is moderate quality evidence quetiapine produced slightly fewer movement disorders (RR for use of antiparkinson drug = 0.43; 95% CI, 0.20 to 0.93; 1 RCT [n=522]).[7] Compared to ziprasidone, however, there is moderate quality evidence that quetiapine resulted in more sedation, increased cholesterol and led more weight gain (RR 2.22; 95% CI, 1.35 to 3.63; 2 RCTs [n=754]).[7] About 60% of subjects who started quetiapine in the RCTs quit taking it within a few weeks.[7] Differences found in the meta-analysis were small and it is unclear whether the differences are clinically meaningful. The authors found that most of the direct head-to-head comparisons were of limited value because of the assumptions and biases identified in the studies.[7]

The efficacy and tolerability of aripiprazole was compared to other SGA drugs in an updated systematic review with meta-analysis published by the Cochrane Collaboration.[13] All RCTs (both open and double-blinded) that evaluated oral aripiprazole with other SGA drugs in patients with schizophrenia or with schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders) were included.[13] Open-label studies were only included because the investigators felt that important data could be provided that might otherwise be overlooked.[13] Comparator SGAs included oral or parenteral formulations of clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Extensive literature searches were used without restriction to language or publication status.[13] Authors of manuscripts and drug sponsors were contacted for missing information.[13] Risk ratios were calculated for dichotomous outcomes based on an ITT analysis and random effects model.[13] Mean differences were calculated for continuous outcomes and were also analyzed based on a random-effects model.[13] Risk of bias for each included study and used GRADE approach to rate quality of evidence.[13] Data from 174 RCTs (n=17,244) were included in the updated systematic review. Overall, 30-40% of study participants in these trials discontinued the study prematurely but there were no differences between groups.[13] The primary outcomes used by the Cochrane investigators were: 1) global state, defined as 'no clinically important response' as defined by the individual studies

(e.g., global impression less than much improved or less than 50% reduction on a rating scale); 2) general functioning, defined as 'no clinically important change in general functioning'; and 3) adverse effects, defined as 'clinically important specific adverse effects'.[13] When compared to clozapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (29 RCTs; n=2132); mental state (Brief Psychiatric Rating Scale [BPRS]) (5 RCTs; n=426) or premature study discontinuation (3 RCTs; n=240).[13] Quality of life (as assessed by the WHO-QOL-100 scale) was statistically superior with aripiprazole compared to clozapine (RR 2.59; 95% CI, 1.43 to 3.74; 2 RCTs; n=132) based on low quality evidence but no difference was seen between aripiprazole and clozapine with regard to extrapyramidal symptoms (EPS).[13] When compared to quetiapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (12 RCTs; n=426); mental state (PANSS positive symptoms) (7 RCTs; n=583); premature study discontinuation (2 RCTs; n=168); or EPS (4 RCTs; n=348).[13] Quality of life (as assessed by the WHO-QOL-100 scale) was statistically superior with aripiprazole compared to quetiapine (MD 2.60; 95% CI, 1.31 to 3.89; 1 RCT; n=100) based on low quality evidence.[13] When compared to risperidone, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (80 RCTs; n=6381) or premature study discontinuation (12 RCTs; n=1239).[13] Mental state status (BPRS) (5 RCTs; n=570) was statistically superior with aripiprazole compared to risperidone (MD 1.33; 95% CI, 2.24 to 0.42) based on low quality evidence.[13] Risperidone use was associated with more EPS compared to aripiprazole (RR 0.39; 95% CI, 0.31 to 0.50; 31 RCTs; n=2605).[13] When compared to ziprasidone, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (6 RCTs; n=442); mental state (BPRS) (1 RCT; n=247) or premature study discontinuation (2 RCTs; n=316).[13] Weight gain was significantly greater in people who received aripiprazole compared to ziprasidone (RR 4.01; 95% CI, 1.10 to 14.60; 3 RCTs; n=232) based on low quality evidence.[13] When compared to olanzapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (11 RCTs; n=1739); mental state (PANSS) (11 RCTs; n=1500) or quality of life using the GQOLI-74 scale (1 RCT; n=68).[13] Significantly more patients on aripiprazole discontinued the study prematurely compared to patients on olanzapine (RR 1.15; 95% CI, 1.05 to 1.25; 9 RCTs; n=2331) based on low quality evidence.[13] However, less patients gained weight on aripiprazole versus olanzapine (RR 0.25; 95% CI, 0.15 to 0.43; 9 RCTs; n=1538) based on low quality evidence.[13] The investigators found large gaps in important outcomes and found all comparisons of limited quality and problematic for clinical application.[13] Long-term data are sparse.[13]

Perphenazine is a first-generation antipsychotic drug with similar potency to haloperidol[14] The efficacy and tolerability of perphenazine was compared to other antipsychotic drugs and placebo in a systematic review with meta-analysis published by the Cochrane Collaboration.[14] All double-blind RCTs that evaluated perphenazine (depot formulations were excluded) with other antipsychotic drugs or placebo in patients with schizophrenia or with schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders) were included.[14] Extensive literature searches were used without restriction to publication status.[14] Authors of manuscripts and drug sponsors were contacted for missing information.[14] Risk ratios were calculated for dichotomous outcomes based on an ITT analysis and random effects model.[14] Mean differences were calculated for continuous outcomes and were also analyzed based on a random-effects model.[14] Risk of bias for each included study and used GRADE approach to rate quality of evidence.[14] Thirty-one parallel group studies, most commonly 12 weeks in duration (range 10 days to 18 months), met inclusion criteria (n=4662).[14] The trial centers were located in Europe, Japan and North America.[14] The primary outcomes were clinical response in global state or mental state, as defined by the individual studies.[14] When perphenazine was compared to placebo, there is low quality evidence that more patients who received placebo either had no improvement in symptoms or deterioration of symptoms when global state was assessed than patients who received perphenazine (RR 0.32; 95% CI, 0.13 to 0.78; 1 RCT; n=61).[14] There was also a non-statistically significant and very imprecise increase in the number of patients who took placebo and relapsed compared to placebo (RR 0.14; 95% CI, 0.02 to 1.07; 1 RCT; n=48) based on low quality evidence.[14] There were no differences between perphenazine and placebo in rates of dystonia (RR 1.00; 95% CI, 0.07 to 15.08; 1 RCT; n=48) based on low quality and imprecise data.[14] There is low quality evidence that there are no differences between perphenazine and other antipsychotic drugs in terms of lack of clinical response (RR 1.04; 95% CI, 0.91 to 1.17; 17 RCTs; n=1879).[14] For the mental state outcome of 'no effect', as defined by individual trials, there was also no significant difference between perphenazine and other antipsychotic drugs (RR 1.24; 95% CI, 0.61 to 2.52; 4 RCTs; n=383) based on low quality evidence.[14] There

was no difference seen in rates of dystonia with perphenazine and other antipsychotic drugs (RR 1.36; 95% CI, 0.23 to 8.16; 4 RCTs; n=416) or serious adverse events (RR 0.98; 95% CI, 0.68 to 1.41; 2 RCTs; n=1760) based on low quality evidence.[14] No deaths were reported in the included studies.[14] The investigators concluded that the reporting of outcomes varied greatly over the span of 50 years of clinical trials of perphanzine, which make it impossible to draw clear conclusions.[14] Evidence for perphanzine is of low quality and the assumptions so far indicate that perphenzine may be equally effective and safe as other antipsychotic drugs in the management of schizophrenia.[14]

Treatment guidelines state that there is no difference in efficacy between first-generation antipsychotic agents.[15] A series of systematic reviews with meta-analyses were conducted by the Cochrane Collaboration to determine whether oral first-generation antipsychotics considered to be highly potent differed in efficacy or safety to oral first-generation antipsychotic agents considered to have low potency in patients with schizophrenia or schizophrenia-like psychosis.[15] Typical examples of low-potency oral antipsychotic drugs are chlorpromazine, chlorprothixene, thioridazine or levomepromazine.[15] In each review, the Cochrane Schizophrenia Group Trials Register was searched to find RCTs that compared high-potency first-generation antipsychotic drugs with first-generation, low-potency antipsychotic drugs for people with schizophrenia or schizophrenia-like psychosis.[15] Risk ratios and 95% CIs were calculated for dichotomous data and MDs were calculated for continuous data on an ITT basis and using a random-effects model.[15] The GRADE approach was used to interpret findings in each review.

The first systematic review compared perphenazine to low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.[15] Four RCTs (n=365) met inclusion criteria.[15] Methods of sequence generation and concealment of allocation were inadequately reported but most studies were rated as low risk of bias in terms of blinding.[15] Attrition bias in the studies was high.[15] There is moderate quality evidence that perphenzine and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (58% for perphenazine vs. 59% for low-potency antipsychotic agents; RR 0.97; 95% CI, 0.74 to 1.26; 2 RCTs; n=138).[15] Early discontinuation in the trials was also similar between the groups (30% for perphenazine vs. 28% for low-potency antipsychotic agents; RR 0.78; 95% CI, 0.35 to 1.76; 3 RCTs; n=323) based on low quality evidence.[15] There were also no significant differences in the incidence of at least one adverse effect and experiencing at least one movement disorder but the overall numbers were low and the data imprecise.[15] Akathisia was more frequent in the perphenazine group (25%) compared to low-potency antipsychotic agents (22%).[15] No data were available for quality of life or sedation.[15] Thus, there is low-quality evidence that suggests perphenazine, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of safety and efficacy.[15]

The second systematic review compared haloperidol to oral low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.[16] Seventeen RCTs (n=877) of 2 to 12 weeks' duration met inclusion criteria.[16] All studies had poorly described sequence generation, allocation procedures and blinding.[16] There is low quality evidence that haloperidol and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (40% for haloperidol vs. 36% for low-potency antipsychotic agents; RR 1.11; 95% CI, 0.86 to 1.44; 14 RCTs; n=574).[16] Early discontinuation in the trials was also similar between the groups (13% for haloperidol vs. 17% for low-potency antipsychotic agents; RR 0.82; 95% CI, 0.38 to 1.77; 11 RCTs; n=408) based on low quality evidence.[16] There were also no significant differences in the incidence of at least one adverse effect but the overall numbers were low and the data imprecise and of low quality.[16] There is moderate evidence that more patients on low-potency antipsychotic drugs experienced sedation (haloperidol 14% vs. low-potency antipsychotics 41%; RR 0.30; 95% CI, 0.11 to 0.82; 2 RCTs; n=44), orthostatic symptoms (haloperidol 25% vs. low-potency antipsychotics 71%; RR 0.35; 95% CI, CI 0.16 to 0.78; 1 RCT; n=41), and weight gain (haloperidol 5% vs. low-potency antipsychotics 29%; RR 0.22, 95% CI, 0.06 to 0.81; 3 RCTs, n=88).[16] However, movement disorders were more frequent reported in the haloperidol group (haloperidol 72% vs. low-potency antipsychotics 41%; RR 1.64; 95% CI, 1.22 to 2.21; 5 RCTs; n=170) based on low quality evidence.[16] No data were available for death or quality of life.[16] Thus, there is low-quality evidence that

suggests haloperidol, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of efficacy but there may be differing harms.[16]

The third systematic review compared trifluoperazine to oral low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.[17] Seven RCTs (n=422) of 4 to 52 weeks' duration met inclusion criteria.[17] All studies had poorly described sequence generation, allocation procedures and blinding.[17] There is moderate quality evidence that trifluoperazine and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (26% for trifluoperazine vs. 27% for low-potency antipsychotic agents; RR 0.96; 95% CI, 0.59 to 1.56; 3 RCTs; n=120).[17] Early discontinuation in the trials was also similar between the groups (20% for trifluoperazine vs. 16% for low-potency antipsychotic agents; RR 1.26; 95% CI, 0.72 to 2.17; 3 RCTs; n=239) based on low quality evidence.[17] There were also no significant differences in the incidence of at least one adverse effect but the overall numbers were low and the data imprecise and of low quality.[17] However, movement disorders were more frequently reported with trifluoperazine (23%) than with low-potency antipsychotic agents (13%) (RR 2.08; 95% CI, 0.78 to 5.55; 2 RCTs; n=123) based on low quality an imprecise data.[17] No data were available for death, sedation and quality of life.[17] Thus, there is low-quality evidence that suggests trifluoperazine, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of safety and efficacy.[17]

Tic disorders (TD) are classified as transient tic disorder (TTD), chronic tic disorder CTD) and Tourette syndrome (TS), and are common neuropsychiatric disorders in children who commonly have other concurrent comorbidities such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, oppositional defiant disorder and other mood disorders.[18] Symptoms include sudden, fast, repetitive, non-rhythmic motor movements and/or phonic production.[18] Management of these symptoms have been controlled by antipsychotic medications like haloperidol, but dystonia typically draw prescribers to use SGA drugs like aripiprazole or risperidone. Oral formulations of aripiprazole recently received an expanded FDA-approved indication for Tourette disorder in December 2014.[19] A recent systematic review assessed to efficacy and safety of aripiprazole for children with TDs.[18] All RCTs and open-label control studies that compared aripiprazole to placebo or other drugs used in the management of TDs (e.g., haloperidol) in children were included.[18] Trials were excluded if the data for the children could not be obtained by the study authors or drug sponsors and if the doses studied were unfair comparisons (e.g., high vs. low doses).[18] Scales used to assess TD symptoms included the Yale Global Tic Severity Scale (YGTSS); the Clinical Global Impression (CGI) Scale; the Tourette Syndrome Global Scale; the Tourette Syndrome Global List; the Clinical Global Impression Tic Severity Scale; and the Tourette Syndrome Severity Scale.[18] Results for dichotomous outcomes are expressed as RR with 95 % CIs.[18] Results for continuous outcomes are expressed as the MD.[18] We evaluated heterogeneity among the included studies using the I^2 test.[18] Twelve poor quality studies (n=935; 76% male; age range between 4 and 18 years) were included.[18] Nine studies were conducted in China, 2 studies in Korea and one in Iran.[18] Studies were short-term and ranged from 8 to 12 weeks in duration.[18] All of the studies used an active control (haloperidol (n=7); tiapride (n=3); risperidone (n=1) and one study used a placebo control.[18] Seven studies (n=600) used the YGTSS scale as the outcome measurement.[18] There was no significant difference in reduction of the total YGTSS score between the aripiprazole and active control groups (MD -0.48; 95% CI, -6.22 to 5.26; p=0.87; I^2=87%).[18] Meta-analysis of 4 studies (n=285) that compared aripiprazole with haloperidol showed that there was no significant difference in reduction of the total YGTSS score (MD 2.50; 95% CI, -6.93 to 11.92; p=0.60; I^2=88%).[18] Meta-analysis of 2 studies (n=255) that compared aripiprazole with tiapride showed that there was no significant difference in reduction of the total YGTSS score (MD -3.15; 95% CI, -11.38 to 5.09; p=0.45; I^2=86%).[18] One double-blind, placebo-controlled RCT also used the total YGTSS score as a primary endpoint and showed a statistically significant reduction of the total YGTSS score (13.6 ±9.1 vs. 19.9 ±9.5; p<0.05) and vocal tic score (5.0 ±4.6 vs. 8.0 ±5.5; p<0.05) with aripiprazole compared to placebo.[18] However, there was no statistically significant difference in reduction of the motor tic score (8.6 ±6.1 vs. 11.9 ±5.5; p>0.05).[18] Overall, aripiprazole has demonstrated efficacy in management of TDs, with comparable effectiveness to haloperidol.

Robust epidemiologic evidence was recently systematically reviewed to compare mortality and risk for significant medical events, such as stroke, ventricular arrhythmia, venous thromboembolism, myocardial infarction, pneumonia and hip fracture between first-generation antipsychotic agents and SGAs.[20] An additional objective was to quantify how much these medical events explain the observed mortality difference between first- and second-generation antipsychotic agents.[20] Studies that evaluated these outcomes in patients with a mean age of 65 years and older were included.[20] Twenty observational cohort studies that reported on 28 associations met inclusion criteria.[20] Among these studies, a higher mortality rate occurred in patients on first-generation antipsychotic drugs compared to SGAs in the first 6 months after initiation of antipsychotic therapy (avg. relative risk = 1.4; risk difference = 4.3% [range 2.5% to 7.3%] in community dwelling and long-term care residents.[20] Based on the model used by the investigators, up to 6.7% of the higher mortality for first-generation antipsychotic drugs was due to stroke, 6.6% to hip fracture, 3.5% to myocardial infarction, and 0.9% to ventricular arrhythmia (17.4% combined).[20] The lower and upper bounds that adjust for poor diagnostic sensitivity and other potential biases were 7.4% and 18.9% for stroke, 1.3% and 9.2% for hip fracture, 4.2% and 9.5% for myocardial infarction, and 3.9% to 4.8% for ventricular arrhythmia (16.8% and 42.4% combined); the lower bounds are higher than the point estimate because poor sensitivity of diagnostic algorithms leads to downward bias.[20] The authors concluded that the current evidence suggests that hip fracture, stroke, myocardial infarction, and ventricular arrhythmias partially explain the mortality difference between first-generation antipsychotic drugs and SGAs.[20]

A systematic review was conducted to assess absolute changes in body weight and body mass index (BMI) as well as the proportion of patients with greater than a 7% increase or decrease in body weight after initiation of a first- or second-generation antipsychotic drug.[21] A 7% weight gain or loss was deemed clinically relevant.[21] Any RCT or controlled clinical trial where patients were randomized into various antipsychotic intervention groups was eligible to be included.[21] No restrictions with regard to diagnosis, age, drug dose or duration of drug exposure were applied.[21] Data from 307 RCTs with ITT analysis were included.[21] Four drug exposure categories were defined based on duration of antipsychotic use: short-term (≤6 weeks), medium short-term (6-16 weeks), medium term (16-38 weeks) and long term (>38 weeks).[21] Most drugs showed a statistically significant change in weight post-baseline, with the exception of amisulpride, aripiprazole, asenapine, sertindole, ziprasidone and placebo, which showed no statistically significant weight change.[21] Although a comparison between antipsychotic agents was not tested, crude data suggested that clozapine and olanzapine were associated with the most severe weight gain post-baseline, while first-generation antipsychotic drugs (e.g., haloperidol) are also associated with significant weight gain.[21] Even over the shortest exposure period of 6 weeks, an increase in body weight post-baseline was evident for most antipsychotic agents.[21] The number of studies reporting data on BMI change in treatment-naïve patients was limited to 18 studies.[21] All antipsychotic agents studied showed a statistically significant increase in BMI.[21] Only 11 studies presented data of 7% weight gain in treatment-naïve patients.[21] Almost all antipsychotic agents reported a statistically significant increase in the proportion of subjects with clinically relevant weight gain.[21] Apart from the short-term exposure (6 weeks), treatment with aripiprazole resulted in an elevated number of subjects with clinically relevant weight gain at each duration of exposure category.[21] Twenty-four studies reported on proportional weight loss.[21] Only data for amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, ziprasidone and placebo were available.[21] Results showed that a statistically significant proportion of the patients had clinically relevant weight loss after initiation of any of these drugs, a duration-response pattern was not observed.[21] The investigators concluded that given prolonged exposure to these drugs, virtually all antipsychotic drugs are associated with weight gain and the rational of switching antipsychotic agents to achieve weight reduction may be overrated.[21]

A systematic review was conducted to identify and analyze data on first-trimester exposure to olanzapine, quetiapine, risperidone and aripiprazole and risk of congenital malformations.[22] Any studies that contained original data on first-trimester exposure and pregnancy outcome with respect to congenital malformations were included.[22] Cumulated data for olanzapine were 1090 first-trimester-exposed pregnancies with 38 malformations resulting in a malformation rate of 3.5%.[22] The corresponding numbers for quetiapine, risperidone and aripiprazole were 443/16 (3.6%), 432/22 (5.1%) and 100/5 (5.0%), respectively.[22] Relative risk estimates were 1.0 (95% CI, 0.7 to 1.4) for olanzapine, 1.0 (95% CI, 0.6 to 1.7) for quetiapine, 1.5 (95% CI, 0.9 to 2.2) for risperidone,

and 1.4 (95% CI, 0.5 to 3.1) for aripiprazole.[22] The authors concluded that first-trimester exposure to olanzapine is not associated with an increased risk of congenital malformation.[22] Data for quetiapine and risperidone also do not suggest a substantially increased risk, while the risk estimate for aripiprazole remains imprecise owing to limited data.[22]

The aim of a recent systematic review was to compare the long-term effects of various antipsychotic drugs on overall cognition and on specific cognitive domains in patients with schizophrenia.[23] To identify relevant publications, multiple databases were searched without language restrictions for RCTs in which an oral formulation of SGA drug (amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine) was compared to placebo or haloperidol or other SGA drugs, for the treatment of schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorders).[23] Nine RCTs of at least 6 months duration (median 52 weeks) were included.[23] A network meta-analysis was used to combine direct and indirect comparisons of the cognitive effects between antipsychotics.[23] The comparison between each treatment on the overall cognitive score showed that quetiapine and olanzapine led to more improvement than amisulpride ($p<0.05$) and haloperidol ($p<0.05$).[23] The significant effect sizes were 0.27 [0.13-0.41] for quetiapine; 0.21 [0.10-0.32] for olanzapine; and 0.16 [0.02-0.30] for risperidone.[23] Quetiapine and olanzapine also provided better improvement in overall cognitive score than amisulpride in cognitive tasks (effect sizes: 0.27 [0.10-0.44], and 0.20 [0.04-0.37], respectively).[23] No statistically significant difference between quetiapine, olanzapine and risperidone in overall cognitive scores was found.[23] When memory tasks were considered, ziprasidone faired better than amisulpride (0.28 [0.02-0.54]) and haloperidol (0.32 [0.09-0.55]).[23] Quetiapine was better than other drugs ($p<0.001$) on attention and processing speed tasks, followed by ziprasidone ($p<0.05$) and olanzapine ($p<0.05$).[23] The effects of quetiapine, risperidone and olanzapine were better than those of amisulpride ($p<0.05$) on executive functions.[23] The authors concluded that differences between antipsychotics in their effect on the overall cognitive score in schizophrenia may exist.[23] Quetiapine and olanzapine were associated with the most positive effects on cognitive function, followed by risperidone, ziprasidone, amisulpride and haloperidol.[23]

New Guidelines:

U.S. Department of Health & Human Services Officer of Inspector General (OIG) analysis of Medicaid claims in five states, 2014.

Second-generation antipsychotics are widely used to treat children enrolled in Medicaid who have mental health conditions.[24] However, SGAs can have serious side effects and little clinical research has been conducted on the safety of treating children with these drugs.[24] Consequently, children's treatment with SGAs needs careful management and monitoring.[24] This OIG report examined the quality of care provided to children receiving SGAs that were paid for by Medicaid based a sample of 687 claims for SGAs prescribed to children in California, Florida, Illinois, New York, and Texas, which represented 39% of total Medicaid payments for SGAs in 2011.[24] Board-certified child and adolescent psychiatrists reviewed medical records related to the sampled claims using 7 criteria related to quality-of-care concerns, which were established on the basis of information and guidelines issued by various Federal and State agencies and professional associations regarding the prescribing of psychotropic drugs to children.[24] Of the claims reviewed, 67% showed quality-of-care concerns, which were further categorized by the 7 identified criteria[24]:

- 41% wrong treatment
- 17% too young
- 7% side effects
- 53% poor monitoring
- 34% taken too long
- 23% wrong dose
- 37% too many drugs

In the 5 states, 8% of SGAs were prescribed for the limited number of medically accepted pediatric indications.[24] There are only 5 SGAs with medically accepted pediatric indications.[24] Medically accepted indications include both uses of drugs approved by the Food and Drug Administration (FDA) and uses supported by one or more of 3 drug compendia.[24] Three of the 11 SGAs carry an FDA boxed warning regarding increased chances of suicidal thinking and behavior in pediatric patients.[24] The investigators found that over a third of SGAs were prescribed in the presence of conditions described in the FDA boxed warning.[24]

To ensure the quality of the care provided to children receiving SGAs, The OIG report made 3 recommendations to the Centers for Medicare & Medicaid Services (CMS). First, the OIG recommended that CMS work with State Medicaid programs to perform utilization reviews of SGAs prescribed to children.[24] Second, the OIG recommended that CMS work with State Medicaid programs to conduct periodic reviews of medical records associated with claims for SGAs prescribed to children.[24] Third, the OIG recommended that CMS work with States to consider other methods of enhanced oversight of SGAs prescribed to children, such as implementing peer review programs.[24] CMS concurred with all three recommendations.[24]

New Safety Alerts:

GEODON (ziprasidone)[25]

FDA labeling addition to Warnings and Precautions [December 2014]: *Severe Cutaneous Adverse Reactions, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome have been reported with ziprasidone exposure. DRESS and other Severe Cutaneous Adverse Reactions (SCAR) are sometimes fatal.*[25] *Discontinue Geodon if DRESS or other types of SCAR are suspected*.[25]

New Formulations or Indications:

Oral formulations of aripiprazole received an expanded FDA-approved indication for Tourette disorder in December 2014.[19] The recommended dosage range for Tourette's disorder is 5-10 mg daily.[19] Doses should be initiated at 2 mg daily and adjusted gradually in increments of 5 mg daily at intervals of no less than 1 week to achieve adequate control of tics.[19] FDA approval was based on 2 short-term placebo-controlled trials (8-10 weeks) in pediatric patients (ages 6-18 years) who met DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) of ≥20-22 on the YGTSS.[19] The primary endpoint in both trials was the change from baseline in the TTS of the YGTSS.[19] Ratings for the TTS are made from 5 domains on a 0-5 scale for motor and vocal tics each (summation of these 10 scores provides a TTS, 0-50).[19] In these trials, aripiprazole statistically significantly reduced YGTSS TTS by -5.3 to -9.3 relative to placebo.[19]

ARISTADA (aripiprazole lauroxil) is an extended-release suspension for intramuscular (IM) injection approved by the FDA in October 2015 for schizophrenia in patients who have established tolerability with oral aripiprazole.[26] Aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) is a prodrug of N-hydroxymethyl aripiprazole, which in turn is a prodrug of aripiprazole.[27] Because aripiprazole lauroxil contains an active moiety (N-hydroxymethyl aripiprazole) that has not been approved in any new drug application by the FDA, it was considered a new drug entity.[27] The efficacy of aripiprazole lauroxil extended-release IM injection was evaluated in a Phase 3 safety and efficacy trial that demonstrated efficacy of 2 doses (441 mg and 882 mg, both given monthly) in patients with schizophrenia.[28] In addition, the FDA considered previous evidence of the safety and efficacy of oral aripirazole when data were reviewed for aripiprazole lauroxil, as well as pharmacokinetic evidence from the sponsor that demonstrated similar serum concentrations for oral aripiprazole given daily at approved doses with aripiprazole lauroxil given monthly at the studied doses.[27] The Phase 3 trial enrolled adult patients with an acute exacerbation of schizophrenia that required hospital admission.[28] All other antipsychotic medications were discontinued.[28] The primary endpoint was change in the PANSS total score from baseline to day 85 using LOCF at the imputation method.[28] The PANSS total score was statistically significantly reduced for the 441 mg dose (LSMD -10.65; 95% CI, -14.30, -6.99) and the 882 mg dose (LSMD -11.94; 95% CI, -15.56, -8.32) compared to placebo.[28] During the first 21 days of the trial, the active treatment arms also received oral aripiprazole while patients who received IM placebo did not.[27] The FDA was concerned that this may confound the study results, and so the primary analysis was repeated using PANSS data from Day 22 and Day 29 as the baseline.[27] The mean difference from placebo was less using data from day 22

for the 441 mg dose (LSMD -5.3; 95% CI, -8.3, -2.3) and 882 mg dose (LSMD -4.6; 95% CI, -7.6, -1.7) but these data were still statistically significant.[27] From Day 29, the mean difference from placebo was also less for the 441 mg dose (LSMD -4.5; 95% CI, -7.4, -1.6) and 882 mg dose (LSMD -4.0; 95% CI, -6.9, -1.1) but these data were also still statistically significant.[27] There were no new safety findings for aripiprazole lauroxil compared to what is known about oral aripiprazole, except for injection site reactions.[27]

INVEGA TRINZA (paliperidone palmitate; PP3M) is an extended-release suspension for IM injection (administered every 3 months) approved by the FDA in May 2015 for schizophrenia in patients who already adequately treated with INVEGA SUSTENNA (paliperidone palmitate; PP1M) administered once monthly for at least 4 months.[29] Paliperidone is the metabolite of risperidone, which is an atypical antipsychotic approved since 1993.[30] The efficacy of PP3M was based on one randomized, double-blind, placebo-controlled relapse-prevention study wherein patients were stabilized for 12 weeks on PP3M after a 17-week transition phase from PP1M.[31] The primary efficacy endpoint was time to relapse after randomization of patients to continue PP3M after the 12-week maintenance phase or switch to placebo.[31] The study was stopped in accordance with the protocol when statistical significance in favor of PP3M was demonstrated at the pre-planned interim analysis of time to relapse data.[31] Approximately 3-time as many patients in the placebo group (29%) as in the PP3M group (9%) experienced a relapse event (hazard ratio 3.45; 95% CI, 1.73 to 6.88), with the most common relapse events being worsening of psychotic symptoms or psychiatric hospitalization.[31] No unique safety findings were noted for PP4M other than a small increase in subjectively rated injection site pain, which may be related to the increased injection volume with PP3M versus PP1M.[29]

SAPHRIS (asenapine) received an expanded FDA-approved indication as monotherapy for pediatric patients ages 10 to 17 years with Bipolar mania in March 2015.[32] The efficacy of asenapine for the management of acute mania associated with Bipolar I disorder was established in one 3-week, placebo-controlled, double-blind trial of 403 pediatric patients 10 to 17 years of age.[33] A total of 302 patients received fixed doses of 2.5 mg, 5 mg and 10 mg twice daily (all initiated at 2.5 mg twice daily).[33] All doses of asenapine were statistically superior to placebo in improving YMRS total score compared to placebo (2.5 mg: LSMD -3.2; 95% CI, -5.6, -0.8; 5 mg: LSMD -5.3; 95% CI, -7.7, -2.9; 10 mg: LSMD -6.2; 95% CI, -8.6, -3.8).[33]

NEW DRUG EVALUATIONS:

See **Appendix 2** 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:

Brexpiprazole

Brexpiprazole is an oral atypical antipsychotic approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).[34]

The efficacy of brexpiprazole for schizophrenia was established in two 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 0.25 to 4 mg daily (see Table 3).[35,36] Overall, 1,310 patients with schizophrenia requiring hospitalization for active psychosis (total Brief Psychiatric Rating Scale (BPRS) score ≥40) were enrolled from multiple countries, with 36% of site reporting from the U.S.[35,36] Both studies enrolled similar patients based on extensive and identical inclusion and exclusion criteria that used the same primary endpoint (change from baseline in total PANSS score at week 6) and the same key secondary endpoint (change from baseline in CGI-S score at week 6).[35,36] Demographic and baseline characteristics were generally similar across treatment groups. Mixed-effects model for repeated measures (MMRM) approach to data analyses was utilized in both trials.[35,36] In the first trial, an improvement in PANSS total score at week 6 was statistically superior for brexpiprazole 4 mg daily arm compared to placebo (least squares mean difference (LSMD) -6.47; 95% CI -10.60, -2.35) but doses of 1 or 2 mg daily did not provide any statistically difference than placebo.[35] Relative to placebo, the CGI-S scores were also improved with brexpiprazole 4 mg daily arm (LSMD -0.38; 95% CI -0.62, -0.15) but not with the 1 or 2 mg daily doses.[35] In the second trial, an improvement in the PANSS total score at week 6 was statistically superior for brexpiprazole 4 mg daily (LSMD -7.64; 95% CI -12.0, -3.30) and 2 mg daily (LSMD -8.72; 95% CI -13.1, -4.37) compared to placebo, but lower doses did not demonstrate efficacy.[36] Relative to placebo, the CGI-S scores were also improved with brexpiprazole for the 2 and 4 mg daily doses (LSMD -0.33; 95% CI -0.56, -0.10, and LSMD -0.38; 95% CI -0.61, -0.15, respectively).[36] There was no clear dose-response observed in the clinical trials for schizophrenia, but daily doses of 2-4 mg appear to be effective and statistically superior to placebo in total PANSS scores by Week 2.[37]

The efficacy of brexpiprazole for use as an adjunctive therapy to antidepressants for the treatment of MDD was established in two 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 1 to 3 mg daily (see Table 3).[38,39] Overall, 2,887 patients with MDD and inadequate response to antidepressant therapy were enrolled from multiple countries, but most centers were located in the U.S.[38,39] In both studies, enrolled patients entered an 8-week, single-blind placebo phase when patients received open-label antidepressant therapy. Patients with an inadequate response at week 8 (<50% reduction in HAM-D17, with HAM-D17 scores that remain ≥14 and CGI-I scores that remain ≥3) entered a double-blind phase, where they were randomized to brexipiprazole (with continued open-label antidepressant therapy) or placebo (with continued open-label antidepressant therapy) for 6 weeks. Demographic and baseline characteristics were generally similar across treatment groups. In the first trial, a 1 and 3 mg daily doses were studied;[38] in the second trial, a 2 mg daily dose was studied.[39] Both studies enrolled similar patients based on identical inclusion and exclusion criteria and antidepressant therapy was limited to a selection of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[38,39] The primary endpoint for both trials was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at week 14 (end of 6-week double-blind treatment phase).[38,39] The key secondary endpoint for both trials was change from baseline in the Sheehan Disability Score (SDS) at week 14 (end of 6-week double-blind treatment phase).[38,39] The study that evaluated the 1 and 3 mg daily doses found a statistical significant improvement in MADRS for the 3 mg dose (LSMD -1.52; 95% CI -2.92, -0.13);[38] likewise, the statistical superiority for the 2 mg daily dose in the second trial was seen (LSMD -3.12; 95% CI -4.70, -1.54).[39] Statistical superiority to placebo of the 2 mg

and 3 mg doses were seen from week 1 and continued through the end of the study periods.[37] A similar statistical trend was also seen with the key secondary endpoint SDS.[38,39] A dose response was not observed between the 2 and 3 mg daily doses, but both were effective as adjunctive therapy with antidepressant drugs.

Cariprazine

Cariprazine is an oral atypical antipsychotic approved by the FDA for the treatment of schizophrenia and bipolar mania/mixed episodes.[40]

The efficacy of cariprazine for schizophrenia was established in three 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 1.5 to 9 mg daily (see Table 4).[41–43] Overall, 1,049 patients with schizophrenia requiring hospitalization for active psychosis were enrolled (mostly from the U.S., Russia, India, Ukraine and Romania). Two studies were a fixed-dose design with atypical antipsychotics risperidone and aripiprazole as active comparators[41,42] and one study was a flexible dose-range study design.[43] All 3 studies enrolled similar patients based on extensive and identical inclusion and exclusion criteria and used the same primary endpoint (change from baseline in total PANSS score at week 6) and the same key secondary endpoint (change from baseline in CGI-S score at week 6). Demographic and baseline characteristics were generally similar across treatment groups. A statistically significant change in PANSS scores at week 6 were evident at all doses compared to placebo by both MMRM and last observation carried forward (LOCF) approaches to data analyses.[41–43] The change from baseline in PANSS was similar between cariprazine 3-6 mg daily and aripiprazole in one trial.[42] In a separate trial, risperidone 4 mg daily improved PANSS by an additional 5 points compared to cariprazine.[42] Though these studies were not powered to detect superiority between the active arms, the limited data available show that cariprazine up to 6 mg daily has efficacy with the range of approved atypical antipsychotics, with a safety profile similar to these approved drugs at doses of 6 mg daily or less. Overall, results show a modest dose-response with cariprazine. In addition, statistically significant improvement in PANSS scores were observed after one week 1 with higher doses compared to 2-3 weeks with lower doses.[44] Though higher doses of cariprazine appear to be more effective and work more quickly than lower doses, long-term studies are needed to determine how the accumulation of DDCAR affects the safety profile of cariprazine and how this might affect long-term maintenance dosing of the drug (see Clinical Safety below).

The efficacy of cariprazine for bipolar mania/mixed episodes was established in three 3-week randomized, placebo-controlled studies with unclear levels of bias at doses from 3 to 12 mg daily (see Table 4).[45–47] Overall, 962 patients were enrolled (mostly from the U.S., India and Russia). Two of the studies used flexible doses of 3-12 mg daily[45,46] and the third study used flexible doses of 3-6 mg daily or 6-12 mg daily.[47] All 3 trials enrolled similar patients based on extensive and identical inclusion and exclusion criteria (primary inclusion criteria was YMRS total score ≥20). Change from baseline in the YMRS total score at week 3 was the primary endpoint in all 3 studies; the same key secondary endpoint, change from baseline in the CGI-S at week 3, was also assessed in each trial. Demographic and baseline characteristics were generally similar across treatment groups. Statistically significant differences from placebo in the YMRS total score were evident between 4 and 7 days, and the effect persisted to endpoint at Week 3.[44] There was no evidence of dose response in the flexible dose-range study that compared 3-6 mg daily to 6-12 mg daily.[47] The trials demonstrated efficacy at daily dose up to 6 mg in patients with bipolar mania/mixed episodes with no evidence to suggest higher daily doses are more efficacious.

Clinical Safety:

In all of the clinical trials, there was a high attrition rate across all arms. However, attrition rates were consistent with attrition rates commonly seen in other clinical trials that study these populations.

The safety profile of brexpiprazole was similar for both the schizophrenia and MDD cohorts and with atypical antipsychotics generally. The FDA did not identify any unique safety concerns with brexpiprazole.[37] Thirteen deaths were reported during the clinical development of brexpiprazole, 9 in patients who were taking

brexpiprazole. However, causes of death varied and no patterns were identified.[37] Deaths were unlikely to be due to the drug but rather the disease itself (e.g., suicide).[37] Serious adverse events were identified in 5.2% of brexpiprazole-treated patients, with most attributed to exacerbation of the psychotic disorder. The most common treatment-emergent adverse events (TEAE) were increased weight, headache, akathisia, somnolence, fatigue, anxiety and increased appetite.[35,36,38,39] Adverse metabolic effects were not any different than what is expected from drugs in this class.

The most frequently reported treatment-emergent adverse events with cariprazine were akathisia, extrapyramidal symptoms, constipation and nausea or vomiting.[41,42,45–48] The primary concern with cariprazine was the dose-relation of adverse events observed during the 6-week schizophrenia trials.[44] Significant dose-related toxicities related to cariprazine were identified with increasing frequency over time during the 6-week clinical trials.[44] Because of the long half-life of the major accumulating active metabolite didesmethylcariprazine (DDCAR), troubling and serious adverse effects like akathisia and other extrapyramidal symptoms were seen as DDCAR approached steady-state (4-6 weeks) in the clinical trials.[44] Overall, the incidence of akathisia, an adverse effect that has been linked to suicide and other dangerous behaviors (i.e., violence) if left untreated, was the most prominent dose-related adverse event associated with cariprazine. Akathisia was evident even at the low doses and was higher than the percentage seen with aripiprazole, the drug with the most obvious association with akathisia to date.[44] The incidence of akathisia was commonly around 15% in short-term clinical trials that assessed daily doses of 6 mg.[44] The drug sponsor responded to such concerns by the FDA by resubmitting a new drug application (NDA) that sought approval of doses that were limited to up to 6 mg daily.[44] The FDA accepted the NDA because the 6-week safety follow-up in the clinical trials would have been sufficient enough to see some of the adverse events associated with accumulation of the DDCAR at steady-state.[44] Besides akathisia, harm outcomes of interest include pulmonary and ocular toxicity, based on reports of pulmonary fibrosis and cataracts found in a 1-year dog study, though the risk for pulmonary and ocular toxicity is yet unclear in humans due to the short duration of the clinical trials.[44] Increased systolic and diastolic blood pressure was also noted with cariprazine and routine monitoring for hypertension is advised.[40] Other adverse events observed with cariprazine, such as extrapyramidal disorders and adverse metabolic effects are well known and predicted with all atypical antipsychotics. Prolongation of the QTc interval does not appear to be a clinically relevant safety concern with cariprazine.[40] Other available treatments for schizophrenia and bipolar disorder have much shorter half-lives than DDCAR. Treatment recommendations after acute response are to continue treatment at the dose that worked acutely.[44] However, this practice may not be prudent with cariprazine because of DDCAR though the safety profile of the drug appears to be similar to other atypical antipsychotics over a 6-week period. Long-term follow-up studies are needed to clarify appropriate long-term maintenance dosing of cariprazine.

Pharmacology and Pharmacokinetic Properties:
Brexpiprazole is a new molecular entity. Brexpiprazole acts as a partial agonist with similar potency at serotonin 5-HT_{1A} and dopamine D_2 receptors, and acts as a potent antagonist at serotonin 5-HT_{2A} receptors. Brexpiprazole has a similar pharmacological profile as aripiprazole except for a lower affinity to the dopamine D_2 receptor, but it is unknown if this translates clinically to less dopamine-related adverse effects, such as EPS, hyperprolactinemia and tardive dyskinesia.

Specific pharmacology and pharmacokinetic properties of brexpiprazole are listed in table 1.

Table 1. Pharmacology and Pharmacokinetic Properties of Brexpiprazole.[34]

Parameter	
Mechanism of Action	Partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors, and an antagonist at serotonin 5-HT_{2A} receptors
Absorption	C_{max} = 4 hours; F = 95%; steady-state = 10-12 days
Distribution and Protein Binding	V_d = 1.56 L/kg, indicating extravascular distribution 99% protein-bound in plasma (albumin and α1-acid glycoprotein)
Metabolism	CYP3A4 and CYP2D6 without active metabolites
Half-Life	$T_{1/2}$ = 91 hours
Elimination	25% in urine (1% unchanged); 46% in feces (14% unchanged)

Abbreviations: C_{max} = maximum plasma concentration of drug; F = oral bioavailability; kg = kilograms; L = Liters; $T_{1/2}$ = terminal elimination half-life; V_d = volume of distribution.

Cariprazine is a new molecular entity. Cariprazine is similar to other atypical antipsychotics with activity at dopamine (D2 and D3) and serotonin (5-HT1A) receptors. Similar to aripiprazole, it acts as a partial agonist at dopamine D2 receptors rather than as an antagonist like other atypical antipsychotics. The drug preferentially binds D3 receptors by 3-10-fold, but the contribution of activity to D3 to clinical efficacy is unknown.[44] In terms of pharmacokinetics, cariprazine is unique because of the long half-life (3-9 days) of the parent compound and its equipotent metabolite DDCAR (half-life 2-3 weeks).[44] The metabolite DDCAR accumulates, and so over time the total active drug exposure increases with the same daily dose of cariprazine.[44]

Specific pharmacology and pharmacokinetic properties of cariprazine are listed in table 2.

Table 2. Pharmacology and Pharmacokinetic Properties of Cariprazine.[40]

Parameter	
Mechanism of Action	Partial agonist at dopamine D_3 (very high affinity) and D_2 receptors (high affinity) and at serotonin 5-HT_{1A} receptors. Antagonist at serotonin 5-HT_{2B} (high affinity) and 5-HT_{2A} receptors (moderate affinity) and histamine H_1 receptors. Low affinity for serotonin 5-HT_{2C} and α_{1A}-adrenergic receptors; no affinity for cholinergic muscarinic receptors.
Absorption	C_{max} = 3-6 hours
Distribution and Protein Binding	91-97% protein-bound in plasma
Metabolism	CYP3A4 (extensive) and CYP2D6 to DCAR and to DDCAR. DDCAR is equipotent to cariprazine and is metabolized by CYP3A4 to a hydroxylated metabolite
Half-Life	Cariprazine (3-9 days); DDCAR (2-3 weeks)
Elimination	21% excreted through urine (1% unchanged)

Abbreviations: C_{max} = maximum plasma concentration of drug; DCAR = desmethylcariprazine; DDCAR = didesmethylcariprazine.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Reduction in total PANSS score (schizophrenia)
2) Improvement in total YMRS score (bipolar mania)
3) Improvement in total MADRS score (MDD)

Primary Study Endpoints (brexpiprazole):

1) Change from baseline in PANSS score over 6 weeks (schizophrenia)
2) Change from baseline in MADRS score over 6 weeks (MDD)

Primary Study Endpoints (cariprazine):

1) Change from baseline in PANSS score over 6 weeks (schizophrenia)
2) Change from baseline in YMRS score over 3 weeks (bipolar mania)

Table 3. Comparative Evidence for Brexpiprazole.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Kane, et al.[35] MC, DB, PC, PG, RCT Phase 3	1. BRX 1 mg PO QD 2. BRX 2 mg PO QD 3. BRX 4 mg PO QD 4. PBO PO QD 2:3:3:3 6 weeks	Demographics: Mean age: 39 y Male: 63% White: 60% Mean PANSS: -total score: 95 -CGI-S score: 4.9 -Duration current psychosis: 2.5 wk Inclusion Criteria: -Age 18-65 y -Schizophrenia (DSM-IV) -Acute psychosis (total BPRS score ≥40; BPRS score ≥4 on ≥2 items (hallucinatory behavior, unusual or disorganized thought content) and CGI-S score ≥4) -h/o relapse and/or untreated symptom exacerbation Exclusion Criteria: -First episode of schizophrenia -Tardive dyskinesia -Severe akathisia -h/o substance abuse ≤6 months -Any psychotropic drug, sleep aid, antihistamine, vitamin or herbal supplement, CYP2D6 inhibitor; CYP3A4 inhibitor or inducer, or varenicline	n: 1. 120 2. 186 3. 184 4. 184 mITT: 1. 117 2. 179 3. 181 4. 180 Attrition: 1. 33% 2. 31% 3. 29% 4. 36%	Primary Endpoint: LS mean Δ PANSS total score from baseline to week 6: 1. -16.90 (SE 1.86) 2. -16.1 (SE 1.49) 3. -20.00 (SE 1.48) 4. -13.53 (SE 1.52) 1 vs. 4: -3.37 (95% CI -8.06, 1.32) 2 vs. 4: -3.08 (95% CI -7.23, 1.07) 3 vs. 4: -6.47 (95% CI -10.6, -2.35) Key Secondary Endpoint: LS mean Δ CGI-S score from baseline to week 6: 1. -0.91 (SE 0.11) 2. -0.99 (SE 0.09) 3. -1.19 (SE 0.08) 4. -0.81 (SE 0.09) 1 vs. 4: -0.10 (95% CI -0.37, 0.16) 2 vs. 4: -0.19 (95% CI -0.42, 0.05) 3 vs. 4: -0.38 (95% CI -0.62, -0.15)	 NS NS NA NS NS NA	SAE:* 1. 2.5% 2. 2.2% 3. 2.2% 4. 5.4% *most indicative of underlying disorder: acute psychosis; psychotic disorder; aggression; schizophrenia D/C due to TEAE: 1. 9.2% 2. 5.9% 3. 7.1% 4. 12.0% Insomnia: 1. 12.5% 2. 13.4% 3. 15.2% 4. 14.7% Headache: 1. 7.5% 2. 10.8% 3. 10.3% 4. 14.7% Akathisia: 1. 4.2% 2. 4.8% 3. 6.5% 4. 7.1% Weight gain: 1. 1.23 kg 2. 1.89 kg 3. 1.52 kg 4. 0.35 kg	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal. Performance Bias: LOW. Double-blinding maintained by using identical tablets and packaging for all treatment arms. Detection Bias: LOW. Sponsor personnel blinded to treatment allocation. Power assumptions appropriate. Attrition Bias: HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication. High attrition rate across all groups. Missing values imputed by MMRM. Reporting Bias: UNCLEAR. All reported endpoints were pre-specified but the sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data. **Applicability**: Patient: Extensive exclusion criteria limit applicability to persons commonly encountered in practice. Intervention: It is unknown whether doses lower than 4 mg/d are more efficacious than placebo at reducing positive and negative symptoms of schizophrenia. Comparator: Placebo demonstrates efficacy but does not allow a comparison with other SGAs. Outcomes: 6 weeks is a limited duration to assess long-term efficacy. Follow-up for safety occurred at 30 days after the last dose of trial medication. Setting: Patients followed weekly at 64 centers from Columbia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan, and USA (36%).

2. Correll, et al.[36] MC, DB, PC, PG, RCT Phase 3	1. BRX 0.25 mg PO QD 2. BRX 2 mg PO QD 3. BRX 4 mg PO QD 4. PBO PO QD 1:2:2:2 6 weeks	Demographics: Mean age: 40 y Male: 63% White: 67% Mean PANSS: -total score: 95 -CGI-S score: 4.9 -Duration current psychosis: 2.6 wk Key Inclusion Criteria: See Kane, et al.[35] Key Exclusion Criteria: See Kane, et al.[35]	n: 1. 90 2. 182 3. 180 4. 184 mITT: 1. 87 2. 180 3. 178 4. 178 Attrition: 1. 38% 2. 32% 3. 33% 4. 40%	Primary Endpoint: LS mean Δ PANSS total score from baseline to week 6: 1. -14.90 (SE 2.23) 2. -20.73 (SE 1.55) 3. -19.65 (SE 1.54) 4. -12.01 (SE 1.60) 1 vs. 4: -2.89 (95% CI -8.27, 2.49) 2 vs. 4: -8.72 (95% CI -13.1, -4.37) 3 vs. 4: -7.64 (95% CI -12.0, -3.30) Key Secondary Endpoint: LS mean Δ CGI-S score from baseline to week 6: 1. -0.85 (SE 0.12) 2. -1.15 (SE 0.08) 3. -1.20 (SE 0.08) 4. -0.82 (SE 0.09) 1 vs. 4: -0.03 (95% CI -0.31, 0.26) 2 vs. 4: -0.33 (95% CI -0.56, -0.10) 3 vs. 4: -0.38 (95% CI -0.61, -0.15)	 NS NA NA NS NA NA	SAE:* 1. 4.4% 2. 2.2% 3. 1.1% 4. 3.8% *most indicative of underlying disorder: acute psychosis; psychotic disorder; aggression; schizophrenia D/C due to TEAE: 1. 13.3% 2. 8.2% 3. 9.4% 4. 17.4% Insomnia: 1. 8.9% 2. 8.8% 3. 8.3% 4. 9.8% Headache: 1. 10.0% 2. 9.3% 3. 12.2% 4. 8.2% Akathisia: 1. 0.0% 2. 4.4% 3. 7.2% 4. 2.2% Weight gain: 1. NR 2. 1.45 kg 3. 1.28 kg 4. 0.42 kg	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal. Performance Bias: UNCLEAR. Unknown what precautions were taken to ensure double-blinding maintained. Detection Bias: UNCLEAR. Unknown what precautions were taken to ensure data assessors were blinded. Power assumptions appropriate. Attrition Bias: HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication. High attrition rate across all groups. Reporting Bias: UNCLEAR. All reported endpoints were pre-specified but the sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data. **Applicability**: Patient: Extensive exclusion criteria limit applicability to persons commonly encountered in practice. Intervention: Doses lower than 2 mg/d may not be any more efficacious than placebo at reducing positive and negative symptoms of schizophrenia. Comparator: Placebo demonstrates efficacy but does not allow a comparison with other SGAs. Outcomes: 6 weeks is a limited duration to assess long-term efficacy. Follow-up for safety occurred at 30 days after the last dose of trial medication. Setting: Patients followed weekly at 65 centers from U.S. (36%), Ukraine, Romania, Servia, Latvia, Malaysia, Japan, Poland, South Korea and Canada.

3. Thase, et al.[38] MC, DB, PC, PG, RCT Phase 3	1. BRX 1 mg PO QD 2. BRX 3 mg PO QD 3. PBO PO QD 1:1:1 7-28-day screening phase 8-week OL titration phase of 1-3 antidepressant(s) 6 weeks	Demographics: Mean age: 46 y Male: 32% White: 85% Mean MADRS: 26.5 Mean SDS: 5.7 Inclusion Criteria: -Age 18-65 y -MDD (DSM-IV) ≥8 wk -Inadequate response to 1-3 trials of OL antidepressants* (HDRS-17 ≥14; <50% reduction from baseline and MADRS scores; CGI-I score ≥3 at each follow-up visit during 8-wk tx phase prior to randomization) Exclusion Criteria: -Antipsychotic drug >3 wk -Electroconvulsive therapy -Psychotherapy -hospitalization -hallucinations or delusions -Other psychiatric disorder -Substance abuse, including alcoholism -Abnormal ECG or laboratory result *Titrated to maximum tolerated dose	n: 1. 226 2. 230 3. 221 mITT: 1. 211 2. 213 3. 203 Attrition: 1. 7% 2. 7% 3. 8%	Primary Endpoint: LS mean Δ MADRS total score from baseline to week 6: 1. NR for mITT population 2. NR for mITT population 1 vs. 3: -1.19 (95% CI -2.58, 0.20) 2 vs. 3: -1.52 (95% CI -2.92, -0.13) Key Secondary Endpoints: LS mean Δ SDS score, measured at week 3 and 6: 1. -1.33 (SE 0.14) 2. -1.21 (SE 0.13) 3. -0.84 (SE 0.13) 1 vs. 3: -0.49 (95% CI -0.87, -0.12) 2 vs. 3: -0.37 (95% CI -0.73, -0.00) LS mean Δ individual SDS scores for work/school, measured at week 3 and 6: 1. -1.16 (SE 0.17) 2. -0.91 (SE 0.18) 3. -0.73 (SE 0.17) 1 vs. 3: -0.43 (95% CI -0.91, 0.04) 2 vs. 3: -0.18 (95% CI -0.66, 0.31) LS mean Δ individual SDS scores for social life, measured at week 3 and 6: 1. -1.39 (SE 0.15) 2. -1.31 (SE 0.15) 3. -0.91 (SE 0.15) 1 vs. 3: -0.48 (95% CI -0.89, -0.07) 2 vs. 3: -0.40	 NS NA NA NA NS NS NA	SAE:* 1. 0.4% 2. 0.4% 3. 0% D/C due to TEAE: 1. 1.3% 2. 3.5% 3. 1.4% Headache: 1. 9.3% 2. 6.1% 3. 7.7% Akathisia: 1. 4.4% 2. 13.5% 3. 2.3% Mean Weight gain: 1. 1.4 kg 2. 1.6 kg 3. 0.2 kg Somnolence: 1. 4.0% 2. 5.7% 3. 0.5% Tremor: 1. 4.0% 2. 5.2% 3. 3.2% Nasopharyngitis: 1. 6.6% 2. 3.1% 3. 1.8%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal. Performance Bias: UNCLEAR. Unknown what precautions were taken to ensure double-blinding maintained. Detection Bias: UNCLEAR. Unknown what precautions were taken to ensure data assessors were blinded. Power assumptions appropriate. Attrition Bias: HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication. Reporting Bias: HIGH. All reported endpoints emphasize per-protocol population, which is a less conservative measure. The sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data. **Applicability**: Patient: MADRS scores largely reflects moderate depression. Intervention: Used as adjunctive to 1 antidepressant (78%); 2 antidepressants (18%); 3 antidepressants (3%) Comparator: Placebo is appropriate if efficacy needs to be established. Adjunctive antidepressant applicable to MDD. Outcomes: 6 weeks is a limited duration to assess long-term efficacy. Difference of 1.91 points vs placebo may have met threshold of MCID. Follow-up for safety occurred at 30 days after the last dose of trial medication. Setting: Patients followed weekly at 92 centers from U.S. (71.7%), Germany, Ukraine, Russia, Hungary, Canada and Romania.

				(95% CI -0.80, 0.01) LS mean Δ individual SDS scores for family life, measured at week 3 and 6: 1. -1.35 (SE 0.15) 2. -1.28 (SE 0.16) 3. -0.80 (SE 0.15) 1 vs. 3: -0.55 (95% CI -0.97, -0.14) 2 vs. 3: -0.48 (95% CI -0.90, -0.06)	NS NA NA			
4. Thase, et al.[39] MC, DB, PC, PG, RCT Phase 3	1. BRX 2 mg PO QD 2. PBO PO QD 1:1 7-28-day screening phase 8-week OL titration phase of 1-3 antidepressant(s) 6 weeks	Demographics: Mean age: 45 y Male: 30% White: 90% Mean MADRS: 26.9 Mean SDS: 6.2 Inclusion Criteria: Thase, et al.[38] Exclusion Criteria: Thase, et al.[38]	n: 1. 188 2. 191 mITT: 1. 187 2. 191 Attrition: 1. 7% 2. 7%	Primary Endpoint: LS mean Δ MADRS total score from baseline to week 6: 1. -8.27 (SE NR) 2. -5.15 (SE NR) MD: -3.12 (95% CI -4.70, -1.54) Key Secondary Endpoints: LS mean Δ SDS score, measured at week 3 and 6: 1. -1.35 (SE 0.17) 2. -0.91 (SE 0.17) MD: -0.45 (95% CI -0.86, -0.03) LS mean Δ individual SDS scores for work/school, measured at week 3 and 6: 1. -1.09 (SE 0.22) 2. -0.90 (SE 0.22) MD: -0.19 (95% CI -0.73, 0.34) LS mean Δ individual SDS scores for social life, measured at week 3 and 6: 1. -1.54 (SE 0.19) 2. -1.04 (SE 0.18)	 NA NA NS	SAE:* 1. 1.1% 2. 1.0% D/C due to TEAE: 1. 3.2% 2. 0% Akathisia: 1. 7.4% 2. 1.0% Mean Weight gain: 1. 1.64 kg 2. 0.36 kg Restlessness: 1. 3.2% 2. 0% Somnolence: 1. 4.3% 2. 0.5% Anxiety: 1. 3.7% 2. 1.6% Sedation: 1. 1.1% 2. 0%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. See Thase, et al.[38] Performance Bias: UNCLEAR. See Thase, et al.[38] Detection Bias: UNCLEAR. See Thase, et al.[38] Attrition Bias: HIGH. See Thase, et al.[38] Reporting Bias: HIGH. See Thase, et al.[38] **Applicability**: Patient: MADRS scores largely reflects moderate depression. Intervention: Used as adjunctive to 1-3 antidepressants (most common were escitalopram, duloxetine, and venlafaxine XR) Comparator: Placebo is appropriate if efficacy needs to be established. Adjunctive antidepressant applicable to MDD. Outcomes: 6 weeks is a limited duration to assess long-term efficacy. Difference of 1.91 points vs placebo may have met threshold of MCID. Follow-up for safety occurred at 30 days after the last dose of trial medication. Setting: Patients followed weekly at 59 centers from U.S. (74.9%), Poland, France, Canada and Slovakia.

				MD: -0.50 (95% CI -0.96, -0.04) LS mean Δ individual SDS scores for family life, measured at week 3 and 6: 1. -1.33 (SE 0.19) 2. -0.73 (SE 0.19) MD: -0.60 (95% CI -1.07, -0.13)	NA NA			

Abbreviations ARR = absolute risk reduction; ATRQ = Antidepressant Treatment Response Questionnaire, Massachusetts General Hospital; BPRS = Brief Psychiatric Rating Scale; BRX = brexpiprazole; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; DB = double blinded; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; HDRS-17 = Hamilton Depression Rating Scale, 17-item; IM = intramuscular; ITT = intention to treat; IVRS = interactive voice response system; IWRS = interactive web response system; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MC = multi-centered; MCID = minimum clinically important difference; MD = mean difference; MDD = major depressive disorder; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PC = placebo controlled; PBO = placebo; PG = parallel group; PO = oral; PSP = Personal and Social Performance Scale; QD = once daily; RCT = randomized controlled trial; SAE = serious adverse effect; SDS = Sheehan Disability Score; SE = standard error; SEM = standard error of the mean; SGA = second-generation antipsychotics; TEAE = treatment emergent adverse events; y = years.

Table 4. Comparative Evidence for Cariprazine.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
SCHIZOPHRENIA								
1. Durgam, et al.[41] MC, DB, AC, PC, PG, RCT	1. CAR 1.5 mg PO QD 2. CAR 3 mg PO QD 3. CAR 4.5 mg PO QD 4. risperidone 4 mg/d 5. PBO 1:1:1:1:1 6 weeks	Demographics: Mean age: 36 y Males: 69% White: 51% PANSS total score: 1. 97.1 (SEM 0.8) 2. 97.2 (SEM 0.7) 3. 96.7 (SEM 0.8) 4. 98.1 (SEM 0.8) 5. 97.3 (SEM 0.8) CGI-S score: 1. 4.7 (SEM 0.1) 2. 4.9 (SEM 0.1) 3. 4.8 (SEM 0.1) 4. 4.8 (SEM 0.1) 5. 4.9 (SEM 0.1) Inclusion Criteria: -Age 18-60 y -Schizophrenia dx per DSM-IV ≥1 y -Current exacerbation <2 wk -≥1 hospitalization in past year for psychotic episode -total PANSS score 80-120 -score ≥4 (moderate) on ≥2 of 4 PANSS positive sxs (delusions, hallucinations, conceptual disorganization, suspiciousness) -CGI-S ≥4 -BMI 18-35 mg/m^2 Exclusion Criteria: -First psychotic episode	n: 1. NR 2. NR 3. NR 4. NR 5. NR (total n=732) mITT: 1. 145 2. 146 3. 147 4. 140 5. 151 Attrition: 1. 38% 2. 34% 3. 33% 4. 28% 5. 48%	Primary Endpoint: Mean Δ PANSS total score from baseline to week 6: 1. -19.4 (SEM 1.6) 2. -20.7 (SEM 1.6) 3. -22.3 (SEM 1.6) 4. -26.9 (SEM 1.6) 5. -11.8 (SEM 1.5) 1 vs. 5: -7.6 (95% CI -11.8, -3.3) 2 vs. 5: -8.8 (95% CI -13.1, -4.6) 3 vs. 5: -10.4 (95% CI -14.6, -6.2) 4 vs. 5: -15.1 (95% CI -19.4, -10.8) Key Secondary Endpoint: LS mean Δ CGI-S score from baseline to week 6: 1. -1.0 (SEM 0.1) 2. -1.1 (SEM 0.1) 3. -1.3 (SEM 0.1) 4. -0.5 (SEM 0.1) 5. -0.7 (SEM 0.1) 1 vs. 5: -0.4 (95% CI -0.6, -0.1) 2 vs. 5: -0.5 (95% CI -0.7, -0.2) 3 vs. 5: -0.6 (95% CI -0.9, -0.4) 4 vs. 5: -0.8 (95% CI -1.1, -0.6)	NA NA NA NA NA NA	Early D/C from AE: 1. 9.7% 2. 5.5% 3. 8.2% 4. 9.3% 5. 14.6% SAE*: 1. 3.4% 2. 0% 3. 2.7% 4. 2.1% 5. 4.6% Akathisia: 1. 9.0% 2. 9.6% 3. 7.5% 4. 8.6% 5. 4.6% EPS: 1. 9.0% 2. 8.9% 3. 11.6% 4. 12.9% 5. 4.6% Insomnia: 1. 10.3% 2. 16.4% 3. 16.3% 4. 15.0% 5. 7.3% Mean Δ FBG: 1. -0.1 mg/dL 2. +0.8 mg/dL 3. +5.1 mg/dL 4. -0.9 mg/dL 5. +3.3 mg/dL	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Method of randomization not disclosed. Allocation concealment unknown. Performance Bias: UNCLEAR. Methods of blinding and to maintain blinding unknown. Washout period 7 days and may be insufficient. Detection Bias: UNCLEAR. Methods to blind data assessors unknown. Appropriate statistical tests used. Power assumptions unclear. Short study duration. Safety outcomes only followed for 2 weeks after study ended. Attrition Bias: HIGH. mITT population assessed for efficacy, which had to take study drug and have ≥1 post-baseline assessment of PANSS. Missing values imputed by LOCF and MMRM. Reporting Bias: UNCELAR. All study outcomes were pre-specified but the sponsor was responsible for the study design, implementation, analysis and interpretation of data, decision to publish, and funding for editorial support. **Applicability**: Patient: extensive inclusion and exclusion criteria limit population studied that may not reflect who is commonly seen in clinical practice. Intervention: studied as monotherapy; initiated at 1.5 mg, and dose titrated rapidly. No other psychotropic drugs were allowed. Comparator: placebo appropriate to establish efficacy; risperidone and placebo compared to 'assess assay sensitivity'; no testing was done to compare to CAR. Outcomes: PANSS assessed weekly; it is a frequently utilized scale in clinical trials to assess symptoms of schizophrenia; however, duration of study may be too short to know if

		-psychotropic drugs -'various DSM-IV disorders' (e.g., schizoaffective, schizophreniform, bipolar I and II) -alcohol/substance abuse/dependence -tx-resistant schizophrenia (poor response to ≥2 antipsychotics) -suicidal or attempt				*most commonly schizophrenia exacerbation or psychotic disorder		study results will reflect what will be seen in clinical practice. Setting: All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 65 centers in the U.S. (38%), India (22%), Russia (22%), Ukraine (16%) and Malaysia (3%).
2. Durgam, et al.[42] MC, DB, AC, PC, PG, RCT	1. CAR 3 mg PO QD 2. CAR 6 mg PO QD 3. aripiprazole 10 mg/d 4. PBO 1:1:1:1 6 weeks	Demographics: Mean age: 38 y Males: 63% White: 64% PANSS total score: 1. 96.1 (SD 8.7) 2. 95.7 (SD 9.4) 3. 95.6 (SD 9.0) 4. 96.5 (SD 9.1) CGI-S score: 1. 4.9 (SD 0.6) 2. 4.8 (SD 0.6) 3. 4.8 (SD 0.6) 4. 4.8 (SD 0.6) Inclusion Criteria: See Durgam, et al.[41] Exclusion Criteria: See Durgam, et al.[41]	n: 1. 155 2. 157 3. 152 4. 153 mITT: 1. 151 2. 154 3. 150 4. 149 Attrition: 1. 33% 2. 38% 3. 25% 4. 38%	Primary Endpoint: Mean Δ PANSS total score from baseline to week 6: 1. -20.2 (SEM 1.5) 2. -23.0 (SEM 1.5) 3. -21.2 (SEM 1.4) 4. -14.3 (SEM 1.5) 1 vs. 4: -6.0 (95% CI -10.1, -1.9) 2 vs. 4: -8.8 (95% CI -12.9, -4.7) 3 vs. 4: -7.0 (95% CI -11.0, -2.9) Key Secondary Endpoint: LS mean Δ CGI-S score from baseline to week 6: 1. -1.4 (SEM 0.1) 2. -1.5 (SEM 0.1) 3. -1.4 (SEM 0.1) 4. -1.0 (SEM 0.1) 1 vs. 4: -0.4 (95% CI -0.6, -0.2) 2 vs. 4: -0.5 (95% CI -0.7, -0.3) 3 vs. 4: -0.4 (95% CI -0.6, -0.2)	 NA NA NA NA NA NA	Early D/C from AE: 1. 9.7% 2. 12.7% 3. 9.2% 4. 11.1% SAE*: 1. 2.6% 2. 4.5% 3. 2.6% 4. 1.3% Akathisia: 1. 7.1% 2. 14.6% 3. 7.2% 4. 4.6% *2 vs. 4: p<0.05* Insomnia: 1. 13.5% 2. 14.0% 3. 10.5% 4. 16.3% Deaths: 1. 0% 2. 1.3% 3. 0% 4. 0% Mean Δ FBG: 1. +2.8 mg/dL	 NA NA NA NA NA NA NA 10%/10 NA NA NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Durgam, et al.[41] Performance Bias: UNCLEAR. See Durgam, et al.[41] Detection Bias: UNCLEAR. See Durgam, et al.[41] Attrition Bias: HIGH. See Durgam, et al.[41] Reporting Bias: UNCLEAR. See Durgam, et al.[41] **Applicability**: Patient: See Durgam, et al.[41] Intervention: See Durgam, et al.[41] Comparator: placebo appropriate to establish efficacy; aripiprazole and placebo compared to 'assess assay sensitivity'; no testing was done to compare to CAR. Outcomes: See Durgam, et al.[41] Setting: All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 65 centers in the U.S., Romania, Russia and Ukraine.

						2. +5.6 mg/dL 3. +0.0 mg/dL 4. -5.8 mg/dL *most commonly schizophrenia exacerbation or psychotic disorder	NA NA	
3. Kane, et al.[43] MC, DB, PC, PG, RCT	1. CAR 3-6 mg PO QD 2. CAR 6-9 mg PO QD 3. PBO 1:1:1 6 weeks	Demographics: Mean age: 38 y Males: 77% Asian: 38% Black: 36% PANSS total score: 1. 96.3 (SD 9.3) 2. 96.3 (SD 9.0) 3. 96.6 (SD 9.3) CGI-S score: 1. 4.8 (SD 0.7) 2. 4.9 (SD 0.7) 3. 4.9 (SD 0.7) Inclusion Criteria: See Durgam, et al.[41] Exclusion Criteria: See Durgam, et al.[41]	n: 1. 151 2. 148 3. 147 mITT: 1. 147 2. 147 3. 145 Attrition: 1. 36% 2. 42% 3. 40%	Primary Endpoint: LSMD Δ PANSS total score from baseline to week 6: 1. -22.8 (SE 1.6) 2. -25.9 (SE 1.7) 3. -16.0 (SE 1.6) 1 vs. 3: -6.8 (95% CI -11.3, -2.4) 2 vs. 3 -9.9 (95% CI -14.5, -5.3) Key Secondary Endpoint: LS mean Δ CGI-S score from baseline to week 6: 1. -1.4 (SE 0.1) 2. -1.6 (SE 0.1) 3. -1.0 (SE 0.1) 1 vs. 3: -0.3 (95% CI -0.6, -0.1) 2 vs. 3: -0.5 (95% CI -0.8, -0.3)	 NA NA NA NA	Early D/C from AE: 1. 9.3% 2. 8.8% 3. 8.8% SAE*: 1. 6.0% 2. 2.0% 3. 8.2% Akathisia: 1. 15.9% 2. 16.9% 3. 3.4% Insomnia: 1. 6.6% 2. 10.8% 3. 10.9% Mean Δ FBG: 1. +7.1 mg/dL 2. +3.2 mg/dL 3. +2.5 mg/dL *most commonly worsening schizophrenia; also HTN and hepatitis were noted to be related to CAR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Durgam, et al.[41] Performance Bias: UNCLEAR. See Durgam, et al.[41] Detection Bias: UNCLEAR. See Durgam, et al.[41] Attrition Bias: HIGH. See Durgam, et al.[41] Reporting Bias: UNCLEAR. See Durgam, et al.[41] **Applicability**: Patient: See Durgam, et al.[41] Intervention: CAR initiated at 1.5 mg/d day 1, 3 mg day 2 and 3, then titrated to specific treatment arm. Comparator: placebo appropriate to establish efficacy but comparison with another antipsychotic would be more beneficial. Outcomes: See Durgam, et al.[41] Setting: All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 41 centers in the U.S., India, Columbia and South Africa.

BIPOLAR MANIA/MIXED EPISODES								
4. Durgam, et al.[45] MC, DB, PC, PG, RCT	1. CAR 3-12 mg PO QD 2. PBO 1:1 3 weeks	Demographics: Mean age: 38 y Males: 66% White: 43% YMRS total score: 1. 30.6 (SEM 0.5) 2. 30.2 (SEM 0.5) CGI-S score: 1. 4.7 (SEM 0.1) 2. 4.6 (SEM 0.1) Inclusion Criteria: -Age 18-65 y -Bipolar I disorder, manic or mixed type, w/ or w/o psychotic symptoms (DSM-IV) -YMRS total score ≥20, w/ ≥4 score on ≥2 of the following: irritability, speech, content, and disruptive/ aggressive behavior. Exclusion Criteria: -First manic episode -Rapid cycling -Axis I disorders other than bipolar I -Severe Axis II disorders -psychotropic drugs -alcohol/substance abuse/dependence -suicide risk -MADRS score ≥18 -electroconvulsive therapy or depot neuroleptics -h/o of malignancy, or hematologic, endocrine, CV, respiratory, renal,	n: 1. 118 2. 120 ITT: 1. 118 2. 117 Attrition: 1. 36% 2. 38%	Primary Endpoint: Mean Δ YMRS total score at week 3: 1. -15.1 (SEM 0.5) 2. -8.9 (SEM 1.1) LSMD -6.1 (95% CI, -8.9 to -3.3) Secondary Endpoints: Mean Δ CGI-S score at week 3: 1. -1.6 (SEM 0.1) 2. -0.9 (SEM 0.1) LSMD -0.6 (95% CI, -1.0 to -0.3)	 NA NA	Early D/C from AE: 1. 14.4% 2. 10.2% SAE*: 1. 3.4% 2. 4.2% Akathisia: 1. 18.6% 2. 5.9% EPS: 1. 24.6% 2. 9.3% Dyspepsia: 1. 12.7% 2. 6.8% Nausea: 1. 15.3% 2. 10.2% Constipation: 1. 15.3% 2. 8.5% Mean Δ FBG: 1. +7.7 mg/dL 2. -0.2 mg/dL *included worsening mania or bipolar disorder, EPS, convulsions, HTN	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Method of randomization not disclosed. Allocation concealment unknown. Performance Bias: UNCLEAR. Methods of blinding and to maintain blinding unknown. Washout period *up to* 4 days only and may be insufficient. Detection Bias: UNCLEAR. Methods to blind data assessors unknown. Appropriate statistical tests used. Power assumptions unclear. Short study duration. Safety outcomes only followed for 2 weeks after study ended. Attrition Bias: HIGH. mITT population assessed for efficacy, which had to take study drug and have ≥1 post-baseline assessment of PANSS. Missing values imputed by LOCF. Reporting Bias: UNCLEAR. All study outcomes were pre-specified but the drug sponsor was responsible for the study design, implementation, analysis and interpretation of data, decision to publish, and funding for editorial support. **Applicability**: Patient: extensive exclusion criteria, including other DSM-IV Axis I diagnoses (e.g., dementia, schizophrenia, schizoaffective disorder, other psychotic disorders); population seen in real world may not reflect subjects in study. 37% patients had experienced current manic episode >1 month. Intervention: studied as monotherapy; initiated at 1.5 mg, and dose doubled up to 12 mg/d over 5 days, then titrated up to 12 mg/d, or as tolerated. Comparator: placebo appropriate to establish efficacy but comparison with another antipsychotic would be more beneficial. Outcomes: YMRS is a frequently utilized scale to assess manic symptoms; however, duration of study may be too short to know if study results will reflect what will be seen in clinical practice.

		hepatic, GI, or neuroleptic disorders -pregnancy or breastfeeding						Setting: All patients hospitalized for screening and for ≥2 weeks of double-blind treatment. 29 centers in the U.S. (60%), India (30%) and Russia (10%). Patients assessed at baseline, and on days 4, 7, 10 and 14, 21.
5. Sachs, et al.[46] MC, DB, PC, PG, RCT	1. CAR 3-12 mg PO QD 2. PBO 1:1 3 weeks	Demographics: Mean age: 36 y Males: 64% Asian: 57% YMRS total score: 1. 32.3 (SD 5.8) 2. 32.1 (SD 5.6) CGI-S score: 1. 4.6 (SD 0.6) 2. 4.6 (SD 0.6) Inclusion Criteria: See Durgam, et al.[45] Exclusion Criteria: See Durgam, et al.[45]	n: 1. 158 2. 154 mITT: 1. 158 2. 152 Attrition: 1. 32% 2. 31%	Primary Endpoint: Mean Δ YMRS total score at week 3: 1. -19.6 (SE 0.9) 2. -15.3 (SE 0.9) LSMD -4.3 (95% CI, -6.7 to -1.9) Secondary Endpoints: Mean Δ CGI-S score at week 3: 1. -1.9 (SE 0.1) 2. -1.5 (SE 0.1) LSMD -0.4 (95% CI, -0.7 to -0.1)	NA NA	Early D/C from AE: 1. 9.5% 2. 7.1% SAE: 1. 3.2% 2. 1.9% Akathisia: 1. 22.2% 2. 4.5% EPS: 1. 15.2% 2. 1.9% Dyspepsia: 1. 10.8% 2. 3.2% Nausea: 1. 10.1% 2. 6.5% Constipation: 1. 8.2% 2. 6.5% Tremor: 1. 11.4% 2. 3.9% Death: 1. 0% 2. 0%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Durgam, et al.[45] Performance Bias: UNCLEAR. Methods of blinding and to maintain blinding unknown. 4-7 day washout prior to study may be insufficient. Detection Bias: UNCLEAR. See Durgam, et al.[45] Attrition Bias: HIGH. See Durgam, et al.[45] Reporting Bias: UNCLEAR. See Durgam, et al.[45] **Applicability**: Patient: extensive exclusion criteria, including other DSM-IV Axis I diagnoses (e.g., dementia, schizophrenia, schizoaffective disorder, other psychotic disorders) excluded; population seen in real world may not reflect subjects in study. Most patients had experienced current manic episode >7 days; 27% for >21 days. Intervention: studied as monotherapy; initiated at 1.5 mg dose, and dose doubled to 6 mg/d over 3 days, then titrated up to 12 mg/d, or as tolerated. Comparator: See Durgam, et al.[45] Outcomes: See Durgam, et al.[45] Setting: All patients hospitalized for screening and for ≥2 weeks of double-blind treatment. 28 centers (18 in India, 10 in U.S.). Patients assessed at baseline, and on days 4, 7, 10 and 14, 21.

6. Calabrese, et al.[47] MC, DB, PC, PG, RCT Phase 3	1. CAR 3-6 mg PO QD 2. CAR 6-12 mg PO QD 3. PBO 1:1:1 3 weeks	Demographics: Mean age: 42 y Males: 53% White: 69% YMRS total score: 1. 33.2 (SD 5.6) 2. 32.9 (SD 4.7) 3. 32.6 (SD 5.8) CGI-S score: 1. 4.8 (SD 0.6) 2. 4.8 (SD 0.6) 3. 4.8 (SD 0.7) Inclusion Criteria: See Durgam, et al.[45] Exclusion Criteria: See Durgam, et al.[45]	n: 1. 167 2. 169 3. 161 mITT: 1. 165 2. 167 3. 160 Attrition: 1. 23% 2. 30% 3. 24%	Primary Endpoint: Mean Δ YMRS total score at week 3: 1. -18.6 (SE 0.8) 2. -18.5 (SE 0.8) 3. -12.5 (SE 0.8) LSMD 1 vs. 3: -6.1 (95% CI, -8.4 to -3.8) LSMD 2 vs. 3: -5.9 (05% CI, -8.2 to -3.6) Secondary Endpoints: Mean Δ CGI-S score at week 3: 1. -1.9 (SE 0.1) 2. -1.9 (SE 0.1) 3. -1.3 (SE 0.1) LSMD 1 vs. 3: -0.6 (95% CI, -0.9 to -0.4) LSMD 2 vs. 3: -0.6 (95% CI, -0.9 to -0.3)	 NA NA NA NA	Early D/C from AE: 1. 9.0% 2. 14.8% 3. 5.0% 2 vs. 3: p<0.01 SAE: 1. 4.2% 2. 0% 3. 1.9% Akathisia: 1. 17.4% 2. 21.9% 3. 3.7% Nausea: 1. 9.6% 2. 11.2% 3. 5.6% Constipation: 1. 4.8% 2. 10.7% 3. 2.5% Tremor: 1. 2.4% 2. 5.3% 3. 1.9% Death: 1. 0.6% 2. 0% 3. 0%	 9.8%/10 NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Durgam, et al.[45] Performance Bias: UNCLEAR. Methods of blinding and to maintain blinding unknown. 1 week washout prior to study may be insufficient. Detection Bias: UNCLEAR. See Durgam, et al.[45] Attrition Bias: HIGH. See Durgam, et al.[45] Reporting Bias: UNCLEAR. See Durgam, et al.[45] **Applicability**: Patient: extensive exclusion criteria, population seen in real world may not reflect subjects in study. Most patients had experienced current manic episode >7 days; 30% for >21 days. Intervention: studied as monotherapy, dose titrated by 1.5 mg to highest tolerable dose allowed within the respective treatment arm. Final mean daily doses were 4.8 mg and 9.1 mg for the 3-6 mg and 6-12 mg groups, respectively. Comparator: See Durgam, et al.[45] Outcomes: See Durgam, et al.[45] Setting: 65 centers in the U.S. (56%), Romania, Russia, Ukraine, Croatia and Serbia. All patients hospitalized for screening and for ≥2 weeks of double-blind treatment. Efficacy evaluations occurred at baseline, day 3, 5, 7, 10, 14 and 21.

Abbreviations: AC = active controlled; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CAR = cariprazine; CGI-S = Clinical Global Impressions-Severity of Illness; CI = confidence interval; CV = cardiovascular; D/C = discontinuation; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EPS = extrapyramidal symptoms or disorder; GI = gastrointestinal; HTN = hypertension; ITT = intention to treat; LOCF = last observation carried forward; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; PO = orally; PP = per protocol; QD = once daily; SAE = serious adverse event; SD = standard deviation; SE = standard error; SEM = standard error of the mean; YMRS = Young Mania Rating Scale; y = years.

References:

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196. doi:10.1016/S0140-6736(12)61729-2.

2. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951-962. doi:10.1016/S0140-6736(13)60733-3.

3. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374(9690):635-645. doi:10.1016/S0140-6736(09)60995-8.

4. Schizophrenia. DynaMed, EBSCO Information Services, Ipswich, MA. http://web.b.ebscohost.com/dynamed/detail?vid=2&sid=55f08351-49cb-4ed8-ab9b-bd9f2fb00a20%40sessionmgr113&hid=123&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#AN=115234&db=dme. Accessed March 24, 2016.

5. Pharmaceutical Services Administrative Rulebook, Chapter 410, Division 121. Division of Medical Assistance Programs Policy and Planning Section, Oregon Health Authority. http://www.oregon.gov/oha/healthplan/Policies/121rb021216.pdf. Accessed March 23, 2016.

6. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

7. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013;11:CD006625. doi:10.1002/14651858.CD006625.pub3.

8. Hermes EDA, Sokoloff DM, Stroup TS, Rosenheck RA. Minimum Clinically Important Difference In The Positive And Negative Syndrome Scale Using Data From The CATIE Schizophrenia Trial. *J Clin Psychiatry*. 2012;73(4):526-532. doi:10.4088/JCP.11m07162.

9. Montgomery-Asberg Depression Rating Scale (MADRS). https://psychology-tools.com/montgomery-asberg-depression-rating-scale/. Accessed March 29, 2016.

10. Duru G, Fantino B. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. *Curr Med Res Opin*. 2008;24(5):1329-1335. doi:10.1185/030079908X291958.

11. Samara MT, Dold M, Gianatsi M, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA Psychiatry*. 2016;73(3):199-210. doi:10.1001/jamapsychiatry.2015.2955.

12. Victoroff J, Coburn K, Reeve A, Sampson S, Shillcutt S. Pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders: a systematic review. *J Neuropsychiatry Clin Neurosci*. 2014;26(4):283-312. doi:10.1176/appi.neuropsych.13110335.

13. Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2014;1:CD006569. doi:10.1002/14651858.CD006569.pub5.

14. Hartung B, Sampson S, Leucht S. Perphenazine for schizophrenia. *Cochrane Database Syst Rev*. 2015;3:CD003443. doi:10.1002/14651858.CD003443.pub3.

15. Tardy M, Huhn M, Engel RR, Leucht S. Perphenazine versus low-potency first-generation antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2014;10:CD009369. doi:10.1002/14651858.CD009369.pub2.

16. Tardy M, Huhn M, Kissling W, Engel RR, Leucht S. Haloperidol versus low-potency first-generation antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2014;7:CD009268. doi:10.1002/14651858.CD009268.pub2.

17. Tardy M, Dold M, Engel RR, Leucht S. Trifluoperazine versus low-potency first-generation antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2014;7:CD009396. doi:10.1002/14651858.CD009396.pub2.

18. Yang C-S, Huang H, Zhang L-L, Zhu C-R, Guo Q. Aripiprazole for the treatment of tic disorders in children: a systematic review and meta-analysis. *BMC Psychiatry*. 2015;15:179. doi:10.1186/s12888-015-0504-z.

19. ABILIFY (aripiprazole) [Prescribing Information]. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd., December 2014.

20. Jackson JW, Schneeweiss S, VanderWeele TJ, Blacker D. Quantifying the role of adverse events in the mortality difference between first and second-generation antipsychotics in older adults: systematic review and meta-synthesis. *PLoS ONE*. 2014;9(8):e105376. doi:10.1371/journal.pone.0105376.

21. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS ONE*. 2014;9(4):e94112. doi:10.1371/journal.pone.0094112.

22. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. *Basic Clin Pharmacol Toxicol*. 2015;116(4):315-320. doi:10.1111/bcpt.12372.

23. Désaméricq G, Schurhoff F, Meary A, et al. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *Eur J Clin Pharmacol*. 2014;70(2):127-134. doi:10.1007/s00228-013-1600-y.

24. Office of Inspector General, Department of Health & Human Services. Second-Generation Antipsychotic Drug Use Among Medicaid-Enrolled Children: Quality-of-Care Concerns. http://oig.hhs.gov/oei/reports/oei-07-12-00320.pdf. Accessed March 9, 2016.

25. FDA Drug Safety Communication: FDA reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions. http://www.fda.gov/drugs/drugsafety/ucm426391.htm. Accessed April 26, 2016.

26. ARISTADA (aripiprazole lauroxil) [Prescribing Information]. Waltham, MA: Alkermes, Inc., October 2015.

27. Aripiprazole Lauroxil Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207533Orig1s000SumR.pdf. Accessed March 10, 2016.

28. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090. doi:10.4088/JCP.14m09741.

29. INVEGA TRINZA (paliperidone palmitate) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc., May 2015.

30. Paliperidone Palmitate Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207946Orig1s000SumR.pdf. Accessed March 10, 2016.

31. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry*. 2015;72(8):830-839. doi:10.1001/jamapsychiatry.2015.0241.

32. SAPHRIS (asenapine) [Prescribing Information]. St. Louis, MO: Forest Pharmaceuticals, Inc., March 2015.

33. Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the Acute Treatment of Pediatric Manic or Mixed Episode of Bipolar I Disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041. doi:10.1016/j.jaac.2015.09.007.

34. REXULTI (brexpiprazole) [Prescribing Information]. Tokyo, Japan; Otsuka Pharmaceutical Co., Ltd., July 2015.

35. Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015;164(1-3):127-135. doi:10.1016/j.schres.2015.01.038.

36. Correll CU, Skuban A, Ouyang J, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. *Am J Psychiatry*. 2015;172(9):870-880. doi:10.1176/appi.ajp.2015.14101275.

37. Brexpiprazole Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205422Orig1Orig2s000SumR.pdf. Accessed March 10, 2016.

38. Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015;76(9):1232-1240. doi:10.4088/JCP.14m09689.

39. Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatry*. 2015;76(9):1224-1231. doi:10.4088/JCP.14m09688.

40. VRAYLAR (cariprazine) [Prescribing Information]. Parsippany, NJ; Actavis Pharma, Inc., September 2015.

41. Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457. doi:10.1016/j.schres.2013.11.041.

42. Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015;76(12):e1574-1582. doi:10.4088/JCP.15m09997.

43. Kane JM, Zukin S, Wang Y, et al. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: Results From an International, Phase III Clinical Trial. *J Clin Psychopharmacol*. 2015;35(4):367-373. doi:10.1097/JCP.0000000000000346.

44. Cariprazine Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf. Accessed March 10, 2016.

45. Durgam S, Starace A, Li D, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. *Bipolar Disord*. 2015;17(1):63-75. doi:10.1111/bdi.12238.

46. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord*. 2015;174:296-302. doi:10.1016/j.jad.2014.11.018.

47. Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015;76(3):284-292. doi:10.4088/JCP.14m09081.

48. Kasper S, Montagnani G, Trespi G, Di Fiorino M. Treatment of depressive symptoms in patients with schizophrenia: a randomized, open-label, parallel-group, flexible-dose subgroup analysis of patients treated with extended-release quetiapine fumarate or risperidone. *Int Clin Psychopharmacol*. 2015;30(1):14-22. doi:10.1097/YIC.0000000000000053.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVEOUT
ANTIPSYCHOTICS, FIRST GENERATION ORAL					
ORAL	CAPSULE	LOXAPINE	LOXAPINE SUCCINATE	Y	Y
ORAL	CAPSULE	THIOTHIXENE	THIOTHIXENE	Y	Y
ORAL	ELIXIR	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	HALOPERIDOL	HALOPERIDOL	Y	Y
ORAL	TABLET	PERPHENAZINE	PERPHENAZINE	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	THIORIDAZINE HCL	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	TRIFLUOPERAZINE HCL	Y	Y
INHALATION	AER POW BA	ADASUVE	LOXAPINE	V	Y
ORAL	TABLET	ORAP	PIMOZIDE	V	Y
ORAL	TABLET	PIMOZIDE	PIMOZIDE	V	Y
ANTIPSYCHOTICS, SECOND GENERATION ORAL					
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y

ORAL	TABLET	CLOZARIL	CLOZAPINE	Y	Y
ORAL	TABLET	FANAPT	ILOPERIDONE	V	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	V	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	V	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	V	Y
ANTIPSYCHOTICS, PARENTERAL					
INJECTION	AMPUL	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
INJECTION	AMPUL	HALDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	AMPUL	HALOPERIDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SUSER SYR	ARISTADA	ARIPIPRAZOLE LAUROXIL	V	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	Y	Y
INTRAMUSC	VIAL	GEODON	ZIPRASIDONE MESYLATE	V	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	OLANZAPINE PAMOATE	V	Y

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VRAYLAR™ (cariprazine) capsules, for oral use
Initial U.S. Approval: 2015

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **VRAYLAR is not approved for the treatment of patients with dementia-related psychosis. (5.1)**

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

VRAYLAR is an atypical antipsychotic indicated for the:

- Treatment of schizophrenia (1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder (1)

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

- Administer VRAYLAR once daily with or without food (2)

	Starting Dose	Recommended Dose
Schizophrenia (2.2)	1.5 mg/day	1.5 mg to 6 mg/day
Bipolar Mania (2.3)	1.5 mg/day	3 mg to 6 mg/day

- Doses above 6 mg daily do not confer significant benefit but increased the risk of dose-related adverse reactions.

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

Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (3)

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

Known hypersensitivity to VRAYLAR (4)

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

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia*: Discontinue if appropriate (5.4)
- *Late-Occurring Adverse Reactions:* Because of VRAYLAR's long half-life, monitor for adverse reactions and patient response for several weeks after starting VRAYLAR and with each dosage change (5.5)
- *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)

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

Most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were (6.1):

- Schizophrenia: extrapyramidal symptoms and akathisia
- Bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Strong CYP3A4 inhibitors: reduce VRAYLAR dosage by half (2.4, 7.1)
- CYP3A4 inducers: do not recommend use with VRAYLAR (2.4, 7.1)

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

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

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

REXULTI® (brexpiprazole) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis (5.1).

• Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.2).
• Safety and effectiveness of REXULTI have not been established in pediatric patients (8.4).

----------INDICATIONS AND USAGE----------
REXULTI is an atypical antipsychotic indicated for:
- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) (1,14.1)
- Treatment of schizophrenia (1,14.2)

----------DOSAGE AND ADMINISTRATION----------
- Administer REXULTI once daily with or without food (2.1, 2.2, 12.3)

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD (2.1)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia (2.2)	1 mg/day	2 to 4 mg/day	4 mg/day

- *Moderate to Severe Hepatic Impairment (Child-Pugh score ≥7)*: Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.3)
- *Moderate, Severe or End-Stage Renal Impairment (CLcr<60 mL /minute)*: Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.4)
- *Known CYP2D6 Poor Metabolizers*: Reduce the usual dosage by half (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to REXULTI or any of its components (4)

----------WARNINGS AND PRECAUTIONS----------
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors (5.7)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)

----------ADVERSE REACTIONS----------
Most common adverse reactions were (6.1):
MDD: Weight increased and akathisia (≥5% and at least twice the rate for placebo)
Schizophrenia: Weight increased (≥4% and at least twice the rate for placebo)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (*www.fda.gov/medwatch*).

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

Factors:	*Dosage Adjustments for REXULTI (2.5)*
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of usual dose
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose
Known CYP2D6 Poor Metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double the usual dose and further adjust based on clinical response

** REXULTI may be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine).*

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2015

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2016

1 exp Aripiprazole/ 1695
2 asenapine.mp. 196
3 brexpiprazole.mp. 17
4 cariprazine.mp. 35
5 exp Clozapine/ 5220
6 iloperidone.mp. 128
7 exp Lurasidone Hydrochloride/ 103
8 olanzapine.mp. 6736
9 exp Paliperidone Palmitate/ 491
10 exp Quetiapine Fumarate/ 2238
11 exp Risperidone/ 5072
12 ziprasidone.mp. 1528
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 17888
14 limit 13 to (english language and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial or systematic reviews)) 368

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2016

1 exp Chlorpromazine/ 1507
2 exp Fluphenazine/ 281
3 exp Haloperidol/ 5380
4 exp Loxapine/ 167
5 exp Perphenazine/ 240
6 exp Thioridazine/ 375
7 exp Thiothixene/ 16
8 exp Trifluoperazine/ 568
9 exp Pimozide/ 264
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 8317
11 limit 10 to (english language and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial or systematic reviews)) 67

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

Class Update: Long-acting Opioids

Date of Review: May 2016 **Date of Last Review:** March 2015

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

Purpose for Class Update:
To evaluate current policies on long-acting opioids (LAOs) that are consistent with recent high-quality systematic reviews and updated clinical practice guidelines.

Research Questions:
1. What is the comparative efficacy or effectiveness of different LAOs in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
2. What are the comparative harms (including addiction and abuse) of different LAOs in adult patients being treated for chronic non-cancer pain? Do harms differ between drugs with and without abuse-deterrent mechanisms or between drugs with different abuse-deterrent mechanisms?
3. Are there subpopulations of patients (specifically by race, age, sex, socio-economic status, type of pain, or comorbidities) with chronic non-cancer pain for which one LAO is more effective or associated with fewer harms?

Conclusions:
- Since the LAOs were last reviewed, there have been 2 high-quality systematic reviews and 2 clinical practice guidelines published.
- The Washington State Agency Medical Directors Group (AMDG), whose recommendations have previously informed opioid-related prior authorization (PA) criteria for the Oregon Health Plan (OHP) fee-for-service (FFS) population, have recently updated their guidelines.[1] The group recommends frequent utilization of prescription drug monitoring programs (PDMP), random urine analyses, and patient-directed goals for patients chronic LAOs.[1] The group continues to recommend against daily opioid doses of 120 mg morphine milligram equivalents (MME) or greater unless evaluated by a pain specialist and provided with a prescription for naloxone.[1] The group continues to reinforce that there are insufficient data to support long-term prescribing of LAOs in chronic noncancer pain.[1] The LAOs should be avoided in patients with comorbid mental health disorders, patients with family history or personal history of substance abuse disorder, or patients on benzodiazepines or sedative hypnotics.[1]
- The Centers for Disease Control and Prevention (CDC) have recently published guidelines for opioid use.[2] Overall, the CDC's recommendations are similar to the AMDG except the CDC recommends against prescribing daily opioid doses that exceed 90 mg MME and prescribing naloxone for any patient who receives a prescription for an opioid that exceeds 50 mg per day MME.[2] The CDC recognizes that daily opioid doses that exceed 100 mg MME do not offer

additional analgesia but patients at these doses are 9-times more likely to overdose compared to doses of 20 mg per day MME.[2] Doses between 50 and 100 mg per day MME are 2.2 to 4.6-times higher risk of overdose compared to doses less than 20 mg per day MME.[2]

- The Drug Effectiveness Review Project (DERP) at Oregon Health & Science University (OHSU) deemed that there is still insufficient evidence of efficacy and effectiveness in terms of improvement in pain, functional improvement, and quality of life to support the use of one LAO over another.[3]
- Comparative evidence of harms between LAOs, including outcomes related to addiction and abuse potential, continue to be insufficient.[3]
- There is insufficient comparative evidence to determine if there are differences in effectiveness or harms between LAOs for different subpopulations based on socio-economic status, type of pain or associated comorbidities.[3]

Recommendations:

- No changes to the Oregon Health Plan (OHP) Preferred Drug List (PDL) are recommended based on clinical evidence alone. Review comparative drug costs in the executive session to inform whether changes to the PDL are recommended.
- Modify current clinical prior authorization (PA) criteria for high dose opioids to include all opioids and opioid-combination products (see **Appendix 4**). Primary changes include a maximum MME of 90 mg per day without a naloxone prescription, and prescriber utilization of the Oregon Prescription Drug Monitoring Program (PDMP) and assessment of pain and functional status at least every 3 months. Patients currently on doses that exceed 90 mg per day MME will be given 12 months to taper the dose to 90 mg per day MME or less.
- Discontinue PAs for methadone, opioid/non-opioid fixed dose combination products, and short-acting fentanyl products. These drugs will be incorporated into the one aforementioned PA. The U.S. Food and Drug Administration (FDA) already requires a Risk Evaluation and Mitigation Strategy (REMS) program to be in place for all short-acting fentanyl products. All prescribers, patients and pharmacies must be enrolled in the program to closely monitor for safety, misuse and abuse of the products.
- Continue current codeine PA to restrict use in pediatric patients.

Previous Conclusions:

- There is low quality evidence that long term use of opioid therapy was associated with increased risk of abuse, overdose, fracture, myocardial infarction and markers of sexual dysfunction. There is insufficient evidence to evaluate benefits and harms of long-term opioid therapy in high risk patients or other subgroups.
- There is low quality evidence of no clinically meaningful change in pain with hydrocodone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (difference in mean change from baseline -0.53; 95% CI -0.88 to -0.18, p= 0.0016).
- There is low quality evidence of no clinically meaningful change in pain with oxycodone/naloxone ER compared to placebo, as rated on an 11-point pain intensity numeric rating scale (4.2 versus 3.7; 95% CI 0.1 to 0.8; p= 0.006).
- There is low quality evidence of no clinically meaningful change in pain with morphine/naltrexone ER compared to placebo, as rated on the Brief Pain Inventory scale (-0.2 vs 0.3; p= 0.0455).
- There is insufficient evidence to establish differences in effectiveness of hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER versus other LAOs.
- There is insufficient evidence to establish differences in safety of hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER from other LAOs.
- There is insufficient evidence to determine whether an abuse-deterrent formulation of any LAO decreases the abuse or misuse of these drugs.

Previous Recommendations:

- Maintain hydrocodone ER, oxycodone/naloxone ER, and morphine/naltrexone ER as non-preferred.
- No changes made to the PDL after comparing costs of other LAOs in the executive session.

Background:

The use of prescription opioids for the treatment of chronic pain, defined as pain lasting longer than 3 months or past the time of normal tissue healing, is a growing epidemic in the United States. Opioid and non-opioid analgesics have been developed and marketed to improve pain, function and quality of life in patients who suffer from chronic pain. It is estimated that 20% of patients presenting with noncancer pain symptoms receive an opioid prescription, despite limited evidence supporting long-term benefits of opioid therapy.[5] The prevalence of opioid use disorder and opioid-related hospitalizations and deaths have increased significantly in recent years. A 2012-2013 survey estimated that 212,000 Oregonians were using prescription pain relievers for non-medicinal purposes.[6] It is estimated that 1 in 5 patients on chronic opioid analgesic therapy will develop opioid use disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[1] In Oregon, hospitalizations due to opioids have increased 285% from 2.6 per 100,000 in 2000 to 10.0 per 100,000 in 2013 and unintentional opioid-related overdose remains one of the leading causes of injury mortality in the state.[6,7] A 2013 Oregon Health Authority (OHA) report found that of the 423 unintentional deaths due to poisoning, 38% were associated with prescription opioids.[6] A study in U.S. Veterans found that patients prescribed LAOs were 2.5-times more likely to experience an unintentional overdose than those prescribed short-acting opioids (SAOs).[8] Opioid use has become a major public health concern at national and state levels. Recently, the CDC has acknowledged the risks associated with opioid use and provided guidance for use of opioid analgesics for chronic noncancer pain.

New guidance places heavy emphasis on the use non-pharmacologic and non-opioid therapy prior to the initiation of opioid analgesics, which reflects the limited evidence of benefits with prolonged opioid use and the well identified risks associated with continued opioid use. In an effort to reduce risks associated with opioid use, supportive measures have been added to guidance documents such as patient directed therapy management goals, utilization of prescription drug monitoring databases, and prescribing of naloxone for high opioid dosages.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:

Long-Acting Opioid Analgesics: An OHSU Drug Effectiveness Review Project (DERP)

The DERP updated a systematic review of LAO analgesics in September 2015.[3] The purpose of the review was to compare the effectiveness and harms between LAOs and between LAOs and SAOs in adults with chronic noncancer pain.[3] Twenty-five head-to-head studies evaluating LAO use for chronic noncancer pain were identified. Eighteen of the 25 trials directly compared a LAO to another LAO. For the purpose of this review, evidence from 7 RCTs and 1 observational study published since the last DERP review will be discussed in detail. With the exception of 1 small RCT, patients at high risk for drug or substance abuse were excluded from trials, thus limiting the evidence of harms in terms of addiction and abuse potential. All studies were eligible for inclusion, regardless of sample size or study duration. The review rated the strength of evidence (high, moderate, low, and insufficient) based on 4 key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence.[3]

There were two 12-week studies with moderate-strength evidence that demonstrated tapentadol ER 100 to 250 mg twice daily had a greater likelihood of reducing pain than patients taking oxycodone CR 20 to 50 mg twice daily in patients with osteoarthritis of the knee.[3] In one study, more patients on tapentadol ER were likely to experience a 30% or greater improvement in pain intensity (43.0% compared to placebo) than those on oxycodone CR (24.9% compared to placebo)(RR of 1.73, 95% CI 1.39 to 2.16).[3] Similarly, more patients on tapentadol ER were likely to obtain 50% or greater improvement in pain intensity (32.0% compared to placebo) than those on oxycodone CR (17.3% compared to placebo) (RR 1.85, 95% CI 1.40 to 2.45).[3] A similarly designed study in patients with low back pain produced low-quality evidence that tapentadol ER was found to have no benefit over oxycodone CR in pain relief.[3] The other trial included patients with low back pain and hip and knee osteoarthritis but had poor quality design.[3] The study found no statistical difference in pain reduction on an 11-point pain numeric rating scale (NRS).[3] Pooled safety analyses of these trials produced moderate-strength evidence favoring the use of tapentadol ER over oxycodone CR.[3] Lower study withdrawal rates due to adverse effects were seen in the tapentadol ER group (20% vs. 39%, RR 0.52, 95% CI 0.47 to 0.59).[3] Of the adverse events reported, gastrointestinal (GI) events were observed less frequently with tapentadol ER vs oxycodone CR (47% vs. 65%, respectively; RR 0.73, 95% CI 0.68 to 0.78).[3] The greatest difference in adverse effects seen was with vomiting (8% for tapentadol ER vs. 20% for oxycodone CR; RR 0.39, 95% CI 0.32 to 0.48), followed by nausea (20% for tapentadol ER vs. 36% for oxycodone CR; RR 0.55, 95% CI 0.49 to 0.62) and constipation (20% for tapentadol ER vs 34% for oxycodone CR; RR 0.58, 95% CI 0.51 to 0.65).[3] Somnolence and dizziness was also reported less frequently in the tapentadol ER group.[3]

The other 3 trials published since the last review did not find conclusive evidence to support the use of one LAO over another.[3] One poor quality study found no difference in pain relief with transdermal buprenorphine compared to transdermal fentanyl at 3, 6, and 12 months.[3] Fifty percent of patients on buprenorphine experienced a 3-point reduction on an 11-point visual analogue scale (VAS) at 3 months compared to 43% in the fentanyl arm.[3] No safety data was reported in this trial.[3] Low-strength evidence from one 20-week trial found no differences in effectiveness or harms between patients with back, arthritic, and neuropathic pain treated with hydromorphone Osmotic Release Oral System (OROS) 8 mg to 32 mg once daily and oxycodone sustained release (SR) 10 mg to 40 mg twice daily (p=0.348).[3] The third trial was the only trial to include patients with opioid use disorder but was poor quality due to dissimilar baseline characteristics and high-level attrition.[3] The trial found no differences on an 11-point pain relief scale between buprenorphine 4-16 mg plus naloxone 1-4 mg daily (87.4% pain reduction from baseline) and methadone 10 to 60 mg daily (88.6 % pain reduction from baseline).[3] In addition, there were no significant differences in safety and abuse outcomes.[3]

A retrospective cohort study of U.S. Veterans (n = 108,492) treated with methadone or LA morphine for back, joint, or limb pain provided low-strength evidence for lower mortality risk with methadone use.[3] The average daily dose of morphine LA was 67.5 mg and the average daily dose of methadone was 25.4 mg.[3] The highest risk of death was during the first 30 days of drug exposure (1.2% in the methadone cohort and 3.7% in the morphine LA cohort).[3] It should be noted that most patients on methadone were younger with fewer medical comorbidities, but had more psychiatric comorbidities than the morphine cohort.[3]

In efficacy and effectiveness analyses, tapentadol ER showed favorable outcomes in pain reduction.[3] However, no studies found evidence of superiority for one LAO over another in terms of functional improvement or quality of life.[3] From the last DERP report, there are no clear or consistent differences in harms between LA oxycodone and LA oxymorphone, morphine ER and LA oxycodone, ER (once-daily) and SR (twice-daily) formulations of morphine, hydromorphone ER and LA oxycodone, or morphine/naltrexone and morphine ER.[3] Head-to-head evidence for other comparisons (race, age, sex, socio-economic status type of pain, or comorbidities) of LAOs was low-strength or insufficient, primarily due to few trials of any one comparison, small sample sizes and methodological shortcomings of included studies.[3]

Tapentadol for Chronic Musculoskeletal Pain in Adults

A Cochrane systematic review was preformed to determine the efficacy, safety, and tolerability of tapentadol ER use in moderate-to-severe chronic musculoskeletal pain.[4] Thirty-seven articles (7 studies) were identified. Five reports (3 studies) were excluded due to trial design. Four moderate quality parallel-designed RCTs met inclusion criteria.[4] All 4 trials compared FDA approved tapendadol ER at doses of 100 to 500 mg daily to oxycodone CR, and 3 of the 4 trials additionally included placebo arms.[4] Two separate meta-analyses were performed for each control; however for the purpose of the class update, the outcomes of the oxycodone CR comparison arm will be discussed. Limitations of this meta-analysis include modest differences between interventions in efficacy outcomes between trials, high heterogeneity within comparisons and outcomes, large participation withdrawal rates, and the use of last-observation-carried-forward due to lack of data access.[4]

All 4 trials reported data on change in pain intensity from baseline.[4] Tapentadol ER demonstrated modest and perhaps clinically insignificant pain reduction and when compared to oxycodone CR.[4] On an 11-point NRS, tapentadol ER reduced pain by 0.24 points from baseline when compared to oxycodone CR (95% CI, -0.43 to -0.05) and a 0.56 point reduction when compared to placebo (95% CI, -0.92 to -0.20).[4] However, 2 of the 4 trials analyzed patients meeting at least 50% pain relief and found no significant difference between tapentadol ER and oxycodone CR (29.6% vs. 20.2%, respectively; RR 1.46; 95% CI, 0.92 to 2.32).[4]

Quality of life outcomes were assessed in 2 trials using standardized EuroQol-5 Dimension (EQ-5D) and the Western Ontario and McMaster Universities (WOMAC) scoring systems. The EQ-5D addresses 5 domains (mobility, self-care, usual activity, pain/discomfort, and anxiety or depression) on a scale of 0 to 1.[9] Tapentadol ER was associated with a higher increase in EQ-5D index (mean change 0.2, least squares mean difference (LSMD) vs. placebo, 0.05; 95% CI, 0.02 to 0.09) when compared to oxycodone CR (mean change 0.1, LSMD vs. placebo, -0.01; 95% CI, -0.05 to 0.02) (mean difference (MD) 0.1; 95% CI, 0.07 to 0.13).[4] It is unclear what a clinically meaningful difference would be. WOMAC is a standardized questionnaire comprised of 24 questions evaluating pain, physical function, and stiffness in osteoarthritis patients. It was unclear which WOMAC scale was used or what value would detect a clinically meaningful difference in pain. However, the 2 trials found no difference in the pain subscale (MD -0.03; 95% CI, -0.23 to 0.17) between tapentadol ER (LSMD vs. placebo -0.27; 95% CI, -0.422 to -0.126) and oxycodone CR (LSMD vs. placebo -1.05; 95% CI, -0.338 to 0.000).[4]

Tapentadol ER was associated with less incidence of discontinuation of therapy due to adverse event (20%) when compared to oxycodone CR (38%) (NNH 6; 95% CI, 5 to 7 for 12 weeks).[4] However, patients on tapentadol ER were more likely to withdrawal from the study early due to lack of efficacy (RR 2.23; 95% CI, 1.45 to 3.42) and loss to follow-up (RR 1.73, 95% CI 1.04 to 2.89).[4] Actual withdrawal rates for each comparison were not provided. In adverse event outcome analyses, tapentadol ER was also associated with a lower risk of constipation and dizziness, but was associated with higher risk of dry mouth.[4] The clinical significance of these findings is not well defined due to study limitations. The review concluded that there is insufficient evidence to support tapentadol ER use in moderate-to-severe chronic musculoskeletal pain.[4]

New Guidelines:

Centers for Disease Control and Prevention: Guideline for Prescribing Opioids for Chronic Pain[2]

The CDC published new guideline recommendations for the use of opioids in the treatment of chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The CDC Advisory Committee has adopted the guideline evidence grading from the CDC Advisory Committee for Immunization Practices (ACIP) Grading of Recommendation Assessments, Development and Evaluation (GRADE) recommendations based on quality of evidence and applicability. Recommendations are based on a graded hierarchy of 4 types of evidence ranging from very confident to little confidence in the effect estimate (see **Table 1**). These recommendations are additionally categorized into applicability to patient population (Category A: applies to all patients and Category B: individual decision-making should apply).

Non-pharmacologic and non-opioid analgesic therapies are preferred for the management of chronic pain. **Table 2** summarizes specific recommendations from the CDC for opioid selection, dosage, duration, follow-up and discontinuation with supporting evidence. Lastly, **Table 3** summarizes the CDC recommendations for assessment of risk and harms with opioid use with supporting evidence.

Table 1. **Evidence Grade Recommendations**.[2]

Evidence Grade	Body of Evidence	Implication
Type 1 evidence	RCTs or overwhelming evidence from observational studies	Indicates that once can be very confident that the true effect lies close to that of the estimate of the effect
Type 2 evidence	RCTs with important limitations, or exceptionally strong evidence from observational studies	True effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Type 3 evidence	Observational studies or RCTs with notable limitations	Confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect
Type 4 evidence	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations	Indicates that one has very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of the effect

Table 2. Current CDC Recommendations for Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation.[2]

Recommendation	Supporting Evidence
Reserve LAO therapy for patients with severe chronic pain who have received SAO daily for at least 1 week. Avoid the use of SAO in combination with LAO. (Recommendation category: A, evidence type: 4)	Continuous, regularly-scheduled use of LAO has not demonstrated superiority in efficacy or safety when compared to SAO. In the setting of LAO use in chronic pain management outside of active cancer pain, palliative care, or end-of-life care, there is insufficient safety data to support the use of SAO for breakthrough pain (expert opinion).
Prescribers should use caution when increasing dose of LAO ≥ 50 MME/day and should generally avoid doses ≥ 90 MME/day. (Recommendation category: A, evidence type: 3)	One RCT showed 52 MME/day provided no further pain or functional benefit than 40 MME/day. Doses of 50-99 MME/day were associated with increased risk of overdose by 1.9 to 4.6-fold when compared to doses of 1-19 MME/day; doses ≥100 MME/day were associated with 2.0-8.9-fold risk than doses of 1-19 MME/day.
Prescribers should evaluate benefits and harms of opioids within 1 to 4 weeks of initiation or dose escalation of opioid therapy. Follow-up should occur at least every 3 months for continuous therapy. If benefits do not outweigh harms, prescribers should work to reduce opioid dose and discontinue the opioid. Note: shorter intervals (within 3 days) of follow up are recommended after methadone is initiated. (Recommendation category: A, evidence type: 4)	Patients who do not experience pain relief with an opioid at 1 month are unlikely to experience pain relief with opioids at 6 months. There is no evidence to support more frequent monitoring of effectiveness in chronic opioid therapy. However, there is a strong correlation between continuation of opioids past 3 months and opioid use disorder.

Abbreviations: LAO = long-acting opioids; MME = morphine milligram equivalents; SAO = short-acting opioids

Table 3. Current CDC Recommendations for Assessing Risk and Addressing Harms of Opioid Use.[2]

Recommendation	Supporting Evidence
Consider prescribing naloxone when high risk factors for opioid overdose are present (e.g., history of overdose, substance abuse disorder, or opioid dose ≥ 50 MME, concurrent use of benzodiazepines, etc.) **(Recommendation category: A, evidence type: 4)**	Expert opinion.
Review PDMP data when starting opioid therapy and, at a minimum, every 3 months during opioid therapy. (Recommendation category: A, evidence type: 4)	To date, the effectiveness of PDMP monitoring has not been studied. However, evidence suggests patients who receive opioid prescriptions from multiple providers or patients who receive high doses of an opioid are at higher risk for death due to opioid overdose.
Conduct a urine drug screen before the initiation of opioid therapy and at least annually throughout therapy. (Recommendation category: B, evidence type: 4).	Expert opinion. Concurrent use of an opioid with other opioid or respiratory depressants (i.e., benzodiazepines) can increase risk for overdose. Urine drug screens can identify unreported medication use and can identify patients who may not take their opioids as prescribed, which may indicate diversion or difficulties with adverse effects.
Avoid prescribing opioids to patients receiving benzodiazepines whenever possible. (Recommendation category: A, evidence type: 3).	Concurrent use of benzodiazepines and opioids are associated with increased risk of respiratory depression and death when compared to opioids alone.
Avoid methadone as first-line therapy for chronic pain. (Recommendation not graded)	Variable and unpredictable pharmacokinetics increase risk of harm.
Use caution in prescribing transdermal fentanyl. Prescribers of transdermal fentanyl must be familiar with the dosing titration and its absorption properties and be prepared to educate their patients about these risks. (Recommendation not graded)	Both prescribers and patients often misunderstand the effects of dose titration or taper, which may lead to increased risk of harm.

Abbreviations: LAO = long-acting opioids; MME = morphine milligram equivalents; PDMP = prescription drug monitoring program; SAO = short-acting opioids

Washington State Agency Medical Directors Group: Interagency Guideline on Prescribing Opioids for Pain[1]

The AMDG consists of state academic leaders, pain experts, and clinicians in Washington state that practice in primary care and specialty settings. The AMDG updated their 2010 guidelines in June 2015, which had focused on the safe and effective management of chronic non-cancer pain. The updated guideline was expanded to include: 1) opioid use in acute, subacute, and perioperative pain phases to prevent inappropriate chronic opioid analgesic therapy when other alternatives for treating pain may be equally effective and safer in the long-term; 2) opioid use in special populations (during pregnancy and neonatal abstinence syndrome, in children and adolescents, in older adults, and in cancer survivors); 3) tapering and opioid use disorder; and 4) opioid use disorder.

The AMDG evaluated recent systematic reviews that examined the effectiveness of opioids for chronic pain and found insufficient data to support broad prescribing of LAOs with only modest effectiveness and minimal functional improvement. Due to the lack of evidence to support chronic use of LAOs, the guideline primarily focused on strategies and recommendations to limit use of LOAs for chronic non-cancer pain (see **Table 4**).

Table 4. 2015 AMDG Recommendations.[1]

Recommendation	Supporting Evidence
Use extreme caution in prescribing LAOs in patients with comorbid mental health disorders; family or personal history of substance abuse disorder; concurrent use of benzodiazepines, sedative-hypnotics, or barbiturates; or medical health conditions that can increase sensitivity to opioid related side effects.	The lifetime prevalence of DSM-V prescription opioid abuse disorder is 21% in patients who receive LAOs. There are increased and dose-dependent risks of opioid overdose and serious fractures with concurrent use of benzodiazepines, sedatives, or barbiturates.
Prescribe opioids in multiples of 7-day supply.	Reduce the incidence of the supply ending on a weekend.
Initiate proper bowel regimen when a LAO is prescribed.	Constipation is one of the most common side effects of opioid use.
Screen for risk of opioid misuse with validated tools (i.e., Opioid Risk Tool, SOAPP-R, DIRE, CAGE-AID)	Expert opinion.
Utilize state PDMP when prescribing opioids. Low Risk — Monitor ≥ once annually Moderate Risk — Monitor ≥ 2 times per year High Risk or opioid doses >120 mg MME/day — Monitor ≥ 3-4 times per year	Expert opinion.
Perform random urine drug tests.	Expert opinion. Frequency should be determined by patients risk category, with similar frequency to PDMP recommendations.
Consult a pain management specialist for opioid doses >120 mg MME/day. If opioid doses must exceed 120 mg MME/day, consider prescribing naloxone.	Opioid doses that exceed 100 mg/day MME do not offer additional analgesia but are 9-times more likely to overdose compared to doses of 20 mg/day MME. Doses between 50 and 100 mg/day MME are 2.2 to 4.6-times higher risk of overdose compared to doses < 20 mg/day MME.
Avoid prescribing methadone unless necessary.	Methadone has been associated with increased risk of cardiac and respiratory deaths due to numerous drug-drug interactions, unpredictable pharmacokinetics, and risk of accumulation.
High risk patients on LAO therapy should be seen in person at least monthly to assess and address aberrant behavior.	Expert opinion.
Screen for depression and for anxiety using validated tools. If comorbid mental health conditions exist in the presence of pain, they need to be treated or the patient's pain will not improve regardless of opioid therapy.	Expert opinion.
Consider tapering off LAO if patient has been maintained on opioid therapy for ≥ 3 months and there is no sustained clinical meaningful improvement in function.	Expert opinion. Validation tools for screening and assessment are available through the guidelines.

Abbreviations: DSM-V = The Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition; LAO = long-acting opioid; MME = morphine milligram equivalents; PDMP = prescription drug monitoring program.

New Safety Alerts:
Tramadol: Drug Safety Communication – FDA Evaluating Risks of Using in Children Aged 17 and Younger (September 21, 2015)[10]

Ultra-rapid metabolizers are more likely to have higher-than-normal levels of active O-desmethyltramadol, placing these patients at higher risk respiratory depression. A recent case-report reported a 5-year-old with respiratory depression after taking a single dose of tramadol oral solution following tonsillectomy. On follow-up the child was found to be an ultra-rapid metabolizer and had high levels of active opioid. Currently tramadol is not FDA-approved for use in children despite its off-label use in recent studies. The current FDA recommendation is to consider prescribing alternative FDA-approved pain medicines in children.[10]

New Formulations or Indications:
Belbuca™ (buprenorphine) film
Buprenorphine buccal film was approved by the FDA in October 2015 for the treatment of severe chronic pain.[11] Buccal film formulations are available in 75, 150, 300, 450, 600, 750, and 900 mcg strips and recommended to be taken once daily or every 12 hours.[11] Buprenorphine film is not recommended for patients on MME doses exceeding 160 mg daily.[11] Three 12-week trials have been completed.[11] Only 2 of the 3 trials demonstrated statistically significant pain reduction on an 11-point NRS in patients with low back pain when compared to placebo.[11]

An open-label study enrolled 749 patients with chronic low back pain.[11] Over 8 weeks, buprenorphine film doses were titrated to 150 mcg every 12 hours and patients were able to continue to increase the dose in 150 mcg dose increments every 4-8 days for up to 6 weeks.[11] Patients who achieved pain relief were then randomized to continue at that dose or matched placebo.[11] Patients on buprenorphine film were more likely to have at least a '30% reduction in pain' score than those on placebo (62% and 47%, respectively).[11] Similarly, more patients on buprenorphine film were likely to have at least a '50% reduction in pain' score from baseline versus placebo (41% and 33%, respectively).[11] Twelve percent of patients on buprenorphine film discontinued therapy early due to either an adverse event (8%) or lack of therapeutic effect (4%).[11] In contrast, early discontinuation rates in the placebo group were 4% due to an adverse event and 11% due to lack of therapeutic effectiveness.[11] No statistical analyses of the data were found.

Another 12-week open-label trial enrolled 810 patients on chronic opioid therapy (30-160 MME mg/day) for chronic pain.[11] Patients previously on 30 to 89 MME mg daily were initiated on 150 mcg buprenorphine film every 12 hours while patients taking 90-160 MME mg daily were initiated on 300 mcg buprenorphine film every 12 hours.[11] Patients were eligible to increase the dose by 150 mcg every 12 hours after 4 days for up to 6 weeks.[11] A higher proportion of buprenorphine film patients (64%) had at least a '30% reduction in pain' score compared to placebo (31%), while 39% of buprenorphine film patients had at least a '50% reduction in pain' score from baseline compared to placebo (17%).[11] Ten percent of patients on buprenorphine film discontinued prematurely due to an adverse event (2%) or lack of therapeutic effect (8%) compared to 30% of patients on placebo who discontinued early, primarily due to lack of efficacy (25%) and adverse events (5%).[11]

MorphaBond™ (morphine sulfate extended-release) tablets

A new morphine sulfate ER tablet formulation (MorphaBond™) with 'abuse-deterrent' properties was approved by FDA in October 2015 for the management of chronic pain.[12] The recommended dosing schedule is every 12 hours.[12] There are no published clinical trials available.

Xartemix XR™ (oxycodone/acetaminophen (APAP) extended-release) tablets

A new oxycodone/APAP XR tablet formulation (Xartemix XR™) with intended abuse-deterrent properties was approved by the FDA in March 2015 for the management of acute pain severe enough to require opioid treatment for which alternative treatment options are inadequate.[13] Tablets are available as a single strength 7.5/325 mg formulation.[13] The recommended dosing is 2 tablets every 12 hours.[13] The FDA reviewed data that showed a reduction in pain intensity over a 48-hour period when compared to placebo in acute post-operative patients.[13] However, results of this trail have not been published.

Randomized Controlled Trials:

A total of 6 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 2 trials are briefly described in **Table 5**. Full abstracts are included in **Appendix 2**.

Table 5. **Description of Randomized Comparative Clinical Trials**.

Study	Comparison	Population	Primary Outcome	Results
Leng, et al.[14] MC, DB, AC, DD, NI, RCT NCT01476774	1. Transdermal buprenorphine (5, 10, and 20 mcg/hour, maximum dose of 20 mcg/hour) 2. Tramadol SR (100 mg, maximum dosage of 400 mg/day)	Adults ≥18 years of age with moderate to severe musculoskeletal pain ≥4 weeks	Difference in VAS pain scores from baseline to treatment completion	Transdermal buprenorphine is non-inferior to tramadol SR. VAS scores decreased -3.30 ± 2.29 vs. -3.75 ± 2.15 (FAS) and -3.86 ± 2.0 vs. -4.28 ± 1.86 (PP) from baseline. Least squares mean difference was 0.45 (95% CI -0.02 to 0.91), which was within the ± 1.5 predefined threshold.
Verthein, et al.[15] MC, OL, CO, R NCT01079117	1. Slow-release oral morphine 2. Methadone Flexible dose regimens were used	Opioid dependent adults ≥18 years of age	Self-reported mental symptoms, rated according to the SCL-27	Slow-release oral morphine was associated with less overall severity of mental symptoms (ARR of 0.07, p = <0.01).

Abbreviations: AC = active-controlled; ARR = absolute risk reduction; CO = crossover study; DB = double blind; DD = double-dummy; FAS = full analysis set; MC = multicenter; NI = non-inferiority; OL = open-label; PP = per protocol set; R = randomized; RCT = randomized clinical trial; SCL-27 = symptom checklist (instrument used to measure depressive, vegetative, and agoraphobic symptoms); SR = sustained-release; VAS = visual analog scale (10 cm horizontal line anchored with word descriptors at each end; 0 cm = no pain and 10 cm = pain as bad as it could possibly be)

References:

1. Interagency Guideline on Prescribing Opioids for Pain, 3rd Edition; June 2015. Washington State Agency Medical Directors' Group. Available at http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf. Accessed 22 February 2016.
2. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain. *Centers for Disease Control and Prevention*. 2016.
3. Selph S, Holmes R, Holzhammer B. Drug Class Review: Long-acting Opioid Analgesics, 7th Update; September 2015. OHSU Drug Effectiveness Review Project, Pacific Northwest Evidence-based Practice Center.
4. Santos J, Alarcão J, Fareleira F, et al. Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.:CD009923.
5. Chou R, Deyo R, Devine B, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain: Executive Summary. *AHRQ Evidence Report/Technology Assessment No. 218*. September 2014; Pub. No. 14-E005-1-EF.
6. Prescription Drug Poisoning/Overdose in Oregon. *Oregon Health Authority Public Health Division: Injury and Violence Prevention Program*. April 24, 2015. Available at https://public.health.oregon.gov/DiseasesConditions/InjuryFatalityData/Documents/Fact%20Sheets/PDO_2015v04242015.pdf. Accessed 22 February 2016.
7. Causes of Death: Opioid-Related Overdose Deaths. *Oregon Health Authority Public Health Division*. July 30, 2015. Available at https://public.health.oregon.gov/ProviderPartnerResources/PublicHealthAccreditation/Documents/indicators/opioidrelateddeaths.pdf. Accessed 22 February 2016.
8. 2014 Drug Overdose Deaths, Hospitalizations, Abuse & Dependency among Oregonians. *Oregon Health Authority Center for Prevention & Health Promotion, Injury & Violence Prevention Section.* May 30, 2014. Available at https://public.health.oregon.gov/DiseasesConditions/InjuryFatalityData/Documents/oregon-drug-overdose-report.pdf. Accessed 22 February 2016.
9. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig.* 2010;30(8):489-505.
10. Tramadol: Drug Safety Communication – FDA Evaluating Risks of Using in Children Aged 17 and Younger. Food and Drug Administration Safety Alerts for Human Medical Products Website. Available at http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm463499.htm. Accessed March 4, 2016.
11. Belbuca™ (buprenorphine) [product information]. Malvern, PA: Endo Pharmaceuticals Inc., Oct 2015.
12. MorphaBond™ (morphine sulfate) [product information]. Valley Cottage, NY: Inspirion Delivery Technologies LLC, Oct 2015.
13. Xartemis XR™ (oxycodone hydrochloride and acetaminophen) [product information]. Hazelwood, MO: Mallinckrodt LLC, Sep 2014.
14. Leng X, Li Z, Lv H, et al. Effectiveness and Safety of Transdermal Buprenorphine versus Sustained-release Tramadol in Patients with Moderate to Severe Musculoskeletal Pain. *Clin J Pain*. 2015;31(7):612-20.
15. Verthein U, Beck T, Haasen C, et al. Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study. *European Addiction Research*. 2015;21:97-104.

Appendix 1: Current Status on Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	TABLET ER	MORPHINE SULFATE ER	MORPHINE SULFATE	Y
ORAL	TABLET ER	MS CONTIN	MORPHINE SULFATE	Y
TRANSDERM	PATCH TD72	DURAGESIC	FENTANYL	Y
TRANSDERM	PATCH TD72	FENTANYL	FENTANYL	Y
ORAL	CAP ER PEL	KADIAN	MORPHINE SULFATE	N
ORAL	CAP ER PEL	MORPHINE SULFATE ER	MORPHINE SULFATE	N
ORAL	CAP ER PO	EMBEDA	MORPHINE SULFATE/NALTREXONE	N
ORAL	CPBP 17-83	TRAMADOL HCL ER	TRAMADOL HCL	N
ORAL	CPBP 25-75	TRAMADOL HCL ER	TRAMADOL HCL	N
ORAL	CPMP 24HR	MORPHINE SULFATE ER	MORPHINE SULFATE	N
ORAL	ORAL CONC	METHADONE HCL	METHADONE HCL	N
ORAL	ORAL CONC	METHADONE INTENSOL	METHADONE HCL	N
ORAL	ORAL CONC	METHADOSE	METHADONE HCL	N
ORAL	SOLUTION	METHADONE HCL	METHADONE HCL	N
ORAL	TAB ER 12H	NUCYNTA ER	TAPENTADOL HCL	N
ORAL	TAB ER 12H	OPANA ER	OXYMORPHONE HCL	N
ORAL	TAB ER 12H	OXYCODONE HCL ER	OXYCODONE HCL	N
ORAL	TAB ER 12H	OXYCONTIN	OXYCODONE HCL	N
ORAL	TAB ER 12H	OXYMORPHONE HCL ER	OXYMORPHONE HCL	N
ORAL	TAB ER 24H	EXALGO	HYDROMORPHONE HCL	N
ORAL	TAB ER 24H	HYDROMORPHONE ER	HYDROMORPHONE HCL	N
ORAL	TAB ER 24H	HYSINGLA ER	HYDROCODONE BITARTRATE	N
ORAL	TAB ER 24H	TRAMADOL HCL ER	TRAMADOL HCL	N
ORAL	TAB ER 24H	ULTRAM ER	TRAMADOL HCL	N
ORAL	TAB IR ERO	XARTEMIS XR	OXYCODONE HCL/ACETAMINOPHEN	N
ORAL	TABLET	DOLOPHINE HCL	METHADONE HCL	N
ORAL	TABLET	LEVORPHANOL TARTRATE	LEVORPHANOL TARTRATE	N
ORAL	TABLET	METHADONE HCL	METHADONE HCL	N
ORAL	TABLET SOL	DISKETS	METHADONE HCL	N
ORAL	TABLET SOL	METHADONE HCL	METHADONE HCL	N
ORAL	TABLET SOL	METHADOSE	METHADONE HCL	N
ORAL	TBMP 24HR	TRAMADOL HCL ER	TRAMADOL HCL	N
TRANSDERM	PATCH TD72	FENTANYL	FENTANYL	N
TRANSDERM	PATCH TDWK	BUTRANS	BUPRENORPHINE	N

Appendix 2: Abstracts of Clinical Trials

Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-release Tramadol in Patients With Moderate to Severe Musculoskeletal Pain: An 8-Week, Randomized, Double-Blind, Double-Dummy, Multicenter, Active-controlled, Noninferiority Study[14]

Objectives: The aim of this noninferiority study was to investigate clinical effectiveness and safety of buprenorphine transdermal system (BTDS) in patients with moderate to severe musculoskeletal pain inadequately controlled with nonsteroidal anti-inflammatory drugs, compared with sustained-release tramadol tablets. *Materials and Methods*: Eligible patients were randomized (1:1) to receive low-dose 7-day BTDS (5, 10, and 20 μg/h, maximum dosage of 20 μg/h) or sustained-release tramadol tablets (100 mg, maximum dosage of 400 mg/d) over an 8-week double-blind treatment period (3-week titration, 5-week maintenance). The primary endpoint was the difference in the VAS pain scores from baseline to treatment completion. Noninferiority was assumed if the treatment difference on the VAS scale was within ±1.5 cm, this threshold indicating a clinically meaningful result. *Results*: Two hundred eighty patients were randomized to BTDS (n=141) or to tramadol (n=139). Both treatments were associated with a significant reduction in pain by the end of the treatment. The least squares mean difference of the change from baseline in VAS scores between the BTDS and tramadol groups were 0.45 (95% CI, -0.02 to 0.91), which was within the ±1.5 cm predefined threshold, indicating that the effectiveness of BTDS was not inferior to the effectiveness of sustained-release tramadol tablets. The incidence of adverse events was comparable between the 2 treatment groups. *Conclusions*: Our results suggest that BTDS is a good therapeutic option for patients experiencing chronic musculoskeletal pain of moderate to severe intensity that is insufficiently controlled by nonsteroidal anti-inflammatory drugs.

Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study[15]

Background: Opioid maintenance treatment is the option of choice to stabilize opioid-dependent patients. Whilst efficacy of methadone and buprenorphine has been studied extensively, fewer data on slow-release oral morphine are available. *Aims:* This study analyzes the effects of slow-release oral morphine compared to methadone with regard to self-reported mental symptoms, drug use and satisfaction with treatment. *Methods:* The study was carried out as an open-label randomized crossover trial in 14 treatment sites in Switzerland and Germany. It comprised 2 crossover periods of 11 weeks each. For measuring mental symptoms, the Symptom Checklist-27 (SCL-27) was used. Drug and alcohol use was assessed by the number of consumption days, and treatment satisfaction by a visual analogue scale. *Results:* A total of 157 patients were included for the analyses (per-protocol sample). Statistically significantly better outcomes for morphine as compared to methadone treatment were found for overall severity of mental symptoms (SCL-27 Global Severity Index), as well as 5 of the 6 syndrome groups of the SCL-27, and for treatment satisfaction. There were no statistically significant differences with regard to drug or alcohol use between groups. *Conclusions:* This study supports positive effects of slow-release oral morphine compared to methadone on patient-reported outcomes such as mental symptoms and treatment satisfaction with comparable effects on concomitant drug use. Slow-release oral morphine represents a meaningful alternative to methadone for treatment of opioid dependence.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014
1 exp Morphine 35325
2 exp Fentanyl 13833
3 exp Tramadol 2415
4 exp Methadone 10875
5 tapentadol.mp. 227
6 exp Oxymorphone 451
7 exp Oxycodone 1555
8 exp Hydromorphone 1075
9 exp Hydrocodone 432
10 exp Levorphanol 599
11 exp Buprenorphine 4007
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 64623
13 exp Transdermal Patch 639
14 exp Administration, Topical 72672
15 long acting.mp. 19562
16 sustained release.mp. 10864
17 13 or 14 or 15 or 16 102603
18 2 and 17 1028
19 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 18 53472
20 limit 19 to yr="2015-Current" 733
21 limit 20 to (English language and humans) 520
22 limit 21 to (clinical conference or 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 multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)

~~High Dose~~ Opioid Analgesics

Goals:

- Restrict use of ~~high dose~~ opioid analgesics to OHP-funded conditions with documented improvement in pain or function and consistent monitoring for misuse and abuse of these agents.
- Promote the safe use of opioid analgesics by restricting use of high doses that have not demonstrated improved benefit and are associated with greater risk for accidental opioid overdose and death.
- Limit the use of non-preferred opioid analgesic products.

Length of Authorization:

60 days~~Up~~ to 6 months (criteria-specific)

Covered Alternatives:

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

Requires a PA:

- All non-preferred opioids and opioid combination products.
- Any opioid listed in Table 1 or opioid combination product that contains an opioid listed in Table 1 that exceeds a morphine milligram equivalent (MME) of 90~~120~~ mg per day.
- Any opioid product listed in Table 2 that exceed quantity limits.

Note:

- Preferred opioid products that do not exceed a MME of 90 mg per day are exempt from this PA.
- Patients with a terminal diagnosis, metastatic cancer, or patients enrolled in a hospice program (ICD10 C6900-C799; C800-C802) are exempt from this PA.
- Pediatric use of codeine is subject to separate clinical PA criteria.

Table 1. Daily Dose Threshold of Opioid Products.

Opioid	Dose Threshold (90 MME/day)	Recommended starting dose for opioid-naïve patients	Considerations
~~**Buprenorphine Transdermal**~~	~~20 mcg/hour (every 7 days)~~	~~5 mcg/hr patch every 7 days~~	~~May increase dose q72 hours patients up to a max of 20 mcg/hr q7 days. Doses >20 mcg/hr every 7 days increase risk of QTc prolongation.~~

Opioid	Dose Threshold (90 MME/day)	Recommended starting dose for opioid-naïve patients	Considerations
Note: Any opioid exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing an opioid and monitor all patients regularly for the development of these behaviors or conditions.			
Codeine	6800 mg/24 hours	30 mg q 4-6 hours	Codeine is a prodrug of morphine. Metabolism and conversion to morphine is subject so multiple polymorphisms in different populations. Subsequently, persons may be hypersensitive to the analgesic and respiratory effects of codeine or may be resistant to the effects of codeine. Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose.
Fentanyl (transdermal patch)	37.550 mcg/hour (q 72 hr)	12.5 mcg/hour q 72 hours	Use only in opioid-tolerant patients who have been taking ≥60 mg MME daily for a ≥1 week. Deaths due to a fatal overdose of fentanyl have occurred when pets, children and adults were accidentally exposed to fentanyl transdermal patch. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure.
Hydrocodone	1290 mg/24 hours	IR: 5-10 mg q 4-6 hours ER: 10 mg q 12 hours	Dosing limits based on combinations (e.g., acetaminophen) may further limit the maximum daily dose. Use the ER formulation with extreme caution due to potentially fatal interaction with alcohol or medications containing alcohol. Accidental consumption of even 1 dose of the ER formulation, especially by children, can result in a fatal overdose.
Hydromorphone	22.530 mg/24 hours	IR: 2 mg q 4–6 hours ER 8 mg q 24 hours	Hydromorphone is a potent opioid. Accidental ingestion of even one dose of hydromorphone ER, especially by children, can result in a fatal overdose of hydromorphone.
Methadone	240 mg/24 hours	2.5-5 mg BID or TID	Methadone is a very effective and inexpensive opioid but should be reserved to prescribers very familiar with the complex pharmacokinetic and pharmacodynamics variability of this drug. Methadone exhibits a non-linear relationship due to its long half-life and accumulates with chronic dosing. Methadone also has complex interactions with several other drugs. The dose should not be increased more frequently than once every 7 days.
Morphine	1290 mg/24 hours	IR 10 mg q 4 hours ER 15 mg q 12 hours	The coingestion of alcohol with morphine ER may result in increased plasma levels and a potentially fatal overdose of morphine. Accidental ingestion of even one dose of morphine, especially by children, can result in a fatal overdose of morphine.

Oxycodone	680 mg/24 hours	IR: 5 mg q 4-6 hours ER: 10 mg q12 hours	Accidental ingestion of even one dose of oxycodone ER, especially by children, can result in a fatal overdose of oxycodone. The concomitant use of oxycodone ER with all cytochrome P450 (CYP-450) 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone ER and any CYP3A4 inhibitor or inducer. Avoid concurrent use of any products containing acetaminophen (maximum combined APAP dose = 4000 mg/day for <10 days or 2500 mg/day for ≥10 days)
Oxymorphone	340 mg/24 hours	IR: 5–10 mg q 4-6 hours ER: 10 mg q 12 hours	Accidental ingestion of even 1 dose of oxymorphone ER, especially by children, can result in a fatal overdose of oxymorphone. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking oxymorphone ER. The coingestion of alcohol with oxymorphone ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone.
Tapentadol	225300 mg/24 hours	IR: 50 mg q 4-6 hours ER: 50 mg q 12 hours	Accidental ingestion of even one dose of tapentadol ER, especially by children, can result in a fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while taking tapentadol ER. The coingestion of alcohol with tapentadol ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol. Tramadol is also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold.
Tramadol	~~Threshold is beyond maximum daily dose~~400 mg/24 hours (IR) 300 mg/24 hours (ER)	IR: 50 mg q 4-6 hours ER: 100 mg per 24 hours	The threshold is based on maximum daily dosing for the IR and ER formulations. The threshold is not equivalent to 90 mg/day MME. Tramadol is also possesses SSRI-like properties and interacts with multiple drugs. Use with caution with other drugs that may increase risk of serotonin syndrome or decrease seizure threshold.

Abbreviations: ER = extended-release or sustained-release formulation(s); IR = immediate-release formulation(s); MME = morphine milligram equivalent.

Table 2. Specific Opioid Products Subject to Quantity Limits

Drug Product	Quantity Limit
AVINZA	1 dose/day
BELBUCA	1 dose/day
BUTRANS	1 patch/7 days
EMBEDA	2 doses/day
EXALGO	1 dose/day
Fentanyl patch	1 dose/72 hrs

Drug Product	Quantity Limit
HYSINGLA ER	2 doses/day
KADIAN	2 doses/day
NUCYNTA ER	2 doses/day
OPANA ER	2 doses/day
OXAYDO	2 doses/day
OXYCONTIN	2 doses/day
ZOHYDRO ER	2 doses/day

Table 3. Common Conditions Not Funded Under the Oregon Health Plan (OHP).

Common indications OHP does not cover:*	ICD10 Codes
Disorders of soft tissue (including Fibromyalgia)	M79.0; M60.9; M79.1; M79.7; M54.10; M79.2; M79.4; M79.3; M72.9; M79.609; M79.5; M79.A19; M79.A29; M79.A3; M79.A9; M79.89; R25.2; Z45.42
Acute and chronic disorders of spine without one of the following neurologic impairments: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder See Prioritized List of Health Services Guideline Notes 37 and 41	M47.812; M47.12; M47.814; M47.817; M47.14; M47.16; M48.20; M48.10; M48.30; M48.9; M47.819; M47.10; M50.20; M51.26; M51.27; M51.24; M51.25; M51.9; M51.9; M51.44; M51.45; M51.46; M51.47; M51.9; M50.30; M51.34; M51.35; M51.36; M51.37; M51.9; M50.00; M51.04; M51.05; M51.06; M51.07; M96.1; M46.40; M51.9; M50.80; M50.90; M46.45; M51.84; M51.85; M46.47; M51.86; M51.87; M48.02; M54.2; M53.0; M54.12; M54.13; M43.6; M54.02; M67.88; M53.82; M48.00; M48.04; M48.06; M48.08; M54.6; M54.5; M54.30; M54.14; M54.15; M54.16; M54.17; M54.89; M54.9; M43.27; M43.28; M53.2X7; M53.3; M53.2X8; M53.3; M54.08; M43.8X9; M53.9 except M53.1; M99.01; M99.02; M99.03; M99.04; M99.05; M99.06; M99.07; M99.08; M990.9; S33.101A; S23.101A; S13.4XXA; S13.8XXA; S23.3XXA; S23.8XXA; S33.5XXA; S33.8XXA; S23.9XXA

*Funded diagnoses are dependent on current funding levels. A list of currently funded diagnoses can be found at www.oregon.gov/OHA/herc/pages/prioritizedlist.aspx

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD10	
2. Is the patient being treated for any of the following: a. Cancer-related pain (ICD10 G893); or b. Terminal diagnosis (<6 months); or c. Hospice care?	**Yes**: Go to #3	**No**: Go to #5
3. Is the requested medication a preferred agent?	**Yes:** Approve for up to 6 months	**No**: Go to #4
4. Will the prescriber change to a preferred product? Note: Preferred opioids are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy. Both oral and transdermal options are available.	**Yes**: Inform prescriber of covered alternatives in class and approve for up to 6 months.	**No**: Approve for up to 6 months

5. Is the diagnosis funded by the OHP?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP May approve for up to 60 days to allow for tapering
6. Will the prescriber change to a preferred product, not to exceed a MME of ~~120~~90 mg per day?	**Yes**: Inform prescriber of covered alternatives in class. Approve for up to 6 months subject to appropriate quantity limits.	**No:** Go to #7
7. Is this new therapy (i.e., no previous prescription for the same drug and same dose in past 30 days)?	**Yes**: Go to #8	**No**: Go to #10
8. Does the prescription exceed quantity limits applied in Table 2 (if applicable)?	**Yes**: Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9
9. Does the total daily opioid dose exceed 90 mg MME?	**Yes**: Go to #10	**No:** Approve for up to 3 months. Subsequent approvals are based on: • Documented UDS in past 1 year • Enrollment in the OR PDMP • Documentation of sustained improvement in pain and function
~~8. Does the total daily opioid dose exceed 120 mg MME?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~ ~~In general, the total dose of opioid should not exceed 120 mg MME. Risk for opioid-related death substantially increases at higher doses.~~	~~**No**: Go to #9~~

~~9.~~10. Has the patient had a urinary drug screen within the past 1 year?	**Yes**: Go to #11 Document date:_____	**No:** Pass to RPh. Deny; medical appropriateness. Recommend UDS.
~~10.~~11. ~~Has~~Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (PDMP) and has the prescriber verified at least once in the past 3 months that the patient has been prescribed analgesics by a single prescribing practice or prescriber and has received those analgesics by a single pharmacy?	**Yes**: Go to #12 Document date PDMP last reviewed:_____	**No:** Pass to RPh. Deny; medical appropriateness. Recommend enrolment in the PDMP and monitor at least every 3 months. May approve once for up to 30 days to allow time for prescriber to enroll in the PDMP.~~Approve 30-90 days.~~ ~~Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.~~
~~11.~~12. Can the prescriber provide documentation of sustained improvement in both function and pain in the past 3 months ~~AND is prescriber aware of additional risk factors (e.g., concurrent benzodiazepines, skeletal muscle relaxants, other LAO or history of drug abuse)~~?	**Yes:** ~~Approve for up to 6 months.~~Go to #13 Documentation date in patient chart:_____ ~~Quantity limits apply to:~~ ~~AVINZA: 1 dose/day~~ ~~BUTRANS: 1 patch/7 days~~ ~~EMBEDA: 2 doses/day~~ ~~EXALGO: 1 dose/day~~ ~~Fentanyl patch: 1 dose/72 hrs~~ ~~KADIAN: 2 doses/day~~ ~~OPANA ER: 2 doses/day~~ ~~OXYCONTIN: 2 doses/day~~	**No:** Pass to RPh. Deny; medical appropriateness May approve for up 60 days to allow for tapering and utilization of other measures for pain management. Chronic opioid patients must be tapered to ≤90 mg/day MME within 12 months.~~Approve 30-90 days to allow for potential tapering of dose.~~ ~~Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.~~

13. Is the patient concurrently on a benzodiazepine chronically (≥1 week supply dispensed in past 30 days)?	**Yes:** Go to #14 Subsequent approval for future benzodiazepine or opioid claims is dependent on concurrent claim for naloxone.	**No:** Go to #14
~~12.~~14. Is the patient concurrently on other ~~long-acting opioids~~ short- or long-acting opioids~~(e.g., fentanyl patch, methadone, or long-acting morphine, long-acting oxycodone, or long-acting oxymorphone, etc.)~~?	**Yes**: Go to #15	**No**: Approve for up to 3 months Subsequent approval for future opioid claims >90 mg/day MME is dependent on concurrent claim for naloxone.
~~13.~~15. Is the duplication due to tapering or switching products? The concurrent use of more than one opioid product (short- or long-acting) ~~multiple long-acting opioids~~ is not recommended unless tapering and switching products. ~~Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain.~~	**Yes**: Approve for up to 6~~9~~0 days after which duplication opioid therapy will no longer be approved.	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 60 days to allow for tapering off one of the opioids and subsequent approval for future opioid claims is dependent on concurrent claim for naloxone.~~May approve for taper only. Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.~~

P&T Review: *5/16 (AG); 3/15; 2/12; 11/11; 12/09; 9/09; 3/09; 12/08*
Implementation: *6/12; 5/12; 1/12; 1/10*

Opioid/non-narcotic Combinations and Excessive Dose Limits

Goal(s):

- Decrease risk for adverse events attributed to high doses of acetaminophen (APAP) or aspirin (ASA) when combined with an opioid product.
- Pay only for conditions funded on the OHP list of prioritized services.

Requires PA:

- Non-preferred drugs.
- Prescriptions exceeding FDA recommendations of 4000 mg/day of APAP or ASA.
- All codeine-containing products for patients under 13 years of age.
  Note:
  - Pharmacy may need to adjust day's supply entry.
  - Prescriber may choose a product with a higher ratio of narcotic to keep APAP or ASA within maximum limits or use a single-ingredient opioid.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does daily dose of APAP or ASA exceed the maximum daily dose?	**Yes:** Go to #3	**No:** Instruct pharmacy to correct day's supply entry
3. Is the diagnosis funded on the OHP list of prioritized services?	**Yes:** Pass to RPh. Deny; medical appropriateness Review FDA maximum dose and provide alternatives.	**No:** Pass to RPh. Deny; not funded by the OHP Review FDA maximum dose and provide alternatives

Examples of products containing ASA:

Aspirin Combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Codeine/ASA/Caffeine/ Butalbital 30/325/40/50 mg	12 tablets	Oxycodone/ASA 4.8355/325 mg	12 tablets
Codeine/ASA/Carisoprodol 16/325/200 mg	12 tablets	Dihydrocodeine/ASA/Caffeine 16/356.4/30 mg	11 capsules

Examples of products containing APAP:

Hydrocodone/APAP combinations			
Drug	**Maximum quantity per day**	**Drug**	**Maximum quantity per day**
Hydrocodone/APAP 5/300 mg	13 tablets	Hydrocodone/APAP 2.5/108 mg per 5 mL	185 mL
Hydrocodone/APAP 7.5/300 mg	13 tablets	Hydrocodone/APAP 5/217 mg per 10 mL	184 mL
Hydrocodone/APAP 10/300 mg	13 tablets	Hydrocodone/APAP 7.5/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 2.5/325 mg	12 tablets	Hydrocodone/APAP 7.5/500 mg per 15 mL	120 mL
Hydrocodone/APAP 5/325 mg	12 tablets	Hydrocodone/APAP 10/325 mg per 15 mL	184.5 mL
Hydrocodone/APAP 7.5/325 mg	12 tablets		
Hydrocodone/APAP 10/325 mg	12 tablets		

Oxycodone/APAP combinations	
Oxycodone/APAP 5/300 mg	13 tablets
Oxycodone/APAP 7.5/300 mg	13 tablets
Oxycodone/APAP 10/300 mg	13 tablets
Oxycodone/APAP 2.5/325 mg	12 tablets
Oxycodone/APAP 5/325 mg	12 tablets

Oxycodone/APAP 7.5/325 mg	12 tablets
Oxycodone/APAP 10/325 mg	12 tablets
Oxycodone/APAP 5/325 per 5 mL	61.5 mL

Codeine/APAP combinations	
Codeine/APAP 12/120 mg per 5 mL	166.5 mL
Codeine /APAP 15/300 mg	13 tablets
Codeine /APAP 30/300 mg	13 tablets
Codeine /APAP 60/300 mg	13 tablets

Other Combinations	
Tramadol/APAP 37.5/325 mg	12 tablets
Dihydrocodeine/APAP/caffeine 16/320.5/30 mg	12 tablets

P&T Review: *5/16 (AG); 5/15; 2/06; 11/99; 2/99*
Implementation: *7/1/15; 9/30/05; 5/16/05; 12/1/03; 5/1/03*

Methadone

Goal(s):

- Promote safe use of methadone upon initiation.

Initiative:

Prescribing Recommendations:

- Opioid-naïve or patients receiving codeine preparations: start at low dose and increase slowly.
  - 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
- Conversion from other opioids
  - Starting dose 2.5 mg-5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly
  - Use short-acting opioid for breakthrough pain until optimum dose reached.

Length of Authorization:

Up to 6 months

Requires PA:

- Patients initiated on methadone (i.e., no previous claim within 90 days) on a total daily dose of 20 mg or more.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Has patient had a recent urinary drug screen (within the past 90 days)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness Recommend UDS

Approval Criteria		
3. Has patient been continuously on opioids other than codeine over the past 90 days?	**Yes:** Go to #4 Document previous opioid therapy.	**No:** Pass to RPh. Deny; medical appropriateness Opioid-naïve or patients receiving codeine preparations should start methadone @ 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly.
4. Was the total daily Morphine Equivalent Dose less than 200 mg? Opioid Dose Calculator at: http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm	**No:** Go to #5	**Yes:** Pass to RPh. Deny; medical appropriateness Recommend initiate methadone @ 2.5mg - 5 mg q8h; upward titration by 2.5 mg q8h no sooner than weekly and use short-acting opioids for break-through pain
5. Is this patient terminal (<6 months) or admitted to hospice?	**Yes:** Approve for up to 6 months	**No:** Go to #6
6. Is patient being treated for oncology pain?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *5/16 (AG); 1/12; 5/11; 3/11*
Implementation: *4/9/12*

Fentanyl Buccal, Intranasal and Sublingual Products

Goals:

The purpose of this prior authorization policy is to ensure that fentanyl for breakthrough pain is appropriately prescribed in accordance to FDA black box warnings:

- Short-acting fentanyl is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.
- Patients considered opioid-tolerant are those who are taking at least 60 mg/day morphine, 50 mcg/hour transdermal fentanyl, or an equianalgesic dose of another opioid for a week or longer.
- Because life-threatening respiratory depression can occur at any dose in patients not taking chronic opioids, transmucosal and buccal fentanyl is contraindicated in the management of acute or postoperative pain.
- This product must not be used in opioid-naïve patients. Short acting (SA) fentanyl is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable and skilled in the use of Schedule II opioids to treat cancer pain.
- When prescribing, do not convert patients from other fentanyl products on a mcg per mcg basis. Pharmacokinetic differences between products could cause fatal over-dose.
- Caution should be used when combining these agents with CYP3A4 inhibitors. Increases in fentanyl concentrations can cause fatal respiratory depression.
- Patients and their caregivers must be instructed that fentanyl products contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly.

Length of Authorization:

Up to 6 months (with quantity limit)

Requires PA:

- Non-preferred short-acting fentanyl buccal, intranasal and sublingual products

Covered Alternatives:

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

Approval Criteria		
1. What is the diagnosis for which fentanyl is being requested?	Record ICD10 code.	
2. Is the pain diagnosis above the line or below the line? (for DMAP, short acting fentanyl is not limited to cancer pain but must be severe chronic pain)	**Above the line:** go to #3.	**Below the line:** No, Pass to RPH; Deny, (Not Covered by the OHP).
3. Is the prescriber an oncologist or pain specialist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny, (Medical Appropriateness), with message: "The described use is not consistent with the FDA labeling which SA fentanyl be used only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."
4. Is client tolerant to opioids (**Check profile)**, defined as chronic long-acting opioid dose of: • Morphine greater than 60 mg per day? OR • Transdermal fentanyl 50 mcg per hour? OR • Equianalgesic dose of another opioid for at least one week?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied because it is not consistent with the FDA labeling. A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*
5. Has the client tried and failed immediate release morphine or oxycodone? OR is the client allergic, unable to swallow or intolerant to morphine and oxycodone?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request was reviewed and denied based on the following: A trial of immediate release morphine or oxycodone is recommended prior to use of SA fentanyl."*

Approval Criteria		
6. Is the quantity >4 doses per day?	**Yes:** Pass to RPH; Deny, (Medical Appropriateness), *with message:* *"Your request for a quantity greater than 4 doses per day has been denied because it exceeds limits."*	**No:** Approve for up to 6 months with quantity limit of 4 lollipops/tablets per day (i.e. 120/30 days).

P&T Review: *5/16 (AG); 5/15; 6/13; 3/10; 12/09, 9/05, 5/05*
Implementation: *1/1/14; 4/26/10; 1/1/10; 6/1/08; 4/1/08; 9/1/06*

Codeine

Goal(s):

- Promote safe use of codeine in pediatric patients

Length of Authorization:

Up to 3 days

Requires PA:

- All codeine products for patients under 13 years of age
- All codeine *analgesic* products for patients aged 13 through 17 years

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. What is the age of the patient?	**Ages 0-12 years:** Pass to RPh. Deny; medical appropriateness	**Ages 13-17 years:** Go to #3
3. Is the prescription for an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
4. Has the patient recently undergone tonsillectomy or adenoidectomy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Does the dose exceed 240 mg per day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve no more than 3-day supply

P&T Review: *5/16 (AG/KK); 9/15; 7/15*
Implementation: *10/9/15*

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

Class Update: Tobacco Cessation Products

Date of Review: May 2016 **Date of Last Review:** March 2014

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

Purpose for Class Update:
Smoking is a significant public health problem that can be associated with substantial health care costs and can cause many preventable diseases including cancers, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD). This review will evaluate current comparative effectiveness evidence to assist in establishing recommendations for the therapeutic agents indicated for smoking cessation.

Research Questions:
1. Is there new comparative evidence for differences in efficacy or effectiveness or safety of pharmacologic agents for the treatment of tobacco cessation?
2. Is there evidence that long term nicotine replacement therapy beyond 12 weeks is more effective in promoting tobacco abstinence?
3. Are there specific subpopulations based on severity of addiction or other disease characteristics that may benefit more from a specific drug or combination of drugs?

Conclusions:
- There is high quality evidence of a benefit of combined pharmacotherapy and behavioral treatment compared to usual care, brief advice, or less intensive support (RR 1.83; 95% CI 1.68 to 1.98).[1]
- There is low quality and inconsistent evidence that the combination of varenicline and nicotine replacement therapy (NRT) is favorable on abstinence rates compared to varenicline alone (44% vs. 35.1%; OR 1.50; 95% CI 1.13 to 1.97).[2]
- There is evidence that increasing varenicline dose (up to 5 mg/day) in smokers with low response to standard dose (2 mg/day) does not improve smoking cessation at 12 weeks compared to standard dose (26% vs. 23%; OR 1.19; 95% CI 0.62-2.28) after the target quit date (TQD) and significantly increases nausea (80% vs. 18%; NNH 2) and vomiting (36% vs. 3%; NNH 3).[3]
- There is insufficient evidence that NRT improves prolonged abstinence rates in pregnant women who continue to smoke.[4,5] There is low quality evidence that infants born to mothers using nicotine replacement therapy (NRT) are more likely to have survived without any impairment than pregnant women who smoker on placebo (OR 1.40; 95% CI 1.05 to 1.86).[5]
- There is low quality evidence that in certain patient populations, including those with serious mental illness, maintenance pharmacotherapy (52 weeks) with varenicline may improve prolonged tobacco abstinence rates at 52 weeks.[6] There is also low quality evidence based on one randomized controlled trial[7] that a “reduce-to-quit” approach with 24 weeks of varenicline may be more effective than placebo for continuous abstinence rates (RR 4.6; 95% CI 3.5 to 6.1)

through 24 weeks. There is also low quality evidence that varenicline improves abstinence compared to placebo in patients who have had a prior quit attempt with varenicline (45% vs. 11.8%; OR 7.08; 95% CI 4.34 to 11.55).[8]
- There is moderate quality evidence that NRT, bupropion and varenicline are not associated with an increase in major adverse cardiovascular events (MACE) and an increase in minor events including palpitations and tachycardia with NRT (RR 1.89; 95% CI 1.31 to 2.73).[9]

Recommendations:
- No changes are warranted to current PDL based on new comparative evidence. Evaluate comparative costs in the executive session.
- Recommend allowing initial treatment with varenicline for 24 weeks.
- Evaluate current prior authorization (PA) policy to ensure it is resulting in the intended goal of the policy.

Previous Conclusions:
- No further review or research needed at this time; update PA criteria.

Previous Recommendations:
- Add Nicotine replacement therapy (NRT) products including the patch, gum and lozenges as preferred drugs on the PDL with a quantity limit for six months of treatment.
- Due to no differences in safety or efficacy between the NRT products, evaluate comparative costs for further decisions.
- Make bupropion sustained release (Zyban) a preferred drug.
- Make varenicline a preferred agent on the PDL with a quantity limit for twelve weeks of treatment within 6 months.
- Require prior authorization criteria for non-preferred products, NRT beyond 6 months in the absence of behavioral counseling, and varenicline beyond 12 weeks requiring the patient has quit for a second fill of varenicline and that the patient is enrolled in a smoking cessation behavioral counseling program in addition to medication therapy.

Background:
Tobacco use is a leading preventable cause of morbidity and premature death worldwide. [2] It is well confirmed that smoking increases risk of respiratory disease, CVD, diabetes mellitus, autoimmune disorders, reproductive system disorders, and many kinds of cancers.[2] Tobacco addiction is caused by the nicotine, which causes a release of dopamine stimulating a pleasurable effect from smoking.[10] There is strong and consistent evidence that tobacco dependence interventions, if delivered in a timely and effective way, can significantly reduce the user's risk of tobacco-related disease. [1] High quality evidence has demonstrated that the most effective method for smoking cessation is the combination of pharmacologic treatment and behavioral support.[11] Tobacco dependence is a chronic disease that often requires repeated interventions and multiple attempts to quit. Current guidelines recommend that clinicians strongly recommend the use of effective tobacco dependence counseling in combination with medication treatments to patients who use tobacco, and that health systems, insurers, and purchasers assist clinicians in making such effective treatments available.[12]

First-line medications for tobacco dependence include NRT, bupropion SR, and varenicline. [12] Bupropion blocks reuptake of dopamine, resulting in increased dopamine in the mesolimbic "reward center" that mimics nicotine. Varenicline is a partial nicotinic agonist that acts on $\alpha_4\beta_2$ nicotinic receptors.[3] Activation of this receptor reduces withdrawal symptoms and also affects the "reward center". All of these agents have shown to be effective in combination with behavioral interventions for achieving abstinence in patients willing and ready to quit, with similar effect sizes for a minimum of 12 weeks. [12] Patient preference,

experience with certain agents, and side effects should be considered when choosing a specific pharmacologic regimen. The use of certain combinations of medications have also demonstrated efficacy in certain patients. Nicotine replacement therapy consists of short-acting agents (gum, lozenge and inhaler) that are titrated to control urges to smoke and other withdrawal symptoms and a long-acting agent, the nicotine patch.

The rate of smoking in people with psychiatric illness remains a difficult population to successfully treat. The rate of smoking in people with schizophrenia is estimated to be 2-4 times of that in the general population.[13] Most studies have excluded this population and so there are limited data on the effectiveness of smoking cessation therapies in those with psychiatric disorders. Smoking during pregnancy can be harmful to women and infants, but the safety and efficacy of smoking cessation medications in pregnancy is unknown. Behavioral support interventions as well as financial incentives appear to be effective in this population.[4] NRT appears to be cautiously accepted for use in pregnancy but there are no data to support the safety of bupropion or varenicline in this population.

Current prior authorization (PA) policy requires a PA for non-preferred products; use of NRT beyond 6 months in the absence of behavioral counseling; and varenicline use beyond 12 weeks. In 2015, approximately half of the PA requests were denied. The U.S. Public Health Service tobacco guideline recommends that health insurers include smoking cessation treatment as a covered service. One retrospective cohort analysis of pharmacy claims data found that about half of the patients did not fill any smoking cessation medication following a rejected varenicline claim.[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 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
A moderate quality systematic review and meta-analysis of RCTs was conducted to evaluate the efficacy and safety of varenicline combined with NRT to achieve abstinence.[2] There were 3 studies (n=904) that compared combination therapy with varenicline plus the nicotine patch versus varenicline alone that were included in the systematic review and meta-analysis. All 3 trials excluded subjects who were breastfeeding or pregnant, and who had current psychiatric illness. One study administered the trial patch 2 weeks before the targeted quit date, while the other 2 studies started the patch on the targeted quite date. None of the 3 studies took place in the U.S., and one study used a 15 mg/16 hours patch while the others used the more common dose of 21 mg/24 hours. Varenicline was titrated up to 2 mg daily and continued for 12 weeks and all studies provided concurrent behavioral counseling. Abstinence was confirmed using measured exhaled carbon monoxide. The overall quality of the included studies was deemed high. Overall, there was a favorable effect on early abstinence rates (4-12 weeks) with combination therapy versus varenicline alone (44.4% vs. 35.1%; OR 1.50; 95% CI 1.14 to 1.97). Two studies measured late abstinence (up to 24 weeks) and also showed a significant increase in the abstinence rate (32.4% vs. 23.1%; OR 1.62; 95% CI 1.18 to 2.23). In terms of safety, the combination therapy

reported more nausea, insomnia, and abnormal dreams compared to varenicline; however, none of these differences reached statistical significance. The small number of trials in a non-US population limits the generalizability of the results. However, the methodology of the systematic review was strong.

Although the benefits of smoking cessation are widely known and supported by the literature, there has been a renewed concern that smoking cessation medications are associated with an increased risk of CVD. A meta-analysis was conducted to examine whether NRT, bupropion, and varenicline are associated with an increased risk in CVD.[9] There was no increased risk in CVD seen with bupropion (RR 0.98; 95% CI 0.54-1.74; 28 RCTs) or varenicline (RR 1.30; 95% CI 0.79 to 2.23; 18 RCTs), although there was an elevated risk associated with NRT (RR 2.29; 95% CI 1.39 to 3.82; 21 RCTs). These data were driven predominantly by less serious events (RR 1.89; 95% CI 1.31 to 2.73) with the most commonly reported adverse event being heart palpitations and tachycardia. There was no evidence of an increase in major adverse cardiovascular events (MACE) with NRT (RR 1.95; 95% CI 0.26 to 4.30), and bupropion appeared to protect against the risk of MACE relative to both NRT (RR 0.23; 95% CI 0.08 to 0.63) and varenicline (RR 0.33; 95% CI 0.16 to 0.87). There was also no significant increase risk in MACE with NRT in trials that only included high-risk CV patients (RR 1.53; 95% CI 0.38 to 6.24). However, overall rates of MACE were low, resulting in wide confidence intervals.

A Cochrane systematic review compared pharmacological interventions (including NRT, varenicline and bupropion) for smoking cessation during pregnancy.[4] A total of 9 trials (n=2210) of pregnant smokers were included. Eight trials included NRT (6 with the patch, one with gum, and one offered a choice) and one trialed bupropion as an adjunct to behavioral support. The bupropion trial had recruitment issues and was only able to recruit 11 subjects and was too small to make any conclusions regarding bupropion use. No trials evaluated the use of varenicline in pregnant subjects. The overall risk of bias was low. Compared to placebo and control groups, there was a decrease in smoking rates later in pregnancy with NRT (RR 1.41; 95% CI 1.03 to 1.93). However, a subgroup of only placebo-controlled trials did not demonstrate a benefit on smoking rates (RR 1.28; 95% CI 0.99 to 1.66) though heterogeneity between studies was substantially reduced. A subgroup with non-placebo controlled trials, however, demonstrated efficacy with NRT (RR 8.51; 95% CI 2.05 to 35.28) but with a wide confidence interval. Studies that reported adherence found that this was generally low and the majority of subjects did not use the NRT that was prescribed to them. A sensitivity analysis relating to adherence could not be done as trials reported adherence so differently. In addition, there was no evidence that NRT was effective in continued abstinence from smoking after childbirth (RR 1.15; 95% CI 0.75 to 1.77). There were no differences between NRT and control groups in rates of miscarriage, stillbirth, premature birth, birthweight, low birthweight, admissions to neonatal intensive care, congenital abnormalities or neonatal death. The authors concluded that NRT used in pregnancy increase smoking cessation rates measured in late pregnancy by approximately 40% but there is evidence suggesting that when potentially biased, non-placebo RTCs are excluded, NRT is no more effective than placebo.

Another Cochrane systematic review from March 2016 evaluated the efficacy of combined pharmacotherapy and behavioral interventions compared to a minimal intervention or usual care for smoking cessation.[1] The primary outcome was abstinence from smoking after at least 6 months of follow up. Fifty-two studies (n=19,488) provided high quality evidence of a benefit of combined pharmacotherapy (most provided NRT) and behavioral treatment compared to usual care, brief advice, or less intensive support (RR 1.83; 95% CI 1.68 to 1.98) with moderate heterogeneity. Many of the trials were conducted in a healthcare setting (RR 1.97; 95% CI 1.79 to 2.18) and most counselling and support was provided by specialist cessation counsellors or trained personnel. How the intervention was delivered varied among the trials (telephone versus face to face, uptake of treatment optional versus required, etc.). There were no differences found in subgroups based on motivation to quit, treatment provider, number or duration of sessions, or take-up of treatment. The Lung Health Study was excluded from the meta-analysis due to the particularly intensive behavioral intervention provided to subjects. However, this type of intervention resulted in an even larger treatment effect for smoking cessation (RR 3.88; 95% CI 3.35 to 4.5). The authors concluded that interventions that combine pharmacotherapy and behavioral support increase smoking cessation success compared to a minimal intervention or usual care.

New Guidelines:
The U.S. Preventive Services Task Force (USPSTF) updated guidelines on interventions for tobacco smoking cessation in adults, including pregnant women. [15] The following main recommendations are provided:

- For all adults, behavioral interventions and FDA-approved pharmacotherapy should be offered for smoking cessation treatment (Grade A recommendation).
- For pregnant women, behavioral interventions should be provided for all pregnant women who continue to use tobacco (Grade A recommendation).
- The current evidence is insufficient to assess the benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women (Grade I statement).
- The current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. (Grade I statement)

New Safety Alerts:
The FDA made changes to the labeling of varenicline warning that it may react with alcohol and result in decreased tolerance, increased drunkenness or unusual aggressive behavior. The warning is based on 48 case reports. Rare reports of seizures were also reported, most of which occurred during the first month after starting varenicline. None of the cases involved excessive amounts of alcohol.[16] Patients should understand the risks of varenicline with alcohol before starting treatment.

Previous warning and precaution labeling for varenicline on the risk of neuropsychiatric side effects was also updated based on Pfizer data and observational studies that found adverse neuropsychiatric effects were not increased with use of varenicline.[16] However, the studies have inherent limitations preventing strong and reliable conclusions to be made. Since this FDA update, a recent RCT (n=8144) corroborated these findings and found no significant increase in neuropsychiatric adverse events from varenicline or buproprion compared to the nicotine patch or placebo.[17]

New Formulations or Indications:
None identified.

Randomized Controlled Trials:
A total of 188 citations were manually reviewed from the literature search. After further review, 176 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). The remaining 12 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
Hajek, et al.[3] DB, RCT, PC	1. Standard Dose Varenicline (2 mg/day) + placebo add on versus 2. varenicline add-on (up to 5 mg/day) started 21 days before their TQD	Varenicline nonresponders (no strong nausea, no clear reduction in smoking enjoyment, less than 50% reduction in their baseline smoking) (n=200)	Self-rated Smoking enjoyment	<u>12-week continued abstinence</u> 1. 23 (23%) 2. 26 (26%) OR 1.19; 95% CI 0.62-2.28); p=0.61 <u>Nausea</u> 1. 18 (18%) 2. 80 (80%) RR 4.4 (2.99-6.7); P<0.001 <u>Vomiting</u> 1. 3 (3%) 2. 36 (36%) RR 12 (95% CI 3.8-48.3); p<0.001
Schnoll, et al.[18] RCT,open-label	Standard (8 week) nicotine patch vs. extended (24 week) vs. maintenance (52 weeks) + behavioral counseling	Adults who smoke at least 10 cigarettes per day and interested in cessation (n=525)	7-day point prevalence abstinence, confirmed with CO levels	<u>24 week abstinence:</u> Standard: 21.7% Extended/Maintenance: 27.2% P=0.17 <u>Multivariate model controlled for covariates; abstinence rates</u> Extended/Maintenance versus standard: OR 1.70; 95% CI 1.02-2.81 <u>52 week abstinence:</u> Standard/extended: 23.8% Maintenance: 20.3% P=0.44; OR 1.17; 95% CI 0.69-1.90
Baker, et al.[19] RCT, OL	Nicotine patch (NRT) vs. varenicline vs. C-NRT (nicotine patch + nicotine lozenge)	Adult smokers (≥ 5 CPD), desire to quit smoking but not engaged in treatment x 12 weeks (n=1086)	7-day point prevalence abstinence at 26 weeks, confirmed with CO levels	<u>26 week abstinence:</u> NRT 22.8% C-NRT: 26.8% RD -4.0%; (95% CI -10.8%-2.8%) NRT 22.8% Var: 23.6% RD -0.76%(95% CI -7.4%-5.9%)

Ebbert, et al.[7] RCT, DB, PC	Varenicline 1 mg BID x 24 weeks vs. placebo	Adult smokers who were not able to quit smoking now but willing to reduce (reduction in 50% by 4 weeks) and make a quit attempt within next 12 weeks (n=1510)	CO confirmed abstinence during weeks 15 through 24	<u>Continuous abstinence rates during weeks 15 through 24:</u> Var: 32.1% Pla: 6.9% RR 4.6; 95% CI 3.5-6.1 <u>Continuous abstinence rates during weeks 24 through 52:</u> Var: 27% Pla: 9.9% RR 2.7; 95% CI 2.1-3.5
Ramon, et al.[20] DB, PC, RCT	Varenicline + nicotine patch 21 mg versus varenicline + placebo patch x 12 weeks With background behavioral counseling	Smokers (≥20 cpd) (n=341)	Continuous abstinence for weeks 2 through 12	<u>Continuous abstinence:</u> Var + NRT: 32.8% VAR: 28.2% OR 1.17; 95% CI 0.4 to 1.9
SNAP[5] DB, PC, RCT	Nicotine patch vs. placebo over 2 years	Pregnant smokers (≥5 cpd currently/ ≥10 cpd prior to pregnancy) (n=1050)	Self-reported prolonged abstinence between TQD and childbirth	<u>Prolonged smoking cessation</u> NRT: 9.4% Pla: 7.6% OR 1.26; 95% CI 0.82 to 1.96 There was a significant improvement at 1 month with NRT that was not sustained until delivery <u>Infant outcomes at 2 years (no impairment):</u> NRT: 72.5% Pla: 65.5% OR 1.40; 95% CI 1.05 to 1.86
Gonzales, et al.[8] RCT, DB, PC	Varenicline vs placebo for 12 weeks	Adult smokers (≥10 cpd) with ≥ 1 prior quit attempt using varenicline and no quit attempts in ≤ 3 months (n=498)	Continued abstinence rates	<u>Continued abstinence rates (weeks 9-12):</u> Var: 45% Pla: 11.8% OR 7.08; 95% CI 4.34 to 11.55 <u>Prolonged abstinence (weeks 9-52):</u> Var: 20.1% Pla: 3.3% OR 9.00; 95% CI 3.97 to 20.41

Chengappa, et al.[21] RCT, DB, PC	Varenicline vs. placebo x 12 weeks	Adults with bipolar disorder; smoking more than 10 CPD and a willingness to quit (n=60)	Abstinence at 12 weeks	<u>Abstinence at 12 weeks</u> Var: 15/31 (48.4%) Pla: 3/29 (10.3%) OR 8.13; 95% CI 2.03-32.53
Koegelenberg, et al.[22] DB, RCT, PC	Nicotine patch + varenicline vs. placebo patch + varenicline x 12 weeks	Adult smokers (n=446)	Continued abstinence weeks 9 to 12	<u>Continued abstinence weeks 9 to 12:</u> NRT + Var: 55.4% Pla + Var: 40.9% OR 1.85; 95% CI 1.19-2.89
Scherprof[23] DB, RCT	Nicotine patch versus placebo x 6-9 weeks	Adolescents aged 12-18 years who smoke at least 7 cpd (n=362)	Abstinence rates at 6 and 12 months	<u>Abstinence rates at 6 months</u> NRT: 8.1% Pla: 5.7% (p=NS) <u>Abstinence rates at 12 months</u> NRT: 8.1% Pla: 8.2% (p=NS)
Ebbert, et al.[24] RCT, DB, PC	Varenicline + bupropion SR vs. varenicline + placebo x 12 weeks	Adults smoking at least 10 cpd for at least 6 months and were motivated to quit (n=506)	Abstinence rates at week 12	<u>Abstinence rates at week 12</u> Var + bup: 53% Var + pla: 43.2% OR 1.49; 95% CI 1.05-2.12 <u>Abstinence rates at week 52</u> Var + bup: 30.9% Var + pla: 24.5% OR 1.39; 95% CI 0.93-2.07
Evins, et al.[6] RCT, DB, PC, PG	Continued varenicline vs. placebo from weeks 12 to 52	Smokers with schizophrenia or bipolar disease who had 2 weeks or more of continuous abstinence at week 12 after 12 weeks' open-label varenicline and behavioral therapy	7 day rate of continuous abstinence at study week 52	<u>Abstinence rates at week 52:</u> Var: (60%) Pla: (19%) OR 6.2; 95% CI 2.2-19.2
EAGLES trial RCT, DB, PC	Varenicline and bupropion vs. nicotine patch or placebo for 12 weeks with 12-week non-treatment follow-up	Motivated to quit smokers with and without psychiatric disorders (n=8144)	Incidence of a composite measure of moderate to severe neuropsychiatric adverse events	<u>Non-psychiatric cohort:</u> Var: 13 (1.3%) Bup: 22 (2.2%) NRT: 25 (2.5%) Pla: 24 (2.4%) NS for all group comparisons <u>Psychiatric cohort:</u> Var: 67 (6.5%) Bup: 68 (6.7%) NRT: 53 (5.2%) Pla: 50 (4.9%) NS for all group comparisons

Abbreviations: CO = carbon monoxide; CPD = cigarettes per day; DB = double blind; NRT = nicotine replacement therapy; C-NRT = combination nicotine replacement therapy; OL = open label; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; TQD = target quit date; RD = risk difference; Var = varenicline

References:

1. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016;3:CD008286. doi:10.1002/14651858.CD008286.pub3.

2. Chang P-H, Chiang C-H, Ho W-C, Wu P-Z, Tsai J-S, Guo F-R. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. [Review]. *BMC Public Health*. 2015. doi:10.1186/s12889-015-2055-0.

3. Hajek P, McRobbie H, Myers Smith K, Phillips A, Cornwall D, Dhanji A-R. Increasing varenicline dose in smokers who do not respond to the standard dosage: a randomized clinical trial. *JAMA Internal Medicine*. 2015;175(2):266-271. doi:10.1001/jamainternmed.2014.6916.

4. Coleman T, Chamberlain C, Davey M-A, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2015;12:CD010078. doi:10.1002/14651858.CD010078.pub2.

5. Cooper S, Lewis S, Thornton JG, et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technology Assessment (Winchester, England)*. 2014;18(54):1-128. doi:10.3310/hta18540.

6. Evins AE, Cather C, Pratt SA, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. *JAMA*. 2014;311(2):145-154. doi:10.1001/jama.2013.285113.

7. Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA*. 2015;313(7):687-694. doi:10.1001/jama.2015.280.

8. Gonzales D, Hajek P, Pliamm L, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clinical Pharmacology & Therapeutics*. 2014;96(3):390-396. doi:10.1038/clpt.2014.124.

9. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation*. 2014;129(1):28-41. doi:10.1161/CIRCULATIONAHA.113.003961.

10. Benowitz NL. Pharmacology of Nicotine: Addiction, Smoking-Induced Disease, and Therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57-71. doi:10.1146/annurev.pharmtox.48.113006.094742.

11. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. [Review]. *Addiction*. 2014;109(9):1414-1425. doi:10.1111/add.12633.

12. 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. *Respir Care*. 2008;53(9):1217-1222.

13. Kishi T, Iwata N. Varenicline for smoking cessation in people with schizophrenia: systematic review and meta-analysis. [Review]. *European Archives of Psychiatry & Clinical Neuroscience*. 2015;265(3):259-268. doi:10.1007/s00406-014-0551-3.

14. Zeng F, Chen C-I, Mastey V, Zou KH, Harnett J, Patel BV. Utilization management for smoking cessation pharmacotherapy: varenicline rejected claims analysis. *Am J Manag Care*. 2010;16(9):667-674.

15. Siu AL, Force USPST. Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement.[Summary for patients in Ann Intern Med. 2015 Oct 20;163(8):I-40; PMID: 26389837]. *Annals of Internal Medicine*. 2015;163(8):622-634. doi:10.7326/M15-2023.

16. US Food and Drug Administration: FDA Drug Safety Communication: FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. March 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm. Accessed 1/7/2016.

17. Anthenellie R, Benowitz N, West R, Aubin L, McRae T. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;Online. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2816%2930272-0/abstract.

18. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Internal Medicine*. 2015;175(4):504-511. doi:10.1001/jamainternmed.2014.8313.

19. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA*. 2016;315(4):371-379. doi:10.1001/jama.2015.19284.

20. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Medicine*. 2014. doi:10.1186/s12916-014-0172-8.

21. Chengappa KNR, Perkins KA, Brar JS, et al. Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 2014;75(7):765-772. doi:10.4088/JCP.13m08756.

22. Koegelenberg CFN, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014;312(2):155-161. doi:10.1001/jama.2014.7195.

23. Scherphof CS, van den Eijnden RJJM, Engels RCME, Vollebergh WAM. Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. *Drug & Alcohol Dependence*. July 2014:217-220. doi:10.1016/j.drugalcdep.2014.04.007.

24. Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA*. 2014;311(2):155-163. doi:10.1001/jama.2013.283185.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET ER	BUPROPION HCL SR	BUPROPION HCL	Y
ORAL	TABLET ER	ZYBAN	BUPROPION HCL	Y
BUCCAL	GUM	NICORELIEF	NICOTINE POLACRILEX	Y
BUCCAL	GUM	NICORETTE	NICOTINE POLACRILEX	Y
BUCCAL	GUM	NICOTINE GUM	NICOTINE POLACRILEX	Y
BUCCAL	LOZENGE	NICORETTE	NICOTINE POLACRILEX	Y
BUCCAL	LOZENGE	NICOTINE LOZENGE	NICOTINE POLACRILEX	Y
TRANSDERM	PATCH DYSQ	NICOTINE PATCH	NICOTINE	Y
TRANSDERM	PATCH TD24	NICODERM CQ	NICOTINE	Y
TRANSDERM	PATCH TD24	NICOTINE PATCH	NICOTINE	Y
ORAL	TAB DS PK	CHANTIX	VARENICLINE TARTRATE	Y
ORAL	TABLET	CHANTIX	VARENICLINE TARTRATE	Y
INHALATION	CARTRIDGE	NICOTROL	NICOTINE	N
NASAL	SPRAY	NICOTROL NS	NICOTINE	N

1. Hajek P, McRobbie H, Myers Smith K, Phillips A, Cornwall D, Dhanji AR. Increasing varenicline dose in smokers who do not respond to the standard dosage: a randomized clinical trial. *JAMA Intern Med.* 2015 Feb;175(2):266-71.

IMPORTANCE: Standard varenicline tartrate dosing was formulated to avoid adverse effects (primarily nausea), but some patients may be underdosed. To our knowledge, no evidence-based guidance exists for physicians considering increasing varenicline dose if there is no response to the standard dosage.

OBJECTIVE: To determine whether increasing varenicline dose in patients showing no response to the standard dosage improves treatment efficacy.

DESIGN, SETTING, AND PARTICIPANTS: In a double-blind randomized placebo-controlled trial, 503 smokers attending a stop smoking clinic commenced varenicline use 3 weeks before their target quit date (TQD). Two hundred participants reporting no strong nausea, no clear reduction in smoking enjoyment, and less than 50% reduction in their baseline smoking on day 12 received additional tablets of varenicline or placebo.

INTERVENTIONS: All participants began standard varenicline tartrate dosing, gradually increasing to 2 mg/d. Dose increases of twice-daily varenicline (0.5 mg) or placebo took place on days 12, 15, and 18 (up to a maximum of 5 mg/d).

MAIN OUTCOMES AND MEASURES: Participants rated their smoking enjoyment during the prequit period and withdrawal symptoms weekly for the first 4 weeks after the TQD. Continuous validated abstinence rates were assessed at 1, 4, and 12 weeks after the TQD.

RESULTS: The dose increase reduced smoking enjoyment during the prequit period, with mean (SD) ratings of 1.7 (0.8) for varenicline vs 2.1 (0.7) for placebo (P = .001). It had no effect on the mean (SD) frequency of urges to smoke at 1 week after the TQD, their strength, or the severity of withdrawal symptoms: these ratings for varenicline vs placebo were 2.7 (1.1) vs 2.6 (0.9) (P = .90), 2.6 (1.1) vs 2.8 (1.0) (P = .36), and 1.5 (0.4) vs 1.6 (0.5) (P = .30), respectively. The dose increase also had no effect on smoking cessation rates for varenicline vs placebo at 1 week (37 [37.0%] vs 48 [48.0%], P = .14), 4 weeks (51 [51.0%] vs 59 [59.0%], P = .32), and 12 weeks (26 [26.0%] vs 23 [23.0%], P = .61) after the TQD. There was significantly more nausea (P < .001) and vomiting (P < .001) reported in the varenicline arm than in the placebo arm.

CONCLUSIONS AND RELEVANCE: Increasing varenicline dose in smokers with low response to the drug had no significant effect on tobacco withdrawal symptoms or smoking cessation. Physicians often consider increasing the medication dose if there is no response to the standard dosage. This approach may not work with varenicline.

2. Schnoll RA, Goelz PM, Veluz-Wilkins A, Blazekovic S, Powers L, Leone FT, Gariti P, Wileyto EP, Hitsman B. Long-term nicotine replacement therapy: a randomized clinical trial. JAMA Intern Med. 2015 Apr;175(4):504-11. doi: 10.1001/jamainternmed.2014.8313.

IMPORTANCE: The US Food and Drug Administration adopted labeling for nicotine patches to allow use beyond the standard 8 weeks. This decision was based in part on data showing increased efficacy for 24 weeks of treatment. Few studies have examined whether the use of nicotine patches beyond 24 weeks provides additional therapeutic benefit.

OBJECTIVE: To compare 8 (standard), 24 (extended), and 52 (maintenance) weeks of nicotine patch treatment for promoting tobacco abstinence.

DESIGN, SETTING, AND PARTICIPANTS: We recruited 525 treatment-seeking smokers for a randomized clinical trial conducted from June 22, 2009, through April 15, 2014, through 2 universities.

INTERVENTIONS: Smokers received 12 smoking cessation behavioral counseling sessions and were randomized to 8, 24, or 52 weeks of nicotine patch treatment.

MAIN OUTCOMES AND MEASURES: The primary outcome was 7-day point prevalence abstinence, confirmed with breath levels of carbon monoxide at 6 and 12 months (intention to treat).

RESULTS: At 24 weeks, 21.7% of participants in the standard treatment arm were abstinent, compared with 27.2% of participants in the extended and maintenance treatment arms ($\chi(2)(1) = 1.98$; P = .17). In a multivariate model controlled for covariates, participants in the extended and maintenance treatment arms reported significantly greater abstinence rates at 24 weeks compared with participants in the standard treatment arm (odds ratio [OR], 1.70 [95% CI, 1.03-2.81]; P = .04), had a longer duration of abstinence until relapse ($\beta = 21.30$ [95% CI, 10.30-32.25]; P < .001), reported smoking fewer cigarettes per day if not abstinent (mean [SD], 5.8 [5.3] vs 6.4 [5.1] cigarettes per day; $\beta = 0.43$ [95% CI, 0.06-0.82]; P = .02), and reported more abstinent days (mean [SD], 80.5 [38.1] vs 68.2 [43.7] days; OR, 1.55 [95% CI, 1.06-2.26]; P = .02). At 52 weeks, participants in the maintenance treatment arm did not report significantly greater abstinence rates compared with participants in the standard and extended treatment arms (20.3% vs 23.8%; OR, 1.17 [95% CI, 0.69-1.98]; P = .57). Similarly, we found no difference in week 52 abstinence rates between participants in the extended and standard treatment arms (26.0% vs 21.7%; OR, 1.33 [95% CI, 0.72-2.45]; P = .36). Treatment duration was not associated with any adverse effects or adherence to the counseling regimen, but participants in the maintenance treatment arm reported lower adherence to the nicotine patch regimen compared with those in the standard and extended treatment arms (mean [SD], 3.94 [2.5], 4.61 [2.0], and 4.7 [2.4] patches/wk, respectively; $F_{2,522} = 6.03$; P = .003).

CONCLUSIONS AND RELEVANCE: The findings support the safety of long-term use of nicotine patch treatment, although they do not support efficacy beyond 24 weeks of treatment in a broad group of smokers.

3. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA*. 2016 Jan 26;315(4):371-9.

IMPORTANCE: Smoking cessation medications are routinely used in health care; it is vital to identify medications that most effectively treat this leading cause of preventable mortality.

OBJECTIVE: To compare the efficacies of varenicline, combination nicotine replacement therapy (C-NRT), and the nicotine patch for 26-week quit rates.

DESIGN, SETTING, AND PARTICIPANTS: Three-group randomized intention-to-treat clinical trial occurring from May 2012 to November 2015 among smokers recruited in the Madison, Wisconsin, and Milwaukee, Wisconsin, communities; 65.5% of smokers offered the study (2687/4102) refused participation prior to randomization.

INTERVENTIONS: Participants were randomized to one of three 12-week open-label smoking cessation pharmacotherapy groups: (1) nicotine patch only (n = 241); (2) varenicline only (including 1 prequit week; n = 424); and (3) C-NRT (nicotine patch + nicotine lozenge; n = 421). Six counseling sessions were offered.

MAIN OUTCOMES AND MEASURES: The primary outcome was carbon monoxide-confirmed self-reported 7-day point-prevalence abstinence at 26 weeks. Secondary outcomes were carbon monoxide-confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52.

RESULTS: Among 1086 smokers randomized (52% women; 67% white; mean age, 48 years; mean of 17 cigarettes smoked per day), 917 (84%) provided 12-month follow-up data. Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including point-prevalence abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, the risk differences for abstinence were, for patch vs varenicline, -0.76% (95% CI, -7.4% to 5.9%); for patch vs C-NRT, -4.0% (95% CI, -10.8% to 2.8%); and for varenicline vs C-NRT, -3.3% (95% CI, -9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion.

CONCLUSIONS AND RELEVANCE: Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 weeks. The results raise questions about the relative effectiveness of intense smoking pharmacotherapies.

4. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu CR, Dutro MP, Park PW. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA. 2015 Feb 17;313(7):687-94.

IMPORTANCE: Some cigarette smokers may not be ready to quit immediately but may be willing to reduce cigarette consumption with the goal of quitting.

OBJECTIVE: To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, placebo-controlled, multinational clinical trial with a 24-week treatment period and 28-week follow-up conducted between July 2011 and July 2013 at 61 centers in 10 countries. The 1510 participants were cigarette smokers who were not willing or able to quit smoking within the next month but willing to reduce smoking and make a quit attempt within the next 3 months. Participants were recruited through advertising.

INTERVENTIONS: Twenty-four weeks of varenicline titrated to 1 mg twice daily or placebo with a reduction target of 50% or more in number of cigarettes smoked by 4 weeks, 75% or more by 8 weeks, and a quit attempt by 12 weeks.

MAIN OUTCOMES AND MEASURES: Primary efficacy end point was carbon monoxide-confirmed self-reported abstinence during weeks 15 through 24. Secondary outcomes were carbon monoxide-confirmed self-reported abstinence for weeks 21 through 24 and weeks 21 through 52.

RESULTS: The varenicline group (n = 760) had significantly higher continuous abstinence rates during weeks 15 through 24 vs the placebo group (n = 750) (32.1% for the varenicline group vs 6.9% for the placebo group; risk difference (RD), 25.2% [95% CI, 21.4%-29.0%]; relative risk (RR), 4.6 [95% CI, 3.5-6.1]). The varenicline group had significantly higher continuous abstinence rates vs the placebo group during weeks 21 through 24 (37.8% for the varenicline group vs 12.5% for the placebo group; RD, 25.2% [95% CI, 21.1%-29.4%]; RR, 3.0 [95% CI, 2.4-3.7]) and weeks 21 through 52 (27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]). Serious adverse events occurred in 3.7% of the varenicline group and 2.2% of the placebo group (P = .07).

CONCLUSIONS AND RELEVANCE: Among cigarette smokers not willing or able to quit within the next month but willing to reduce cigarette consumption and make a quit attempt at 3 months, use of varenicline for 24 weeks compared with placebo significantly increased smoking cessation rates at the end of treatment, and also at 1 year. Varenicline offers a treatment option for smokers whose needs are not addressed by clinical guidelines recommending abrupt smoking cessation.

5. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Med.* 2014 Oct 8;12:172.

BACKGROUND: Some smokers may benefit from a therapy that combines different nicotine replacement therapies (NRT) or drugs with different mechanisms of action. The aim of this study was to determine the efficacy of the combined therapy of varenicline and nicotine patches versus varenicline monotherapy.

METHODS: Three hundred forty-one smokers who smoked 20 or more cigarettes per day were recruited from a smoking cessation clinic between February 2012 and June 2013. The participants were randomized to receive a varenicline plus nicotine patch of 21 mg every 24 hours (170) or varenicline plus a placebo patch (171). All of the smokers received a standard 12-week course of varenicline and an 11-week course of either the placebo patch or the active patch after the target quit day. Both groups received behavioral support. The primary outcome was continuous abstinence for weeks 2 through 12 confirmed by exhaled levels of carbon monoxide. Post hoc subgroup analyses were performed to evaluate the treatment effects for a specific endpoint in subgroups of smokers.

RESULTS: The combination of the nicotine patch with varenicline was not associated with higher rates of continuous abstinence at 12 weeks (39.1% versus 31.8%; odds ratio (OR) 1.24; 95% confidence interval (CI) 0.8 to 2.6) and 24 weeks (32.8% versus 28.2%; OR 1.17; 95% CI 0.4 to 1.9). When participants were analyzed by subgroups according to cigarette consumption, the abstinence rates among smokers who smoked more than 29 cigarettes per day at 12 weeks (OR 1.39; 95% CI 1.2 to 2.5) and 24 weeks (OR 1.46; 95% CI 1.2 to 2.8) were significantly higher in the combination group. Other post hoc analyses based on level of dependence and previous quit attempts did not show subgroup differences. No differences between the groups for the reported adverse events were observed ($\chi 2$ value 0.07; P 0.79).

CONCLUSIONS: The combination of varenicline with the nicotine patch does not improve abstinence rates at 12 and 24 weeks compared with varenicline used as monotherapy when all smokers were analyzed as a whole, independent of consumption level.

6. Cooper S, Lewis S, Thornton JG, Marlow N′ et al. The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy--clinical effectiveness and safety until 2 years after delivery, with economic evaluation. *Health Technol Assess.* 2014 Aug;18(54):1-128.

BACKGROUND: Smoking during pregnancy causes many adverse pregnancy and birth outcomes. Nicotine replacement therapy (NRT) is effective for cessation outside pregnancy but efficacy and safety in pregnancy are unknown. We hypothesised that NRT would increase smoking cessation in pregnancy without adversely affecting infants.

OBJECTIVES: To compare (1) at delivery, the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of NRT patches with placebo patches in pregnancy and (2) in infants at 2 years of age, the effects of maternal NRT patch use with placebo patch use in pregnancy on behaviour, development and disability.

DESIGN: Randomised, placebo-controlled, parallel-group trial and economic evaluation with follow-up at 4 weeks after randomisation, delivery and until infants were 2 years old. Randomisation was stratified by centre and a computer-generated sequence was used to allocate participants using a 1 : 1 ratio. Participants, site pharmacies and all study staff were blind to treatment allocation.

SETTING: Seven antenatal hospitals in the Midlands and north-west England.

PARTICIPANTS: Women between 12 and 24 weeks' gestation who smoked ≥ 10 cigarettes a day before and ≥ 5 during pregnancy, with an exhaled carbon monoxide (CO) reading of ≥ 8 parts per million (p.p.m.).

INTERVENTIONS: NRT patches (15 mg per 16 hours) or matched placebo as an 8-week course issued in two equal batches. A second batch was dispensed at 4 weeks to those abstinent from smoking.

MAIN OUTCOME MEASURES: PARTICIPANTS: self-reported, prolonged abstinence from smoking between a quit date and childbirth, validated at delivery by CO measurement and/or salivary cotinine (COT) (primary outcome). Infants, at 2 years: absence of impairment, defined as no disability or problems with behavior and development. Economic: cost per 'quitter'.

RESULTS: One thousand and fifty women enrolled (521 NRT, 529 placebo). There were 1010 live singleton births and 12 participants had live twins, while there were 14 fetal deaths and no birth data for 14 participants. Numbers of adverse pregnancy and birth outcomes were similar in trial groups, except for a greater number of caesarean deliveries in the NRT group. Smoking: all participants were included in the intention-to-treat (ITT) analyses; those lost to follow-up (7% for primary outcome) were assumed to be smoking. At 1 month after randomisation, the validated cessation rate was higher in the NRT group {21.3% vs. 11.7%, odds ratio [OR], [95% confidence interval (CI)] for cessation with NRT, 2.05 [1.46 to 2.88]}. At delivery, there was no difference between groups' smoking cessation rates: 9.4% in the NRT and 7.6% in the placebo group [OR (95% CI), 1.26 (0.82 to 1.96)]. Infants: at 2 years, analyses were based on data from 888 out of 1010 (87.9%) singleton infants (including four postnatal infant deaths) [445/503 (88.5%) NRT, 443/507 (87.4%) placebo] and used multiple imputation. In the NRT group, 72.6% (323/445) had no impairment compared with 65.5% (290/443) in placebo (OR 1.40, 95% CI 1.05 to 1.86). The incremental cost-effectiveness ratio for NRT use was £4156 per quitter (£4926 including twins), but there was substantial uncertainty around these estimates.

CONCLUSIONS: Nicotine replacement therapy patches had no enduring, significant effect on smoking in pregnancy; however, 2-year-olds born to women who used NRT were more likely to have survived without any developmental impairment. Further studies should investigate the clinical effectiveness and safety of higher doses of NRT.

7. Gonzales D, Hajek P, Pliamm L, Nackaerts K, Tseng LJ, McRae TD, Treadow J. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2014 Sep;96(3):390-6.

The efficacy and safety of retreatment with varenicline in smokers attempting to quit were evaluated in this randomized, double-blind, placebo-controlled, multicenter trial (Australia, Belgium, Canada, the Czech Republic, France, Germany, the United Kingdom, and the United States). Participants were generally healthy adult smokers (≥ 10 cigarettes/day) with ≥ 1 prior quit attempt (≥ 2 weeks) using varenicline and no quit attempts in ≤ 3 months; they were randomly assigned (1:1) to 12 weeks' varenicline (n = 251) or placebo (n = 247) treatment, with individual counseling, plus 40 weeks' nontreatment follow-up. The primary efficacy end point was the carbon monoxide-confirmed (≤ 10 ppm) continuous abstinence rate for weeks 9-12, which was 45.0% (varenicline; n = 249) vs. 11.8% (placebo; n = 245; odds ratio: 7.08; 95% confidence interval: 4.34, 11.55; P < 0.0001). Common varenicline group adverse events were nausea, abnormal dreams, and headache, with no reported suicidal behavior. Varenicline is efficacious and well tolerated in smokers who have previously taken it. Abstinence rates are comparable with rates reported for varenicline-naive smokers.

8. Chengappa KN, Perkins KA, Brar JS, Schlicht PJ, Turkin SR, Hetrick ML, Levine MD, George TP.Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014 Jul;75(7):765-72.

OBJECTIVE: Virtually no clinical trials for smoking cessation have been undertaken in bipolar disorder. Varenicline has shown efficacy for smoking cessation, but warnings about neuropsychiatric adverse events have been issued. We assessed the efficacy and safety of varenicline in euthymic bipolar subjects motivated to quit smoking.

METHOD: Clinically stable adult patients with DSM-IV bipolar disorder (n = 60) who smoked ≥ 10 cigarettes per day were randomized to a 3-month, double-blind, placebo-controlled varenicline trial and a 3-month follow-up. Study enrollment was completed from February 2010 through March 2013. Varenicline was dosed using standard titration, and smoking cessation counseling was provided to all patients. The primary outcome was defined as a 7-day point prevalence of self-reported no smoking verified by expired carbon monoxide level < 10 ppm at 12 weeks. Psychopathology and side-effects were assessed at each visit.

RESULTS: At 3 months (end of treatment), significantly more subjects quit smoking with varenicline (n/n = 15/31, 48.4%) than with placebo (n/n = 3/29, 10.3%) (OR = 8.1; 95% CI, 2.03-32.5; P < .002). At 6 months, 6 of 31 varenicline-treated subjects (19.4%) remained abstinent compared to 2 of 29 (6.90%) assigned to placebo (OR = 3.2; 95% CI, 0.60-17.6; P = .17). Psychopathology scores remained stable. Ten serious adverse events occurred (n = 6, varenicline; n = 4, placebo). Abnormal dreams occurred significantly more often in varenicline-treated subjects (n/n = 18/31, 61.3%) than in those receiving placebo (n/n = 9/29, 31%; Fisher exact test, P = .04). Eight varenicline-treated and 5 placebo-assigned subjects expressed fleeting suicidal ideation, a nonsignificant difference.

CONCLUSIONS: Varenicline shows efficacy for initiating smoking cessation in bipolar patients, but medication trials of longer duration are warranted for maintaining abstinence. Vigilance for neuropsychiatric adverse events is prudent when initiating varenicline for smoking cessation in this patient population.

9. Koegelenberg CF[1], Noor F[1], Bateman ED[2], Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014 Jul;312(2):155-61.

IMPORTANCE: Behavioral approaches and pharmacotherapy are of proven benefit in assisting smokers to quit, but it is unclear whether combining nicotine replacement therapy (NRT) with varenicline to improve abstinence is effective and safe.

OBJECTIVE: To evaluate the efficacy and safety of combining varenicline and a nicotine patch vs varenicline alone in smoking cessation.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, blinded, placebo-controlled clinical trial with a 12-week treatment period and a further 12-week follow-up conducted in 7 centers in South Africa from April 2011 to October 2012. Four hundred forty-six generally healthy smokers were randomized (1:1); 435 were included in the efficacy and safety analyses.

INTERVENTIONS: Nicotine or placebo patch treatment began 2 weeks before a target quit date (TQD) and continued for a further 12 weeks. Varenicline was begun 1 week prior to TQD, continued for a further 12 weeks, and tapered off during week 13.

MAIN OUTCOMES AND MEASURES: Tobacco abstinence was established and confirmed by exhaled carbon monoxide measurements at TQD and at intervals thereafter up to 24 weeks. The primary end point was the 4-week exhaled carbon monoxide-confirmed continuous abstinence rate for weeks 9 through 12 of treatment, ie, the proportion of participants able to maintain complete abstinence from smoking for the last 4 weeks of treatment, as assessed using multiple imputation analysis. Secondary end points included point prevalence abstinence at 6 months, continuous abstinence rate from weeks 9 through 24, and adverse events. Multiple imputation also was used to address loss to follow-up.

RESULTS: The combination treatment was associated with a higher continuous abstinence rate at 12 weeks (55.4% vs 40.9%; odds ratio [OR], 1.85; 95% CI, 1.19-2.89; P = .007) and 24 weeks (49.0% vs 32.6%; OR, 1.98; 95% CI, 1.25-3.14; P = .004) and point prevalence abstinence rate at 6 months (65.1% vs 46.7%; OR, 2.13; 95% CI, 1.32-3.43; P = .002). In the combination treatment group, there was a numerically greater incidence of nausea, sleep disturbance, skin reactions, constipation, and depression, with only skin reactions reaching statistical significance (14.4% vs 7.8%; P = .03); the varenicline-alone group experienced more abnormal dreams and headaches.

CONCLUSIONS AND RELEVANCE: Varenicline in combination with NRT was more effective than varenicline alone at achieving tobacco abstinence at 12 weeks (end of treatment) and at 6 months. Further studies are needed to assess long-term efficacy and safety.

10. Scherphof CS, van den Eijnden RJ, Engels RC, Vollebergh WA. Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: a randomized controlled trial. Drug Alcohol Depend. 2014 Jul 1;140:217-20.

BACKGROUND: A double-blind RCT on the short-term efficacy of nicotine patches compared to placebo patches among Dutch adolescents was conducted. The findings demonstrated that nicotine patches are efficacious for smoking cessation at end-of-treatment; however, only in highly compliant participants. We tested whether the effects of NRT also held in 6- (T7) and 12-month (T8) follow-up assessments.

METHODS: Adolescents aged 12-18 years, who smoked at least seven cigarettes a day and who were motivated to quit smoking were recruited at school yards and randomly assigned to either a nicotine patch (n=182) or a placebo patch (n=180) condition according to a computer generated list. Participants (N=257, age: 16.7 ± 1.13 years) attended an information meeting followed by a 6- or 9-week treatment. Smoking cessation, compliance, and potential covariates were measured by means of online questionnaires. Smoking cessation at T8 was biochemically validated by saliva cotinine.

RESULTS: At T7, 8.1% and 5.7% of participants were abstinent in the nicotine and placebo patch groups, respectively. At T8, abstinence was 4.4% and 6.6%, respectively. Intention-to-treat analyses showed no significant effects of NRT on abstinence rates at T7 (OR=1.54, 95% CI=0.57, 4.16) and validated abstinence rates at T8 (OR=0.64, 95% CI=0.21, 1.93) neither after considering compliance nor after adjusting for covariates.

CONCLUSIONS: NRT fails in helping adolescents quit smoking at 6- and 12-month follow-ups. This finding suggests that a more intensive approach is needed to assist youngsters in their quit attempts.

11. Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, Hurt RD. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA.* 2014 Jan 8;311(2):155-63.

IMPORTANCE: Combining pharmacotherapies for tobacco-dependence treatment may increase smoking abstinence.

OBJECTIVE: To determine efficacy and safety of varenicline and bupropion sustained-release (SR; combination therapy) compared with varenicline (monotherapy) in cigarette smokers.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, blinded, placebo-controlled multicenter clinical trial with a 12-week treatment period and follow-up through week 52 conducted between October 2009 and April 2013 at 3 midwestern clinical research sites. Five hundred six adult (≥18 years) cigarette smokers were randomly assigned and 315 (62%) completed the study.

INTERVENTIONS: Twelve weeks of varenicline and bupropion SR or varenicline and placebo.

MAIN OUTCOMES AND MEASURES: Primary outcome was abstinence rates at week 12, defined as prolonged (no smoking from 2 weeks after the target quit date) abstinence and 7-day point-prevalence (no smoking past 7 days) abstinence. Secondary outcomes were prolonged and point-prevalence smoking abstinence rates at weeks 26 and 52. Outcomes were biochemically confirmed.

RESULTS: At 12 weeks, 53.0% of the combination therapy group achieved prolonged smoking abstinence and 56.2% achieved 7-day point-prevalence smoking abstinence compared with 43.2% and 48.6% in varenicline monotherapy (odds ratio [OR], 1.49; 95% CI, 1.05-2.12; P = .03 and OR, 1.36; 95% CI, 0.95-1.93; P = .09, respectively). At 26 weeks, 36.6% of the combination therapy group achieved prolonged and 38.2% achieved 7-day point-prevalence smoking abstinence compared with 27.6% and 31.9% in varenicline monotherapy (OR, 1.52; 95% CI, 1.04-2.22; P = .03 and OR, 1.32; 95% CI, 0.91-1.91; P = .14, respectively). At 52 weeks, 30.9% of the combination therapy group achieved prolonged and 36.6% achieved 7-day point-prevalence smoking abstinence compared with 24.5% and 29.2% in varenicline monotherapy (OR, 1.39; 95% CI, 0.93-2.07; P = .11 and OR, 1.40; 95% CI, 0.96-2.05; P = .08, respectively). Participants receiving combination therapy reported more anxiety (7.2% vs 3.1%; P = .04) and depressive symptoms (3.6% vs 0.8%; P = .03).

CONCLUSIONS AND RELEVANCE: Among cigarette smokers, combined use of varenicline and bupropion, compared with varenicline alone, increased prolonged abstinence but not 7-day point prevalence at 12 and 26 weeks. Neither outcome was significantly different at 52 weeks. Further research is required to determine the role of combination therapy in smoking cessation.

12. Eden Evins, MD, MPH; Corinne Cather, PhD; Sarah A. Pratt, PhD; et al. Maintenance Treatment With Varenicline for Smoking Cessation in Patients With Schizophrenia and Bipolar Disorder A Randomized Clinical Trial *JAMA.* 2014;311(2):145-154.

IMPORTANCE It is estimated that more than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy.

OBJECTIVE To determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial conducted in 10 community mental-health centers. Of 247 smokers with schizophrenia or bipolar disease recruited from March 2008-April 2012, 203 received 12-weeks' open-label varenicline and cognitive behavioral therapy and 87 met abstinence criteria to enter the relapse prevention intervention.

INTERVENTIONS Participants who had 2 weeks or more of continuous abstinence at week 12 of open treatment were randomly assigned to receive cognitive behavioral therapy and double-blind varenicline (1 mg, 2 per day) or placebo from weeks 12 to 52. Participants then discontinued study treatment and were followed up to week 76.

MAIN OUTCOMES AND MEASURES Seven-day rate of continuous abstinence at study week 52, the end of the relapse-prevention phase, confirmed by exhaled carbon monoxide. Secondary outcomes were continuous abstinence rates for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behavior.

RESULTS Sixty-one participants completed the relapse-prevention phase; 26 discontinued participation (7 varenicline, 19 placebo) and were considered to have relapsed for the analyses; 18 of these had relapsed prior to dropout. At week 52, point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) vs 19% (9 of 47) in the placebo group (odds ratio [OR], 6.2; 95% CI, 2.2-19.2; $P < .001$). From weeks 12 through 64, 45% (18 of 40) among those in the varenicline group vs 15% (7 of 47) in the placebo group were continuously abstinent (OR, 4.6; 95% CI, 1.5-15.7; $P = .004$), and from weeks 12 through 76, 30% (12 of 40) in the varenicline group vs 11% (5 of 47) in the placebo group were continuously abstinent (OR, 3.4; 95% CI, 1.02-13.6; $P = .03$). There were no significant treatment effects on psychiatric symptom ratings or psychiatric adverse events.

CONCLUSIONS AND RELEVANCE Among smokers with serious mental illness who attained initial abstinence with standard treatment, maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2016
1 bupropion.mp or Bupropion/ 3210
2 venlafaxine.mp. or Vanlafaxine Hydrochloride/ 3048
3 Nicotinic Agonists/ or "Tobacco Use Cessation Products"/ or nicotine replacement.mp.
4 smoking cessation.mp or Smoking Cessation/ 24510
5 "Tobacco use Disorder"/ 7902
6 nicotine lozenge.mp. or "Tobacco Use Cessation Products"/ 987
7 nicotine gum.mp. 342
8 nicotine patch.mp. or "Tobacco Use Cessation Products"/ 1509
9 nicoderm.mp. 16
10 1 or 2 or 3 or 6 or 7 or 8 or 9 13732
11 4 or 5 28713
12 10 and 11
13 limit 12 to (English language and humans and yr="2014-Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) 188
14 from 13 keep 10-12, 17, 19, 23-24, 27, 29…….. 20

Appendix 4: Prior Authorization Criteria

Smoking Cessation

Goal(s):

- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products

Length of Authorization:

3-6 months

Requires PA:

- Non-preferred drugs
- Nicotine replacement therapy (NRT) and varenicline beyond 6 months in the absence of behavioral counseling
-

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis for tobacco dependence? (ICD-10 F17200)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for a preferred NRT product?	**Yes:** Go to #5	**No:** Go to #4
4. Is the request for varenicline?	**Yes:** Go to #5	**No:** Go to #7
5. Has patient quit?	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Go to #6

Approval Criteria		
6. Is the patient enrolled in a smoking cessation behavioral counseling program (e.g. Quit Line at: 800-QUIT-NOW (800-784-8669).	**Yes:** Approve NRT for 6 additional months or approve varenicline for 12 additional weeks	**No:** Pass to RPh. Deny; medical appropriateness
7. Will the prescriber change to a preferred product? Message: • Preferred products do not require a PA for initial treatment. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve treatment for up to 6 months

P&T Review: *5/16 (MH); 4/12*
Implementation: *7/23/12*

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

Class Update: Cough & Cold Preparations

Date of Review: May 2016 **Date of Last Review:** May 2013; Codeine DUE July 2015

Current Status of Preferred Drug List (PDL) Class:
See **Appendix 1**.

Purpose for Class Update: Four reviews[1,2,3,4] that help to clarify the available evidence for cough treatments, new United States Food and Drug Administration (FDA) safety warnings on codeine in children,[5,6] and new treatment guidelines[7] were published since the last class update.

Research Questions:
1. What is the comparative evidence for available cough and cold treatments (including over-the-counter [OTC]) to reduce the severity or frequency of cough and cold?
2. What is the comparative evidence for available cough and cold treatments for safety?
3. Are there specific populations (e.g. children) where cough and cold treatments are safer or more effective?

Conclusions:
- The evidence is limited by few direct comparisons of the multiple combination products available, heterogeneous cough etiologies and small study sizes.
- There is insufficient evidence for efficacy of expectorants for cough[1] and expectorants are not recommended for cough secondary to any cause.[8]
- There is low quality evidence that various opioids (primarily codeine) and dextromethorphan reduce cough severity and cough frequency compared to placebo in patients with unexplained or refractory cough symptoms.[1] Comparisons of opioids to dextromethorphan had mixed results.[1] There was insufficient evidence of efficacy for benzonatate or antihistamines.[1]
- There is low quality evidence that various combinations of antihistamines and decongestants have limited effect on "global effectiveness" for the common cold in adults and older children.[9] There is no evidence of benefit in young children.[9]
- There is insufficient comparative safety evidence.
- There is low quality evidence that OTC cough products provide no benefit in children with acute cough.[2]
- There is low quality evidence of increased risk of death in young children associated with the use over-the-counter (OTC) cough and cold products[3,10] and codeine cough remedies.[5]

Recommendations:
- Prefer no expectorants and remove all guaifenesin single ingredient products (HSN = 000271) from the PDL.
- Ensure there is a minimum of 1 product with codeine and 1 with dextromethorphan preferred on the PDL for refractory cough as these have the strongest evidence of efficacy. Make other selections based upon cost in the Executive Session.
- Expand the pediatric restriction (children 13 years of age and older) to all cough and cold products (with or without codeine) (**Appendix 4**).

Previous Conclusions:

- The level of comparative evidence of efficacy and safety is insufficient to identify differences between products.
- The overall evidence of efficacy of over-the-counter cough remedies to suppress cough was poor quality and showed conflicting results.
- The FDA recommended cough and cold preparations not be used to treat infants and children under 2 years old in 2008.
- The FDA issued a black box warning restricting the use of codeine in children under 13 for post-operative pain.[6]
- FDA warns about potential risk of serious side effects of using codeine-containing medicines to treat cough and colds in children under 18 years old.[5]

Previous Recommendations:

- Create a PDL class for Cough & Cold Preparations (May 2013)
- Prefer: guaifenesin liquid 100 mg/5 mL, guaifenesin/dextromethorphan syrup, guaifenesin/codeine phosphate liquid, pseudoephedrine HCL tablets 30 mg and 60 mg, benzonatate capsules (May 2013)
- Mucinex™ made preferred (July 2015).
- Age restriction (<18 years) added to all codeine cough products (July 2015).

Background: Symptomatic treatment of common upper respiratory infections (URI) (Line 617) and rhinitis (Line 564) are not funded diagnoses on the Oregon Health Plan List of Prioritized Services.[11] The Cough & Cold PDL class includes antitussives, expectorants, oral decongestants and combinations of all 3 with or without antihistamines.[12] This class ranked 36 of 110 classes by number of prior authorization (PA) requests during Q1 2016. A total of 29 requests for non-preferred drugs were made (12 approved, 16 denied, 1 cancelled).[13] The most commonly requested product was promethazine-codeine (9 requests) followed by hydrocodone-homatropine (8 requests).[13] All other drugs had 2 or fewer requests.[13] The Codeine Age Limit PA was not yet implemented in Q1-2016.

There is low quality evidence that various combinations of antihistamines and decongestants have limited effect on "global effectiveness" for the common cold in adults and older children.[9] There is no evidence of benefit in young children.[9]

The effectiveness of cough treatments is often evaluated for subjective severity rating and cough frequency. Cough can also be experimentally induced in patients using varying concentrations of inhaled capsaicin to cause 2 – 5 coughs (C2 – C5). This model has been called into question as to its predictive accuracy of disease.[14] It is also recognized there is a significant placebo effect associated with cough treatments for young children. [4,15]

The American College of Chest Physicians published evidence-based clinical practice guidelines for diagnosis and management of cough in 2006.[8] The recommendations scale was as follows: A-strong; B-moderate; C-weak; D-negative.[8] Acute cough (<3 week) is most frequently associated with the URI, acute bronchitis, allergic rhinitis or community-acquired pneumonia.[8] Cough occurs sub-acutely (3-8 weeks) post-infectiously or with pertussis.[8] Chronic cough (> 8 weeks) in adults is likely secondary to angiotensin-converting enzyme use, smoking, gastroesophageal reflux, asthma, chronic obstructive pulmonary disease, environmental irritant exposure, chronic sinusitis or allergic rhinitis.[8,16] The primary cause of the cough should be addressed first in each case.[8,16] Antitussives and expectorants have a very limited role. Antitussives, antihistamines or zinc containing products are *not* recommended for URI associated cough (Recommendation Grade D).[8] Ipratropium is recommended for cough suppression for URI or chronic bronchitis (Recommendation Grade A). Hydrocodone, dihydrocodeine, codeine or dextromethorphan are recommended for short-term symptomatic relief of cough due to chronic bronchitis in adults (Recommendation Grade B).[8] Hypertonic saline is recommended to increase cough clearance for patients with bronchitis or cystic fibrosis.[8] Expectorants are *not* recommended for chronic bronchitis (Recommendation Grade D).[8] Benzonatate is not mentioned in the guidelines.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
There have been 3 high quality systematic reviews[1] or updates[2,4] of cough treatments and 1 "short-cut review"[3] of the safety of OTC cough and cold preparations published since the last scan in May 2013.

Yancey et al.[1] compared treatments (pharmacologic and nonpharmacologic) for unexplained or refractory cough. The review was commissioned by the Agency for Health Research and Quality. It contained a meta-analysis of the English language medical literature through June 2012.[1] The overall strength of evidence was limited by inconsistent and imprecise results, small numbers of direct comparisons and small studies.[1] Forty-nine studies (n=3067) met inclusion criteria. There were 11 comparisons of opioids (primarily codeine) with placebo with 8 showing the opioid more effective for decreasing cough frequency and cough severity. Standardized mean differences for cough severity for opioids were 0.55 (95% CI, 0.38-0.72) and for rate ratios for cough frequency 0.57 (95% CI, 0.36-0.91).[1] No one opioid was superior to another although codeine had a dose-response improvement.[1] Comparisons of codeine to dextromethorphan were mixed. Six studies of dextromethorphan compared to placebo provided mean difference in cough severity of 0.37 (95% CI, 0.19-0.56) and rate ratios for cough frequency of 0.40 (95% CI, 0.18-0.85).[1] Benzonatate effectiveness was mixed in 3 low quality studies; one placebo-controlled study was negative and 2 studies found it more effective than opioids.[1] Two studies evaluated antihistamines (one of diphenhydramine and one of loratadine) but were limited by extremely small samples (<20). There were 6 negative studies comparing various expectorants (oral N-acetylcysteine, inhaled N-acetylcysteine, bromhexime, ambroxol, inhaled 2-mercaptoethan sulfonate, narcotine-glycerol) to placebo. One good quality study (n=60) for guaifenesin showed improvement over placebo in a sub-group of patients who produced a high volume of sputum.[1] Only 3 studies address cough in children and none of these evaluated antitussives or expectorants.[1]

Cochrane published an updated review of OTC cough medications for acute cough in children and adults in 2014.[2] The literature was searched through March 2014. The evidence was limited by few trials for each comparison as well as heterogeneous participants, interventions and outcomes such that pooling could not be done. There were 19 adult trials (n=3799) and 10 pediatric trials (n=1036) included.[2] The adult placebo controlled trials included: 2 comparing codeine with non-significant results, 4 comparing dextromethorphan with mixed results, and 3 comparing guaifenesin with mixed results.[2] In the pediatric studies, antitussives, antihistamines, antihistamine-decongestants and antitussive-bronchodilator combinations were no more effective than placebo.[2] Adverse effects were reported in 21 studies with higher rates for those taking antihistamines or dextromethorphan.[2]

Cochrane published an updated review of honey for acute cough in children 1 to 18 years old.[4] The search was current through November 2014 and identified 3 RCTs (n=568). The authors conclude honey was better than: no treatment in reducing the frequency of cough (mean difference [MD] -1.05; 95% confidence

interval [CI] -1.48 to -0.62; I2 statistic 23%; two studies, 154 participants), placebo at reduction of cough frequency (MD -1.85; 95% CI -3.36 to -0.33; one study, 300 participants) and diphenhydramine in reducing cough frequency (MD -0.57; 95% CI -0.90 to -0.24; one study, 80 participants).[4] Honey was no different than dextromethorphan at reducing cough frequency (MD -0.07; 95% CI -1.07 to 0.94; two studies, 149 participants).[4] Honey should not be given to infants because of their poor immunity against *Clostridium botulinum* that may be present in honey.[4]

A "short-cut review" identified 3 case-series (n=214) reporting deaths associated with OTC cough and cold preparations in children under the age of 12 years old from 1950 to 2007.[3]

New Treatment Guidelines: The American College of Chest Physicians updated treatment guidelines for treatment of unexplained cough in January 2016.[7] The guidelines were based upon a high quality systematic review evaluating the efficacy of treatments on cough severity and frequency for adults and adolescents 12 years or older with chronic cough of more than 8 weeks duration and unexplained after systematic workup. The review included the previously mentioned Yancy et al.[1] The authors concluded the evidence was limited by the heterogeneity of therapeutic interventions with few studies available in each category, inconsistent outcome assessment tools and differing definitions of unexplained cough. The treatment algorithm adds empiric trials of speech therapy and gabapentin as last resort options.

New FDA Safety Alerts: The FDA is investigating the safety of codeine containing products to treat cough and cold in children under 18 years old. This was in reaction to the European Medicines Agency recommendation that codeine use is contraindicated in children under 12 years old and is not recommended in older children between 12 and 18 who have breathing problems.[6]

New FDA Drug Approvals: No new molecular entities approved by the FDA for cough treatment were identified from 2013 to date.

New Formulations: Unable to report because of unclear tracking of over-the-counter formulations on the FDA website.

Randomized Controlled Trials:
A total of 30 citations were reviewed from the literature search (**Appendix 3)**. After further review, 25 citations were excluded because the population, intervention or outcomes were not of interest. The search identified 4 recent reviews[1,2,3,4] and 1 new treatment guideline[7] that were included. No RCTs were included.

References:

1. Yancy WS, McCrory DC, Coeytaux RR, et al. Efficacy and tolerability of treatments for chronic cough. *Chest*. 2013;144(6):1827-1838. doi:10.1378/chest.13-0490.

2. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. In: *The Cochrane Library*. John Wiley & Sons, Ltd; 2014. http://onlinelibrary.wiley.com.liboff.ohsu.edu/doi/10.1002/14651858.CD001831.pub5/abstract. Accessed April 19, 2016.

3. Deschler D, Judge B. BET 3: Paediatric deaths associated with over the counter cough and cold medicines. *Emerg Med J.* 2014;31(2):171-172. doi:10.1136/emermed-2013-203506.3.

4. Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Honey for acute cough in children. In: The Cochrane Collaboration, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2014. http://doi.wiley.com/10.1002/14651858.CD007094.pub4. Accessed April 21, 2016.

5. Safety Alerts for Human Medical Products - Codeine cough-and-cold medicines in children: Drug Safety Communication - FDA Evaluating Potential Risk of Serious Side Effects. http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm453379.htm. Accessed April 19, 2016.

6. Safety Alerts for Human Medical Products - Codeine use in certain children after tonsillectomy and/or adenoidectomy: Drug Safety Communication - Risk of Rare, But Life-Threatening Adverse Events or Death. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm315627.htm. Accessed April 19, 2016.

7. Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS. Treatment of unexplained chronic cough. *Chest*. 2016;149(1):27-44. doi:10.1378/chest.15-1496.

8. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary. *Chest*. 2006;129(1):1S-23S. doi:10.1378/chest.129.1_suppl.1S.

9. De Sutter AI, van Driel ML, French L. Oral antihistamine-decongestant-analgesic combinations for the common cold. In: The Cochrane Collaboration, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. http://doi.wiley.com/10.1002/14651858.CD004976.pub2. Accessed April 21, 2016.

10. United States Food and Drug Administration. 2008 - Public Health Advisory: FDA recommends that over-the-counter (OTC) cough and cold products not be used for infants and children under 2 years of age. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm051137.htm. Accessed April 21, 2016.

11. Oregon Health Plan Prioritized List of Health Services. Oregon Health Authority - Health Evidence Review Commission. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Published January 1, 2016. Accessed April 21, 2016.

12. Oregon Health Plan Drug Class List - Cough and Cold. OHA-Medical Assistance Program: OSU Drug Use Research & Management. http://orpdl.org/drugs/drugclass.php?cid=1110. Accessed April 21, 2016.

13. OSU Drug Use Research & Management. OHA FFS Drug PA Report (Internal Report). Q1 2016.

14. Hilton ECY, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. *J Allergy Clin Immunol*. 2013;132(4):847-855.e5. doi:10.1016/j.jaci.2013.04.042.

15. Paul IM, Beiler JS, Vallati JR, Duda LM, King TS. Placebo effect in the treatment of acute cough in infants and toddlers: a randomized clinical trial. *JAMA Pediatr.* 2014;168(12):1107. doi:10.1001/jamapediatrics.2014.1609.

16. Metersky M (ed), Miner DS (ed). Chronic cough in adults. In: *Dynamed (on-Line Database)*. 2016th ed. USA: EBSCO Information Services; 2015. http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/. Accessed April 14, 2016.

Appendix 1: Preferred Alternatives:

HSN	Generic Drug Name
001929	Benzonatate
000271	Guaifenesin
000206	Guaifenesin/Codeine PHOS
000223	Guaifenesin/D-methorphan HB
002091	Pseudoephedrine HCL

Appendix 2: Abstracts of Included Clinical Trials
No RCTs included in this review

Appendix 3: Medline Search Strategy

Database: Ovid MEDLINE(R) <1946 to April Week 1 2016> Search Strategy:

---

1 exp Cough/ (13323)
2 exp Antitussive Agents/ (21643)
3 exp Expectorants/ (14917)
4 2 or 3 (36207)
5 1 and 4 (1458)
6 limit 5 to (English language and humans and yr="2013 -Current" and (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))

30 text results returned

****

1. Ternesten-Hasseus E, Johansson EL, Millqvist E. Cough reduction using capsaicin. Respir Med. 2015;109(1):27-37. doi:10.1016/j.rmed.2014.11.001
EXCLUDED: INTERVENTION NOT FDA APPROVED

2. Barth A, Hovhannisyan A, Jamalyan K, Narimanyan M. Antitussive effect of a fixed combination of Justicia adhatoda, Echinacea purpurea and Eleutherococcus senticosus extracts in patients with acute upper respiratory tract infection: A comparative, randomized, double-blind, placebo-controlled study. Phytomedicine. 2015;22(13):1195-200. doi:10.1016/j.phymed.2015.10.001
EXCLUDED: INTERVENTION NOT FDA APPROVED

3. O'Donnell K, Mansbach JM, LoVecchio F, et al. Use of Cough and Cold Medications in Severe Bronchiolitis before and after a Health Advisory Warning against Their Use. J Pediatr. 2015;167(1):196-8.e1-2. doi:10.1016/j.jpeds.2015.03.037
EXCLUDED: OUTCOME NOT OF INTEREST

4. Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative Methadone for the Prevention of Postoperative Pain: A Randomized, Double-blinded Clinical Trial in Cardiac Surgical Patients. Anesthesiology. 2015;122(5):1112-22. doi:10.1097/ALN.0000000000000633
EXCLUDED: OUTCOME/POPULATION NOT OF INTEREST

5. Abdulqawi R, Dockry R, Holt K, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2015;385(9974):1198-205. doi:10.1016/S0140-6736(14)61255-1
EXCLUDED: INTERVENTION NOT FDA APPROVED

6. Garaiova I, Muchova J, Nagyova Z, et al. Probiotics and vitamin C for the prevention of respiratory tract infections in children attending preschool: a randomised controlled pilot study. Eur J Clin Nutr. 2015;69(3):373-9. doi:10.1038/ejcn.2014.174
EXCLUDED: OUTCOME NOT OF INTEREST

7. Boulet LP, Coeytaux RR, McCrory DC, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. Chest. 2015;147(3):804-14. doi:10.1378/chest.14-2506
EXCLUDED: OUTCOME NOT OF INTEREST

8. Dicpinigaitis PV, Canning BJ, Garner R, Paterson B. Effect of memantine on cough reflex sensitivity: translational studies in guinea pigs and humans. J Pharmacol Exp Ther. 2015;352(3):448-54. doi:10.1124/jpet.114.221218
EXCLUDED: POPULATION NOT OF INTEREST

9. Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Honey for acute cough in children. Cochrane Database Syst Rev. 2014;12:CD007094. doi:10.1002/14651858.CD007094.pub4
INCLUDED

10. Paul IM, Beiler JS, Vallati JR, Duda LM, King TS. Placebo effect in the treatment of acute cough in infants and toddlers: a randomized clinical trial. Jama, Pediatr.. 2014;168(12):1107-13. doi:10.1001/jamapediatrics.2014.1609
EXCLUDED: INTERVENTION NOT OF INTEREST

11. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev. 2014;11:CD001831. doi:10.1002/14651858.CD001831.pub5
EXCLUDED; UPDATE WITH NO NEW TRIALS OR CONCLUSIONS

12. Faruqi S, Wright C, Thompson R, Morice AH. A randomized placebo controlled trial to evaluate the effects of butamirate and dextromethorphan on capsaicin induced cough in healthy volunteers. Br J Clin Pharmacol. 2014;78(6):1272-80. doi:10.1111/bcp.12458
EXCLUDED: POPULATION NOT OF INTEREST

13. Lee JH, Choi SH, Choi YS, Lee B, Yang SJ, Lee JR. Does the type of anesthetic agent affect remifentanil effect-site concentration for preventing endotracheal tube-induced cough during anesthetic emergence? Comparison of propofol, sevoflurane, and desflurane. J Clin Anesth. 2014;26(6):466-74. doi:10.1016/j.jclinane.2014.02.002
EXCLUDED: POPULATION NOT OF INTEREST

14. Fassoulaki A, Chassiakos D, Melemeni A. Intermittent epidural vs continuous wound infusion of ropivacaine for acute and chronic pain control after hysterectomy or myomectomy: a randomized controlled trial. PAIN MED. 2014;15(9):1603-8. doi:10.1111/pme.12523
EXCLUDED: OUTCOME/POPULATION NOT OF INTEREST

15. Guenin E, Armogida M, Riff D. Pharmacokinetic profile of dextromethorphan hydrobromide in a syrup formulation in children and adolescents. Clin Drug Invest. 2014;34(9):609-16. doi:10.1007/s40261-014-0210-5
EXCLUDED: OUTCOME NOT OF INTEREST

16. Khalid S, Murdoch R, Newlands A, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. J Allergy Clin Immunol. 2014;134(1):56-62. doi:10.1016/j.jaci.2014.01.038
EXCLUDED: INTERVENTION NOT FDA APPROVED

17. Canciani M, Murgia V, Caimmi D, Anapurapu S, Licari A, Marseglia GL. Efficacy of Grintuss pediatric syrup in treating cough in children: a randomized, multicenter, double blind, placebo-controlled clinical trial. Ital. J. Pediatr.. 2014;40:56. doi:10.1186/1824-7288-40-56
EXCLUDED: INTERVENTION NOT FDA APPROVED

18. Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev. 2014;3:CD006088. doi:10.1002/14651858.CD006088.pub4
EXCLUDED: UPDATE OF PREVIOUS REVIEW- NO NEW STUDIES INDENTIFIED

19. Wise PM, Breslin PA, Dalton P. Effect of taste sensation on cough reflex sensitivity. Lung. 2014;192(1):9-13. doi:10.1007/s00408-013-9515-z
EXCLUDED: INTERVENTION NOT OF INTEREST

20. Deschler D, Judge B. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 3: Paediatric deaths associated with over the counter cough and cold medicines. Emerg Med J. 2014;31(2):171-2. doi:10.1136/emermed-2013-203506.3
INCLUDED

21. Zanasi A, Mazzolini M, Tursi F, Morselli-Labate AM, Paccapelo A, Lecchi M. Homeopathic medicine for acute cough in upper respiratory tract infections and acute bronchitis: a randomized, double-blind, placebo-controlled trial. Pulm Pharmacol Ther. 2014;27(1):102-8. doi:10.1016/j.pupt.2013.05.007
EXCLUDED: INTERVENTION NOT OF INTEREST

22. Yancy WS Jr, McCrory DC, Coeytaux RR, et al. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. Chest. 2013;144(6):1827-38. doi:10.1378/chest.13-0490
INCLUDED

23. Bhattacharya M, Joshi N, Yadav S. To compare the effect of dextromethorphan, promethazine and placebo on nocturnal cough in children aged 1-12 y with upper respiratory infections: a randomized controlled trial. Indian J Pediatr. 2013;80(11):891-5. doi:10.1007/s12098-013-1002-2
EXCLUDED: NOT AVAILABLE (INCLUDED IN COCHRANE REVIEW OF OTC ANTITUSSIVES)

24. Hilton EC, Baverel PG, Woodcock A, Van Der Graaf PH, Smith JA. Pharmacodynamic modeling of cough responses to capsaicin inhalation calls into question the utility of the C5 end point. J Allergy Clin Immunol. 2013;132(4):847-55.e1-5. doi:10.1016/j.jaci.2013.04.042
EXCLUDED: OUTCOME NOT OF INTEREST

25. Raeessi MA, Aslani J, Raeessi N, Gharaie H, Karimi Zarchi AA, Raeessi F. Honey plus coffee versus systemic steroid in the treatment of persistent post-infectious cough: a randomised controlled trial. Prim. care respir. j.. 2013;22(3):325-30. doi:10.4104/pcrj.2013.00072
EXCLUDED: INTERVENTION NOT OF INTEREST

26. Chalumeau M, Duijvestijn YC. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. Cochrane Database Syst Rev. 2013;5:CD003124. doi:10.1002/14651858.CD003124.pub4
EXCLUDED: OUTCOME NOT OF INTEREST

27. Gavliakova S, Biringerova Z, Buday T, et al. Antitussive effects of nasal thymol challenges in healthy volunteers. Respir Physiolo Neurobiol. 2013;187(1):104-7. doi:10.1016/j.resp.2013.02.011
EXCLUDED: POPULATION NOT OF INTEREST

28. Johnstone KJ, Chang AB, Fong KM, Bowman RV, Yang IA. Inhaled corticosteroids for subacute and chronic cough in adults. Cochrane Database Syst Rev. 2013;3:CD009305. doi:10.1002/14651858.CD009305.pub2
EXCLUDED:INTERVENTION NOT OF INTEREST

29. Millqvist E, Ternesten-Hasseus E, Bende M. Inhalation of menthol reduces capsaicin cough sensitivity and influences inspiratory flows in chronic cough. Respir Med. 2013;107(3):433-8. doi:10.1016/j.rmed.2012.11.017
EXCLUDED: OUTCOME NOT OF INTEREST

30. Faruqi S, Wright C, Thompson R, Morice AH. A randomized placebo controlled trial to evaluate the effects of butamirate and dextromethorphan on capsaicin induced cough in healthy volunteers. Br J Clin Pharmacol. 2014;78(6):1272-80. doi:10.1111/bcp.12458
EXCLUDED: POPULATION NOT OF INTEREST

Cough and Cold Preparations

Goal(s):

- Limit use of cough and cold preparations to OHP-funded diagnoses.
- Symptomatic treatment of upper respiratory tract infections is not funded by the OHP.

Length of Authorization:

Up to 12 months

Requires PA:

- All drugs (expectorants, antitussives, oral decongestants and combinations) in TC = 16, 17 except those listed below.
- All ~~codeine-containing~~ products for patients under 13 years of age.

Covered Alternatives:

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

HSN	Generic Drug Name
001929	Benzonatate
~~000271~~	~~Guaifenesin~~
000206	Guaifenesin/Codeine PHOS
000223	Guaifenesin/D-methorphan HB
002091	Pseudoephedrine HCL

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded diagnosis? All indications need to be evaluated to see if funded on the Oregon Health Plan list of prioritized services.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Has the patient tried and failed, or have contraindications to, one of the covered alternatives listed above?	**Yes:** document failure. Approve for up to 1 year.	**No:** Pass to RPh. Deny; cost-effectiveness

Codeine

Goal(s):

- Promote safe use of codeine in pediatric patients

Length of Authorization:

Up to 3 days

Requires PA:

- All codeine products for patients under 13 years of age
- All codeine *analgesic* products for patients aged 13 through 17 years

Covered Alternatives:

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

Approval Criteria		
4. What diagnosis is being treated?	Record ICD10 code.	
5. What is the age of the patient?	**Ages 0-12 years:** Pass to RPh. Deny; medical appropriateness	**Ages 13-17 years:** Go to #3
6. Is the prescription for an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP
7. Has the patient recently undergone tonsillectomy or adenoidectomy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
8. Does the dose exceed 240 mg per day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve no more than 3-day supply

P&T Review: *5/16 (KK); 9/15; 7/15 (AG)*
Implementation: *10/15*

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: lisdexamfetamine dimesylate capsule

New Indication: Binge Eating Disorder (BED)

Date of Review: May 2016
Generic Name: lisdexamfetamine
PDL Class: ADHD

End Date of Literature Search: Week 2, March 2016
Brand Name (Manufacturer): Vyvanse™ (Shire, Inc.)
AMCP Dossier Received: February 9, 2016

Research Questions:

- Is lisdexamfetamine more effective than currently available treatments at reducing binge-eating episodes (BEE) for patients with BED?
- Is lisdexamfetamine safer than currently available treatments for patients with BED?
- Is lisdexamfetamine more effective or safer than currently available treatments for any subgroup of patients with BED?

Conclusions:

- There is moderate quality evidence that lisdexamfetamine 50-70 mg daily is more efficacious than placebo at reducing BEE days per week and maintaining BEE cessation for 4 weeks (NNT:3-4) when used for 11 weeks in patients without mental health co-morbidities or substance abuse history. Comparisons to psychotherapy, behavioral weight loss therapy, topiramate or second-generation antidepressants have not been made.
- No new safety concerns were identified.
- Lisdexamfetamine has not been evaluated in patients with anorexia, bulimia, other mental health co-morbidities or substance abuse history.

Recommendations:

- Update the current prior authorization criteria to include BED as an accepted diagnosis for approval of lisdexamfetamine **(Appendix 2).**

Background:

Lisdexamfetamine is currently "preferred" with a dose limit of 70 mg daily or 0.5 mg/kg/day and age limit of greater than 6 years old. Medical and psychotherapy of BED is a funded Oregon Health Plan condition (Line 386).

BED is characterized by recurrent episodes of eating more food in a discreet time period (e.g. 1-2 hours) than most people would under similar circumstances.[1] Patients often feel a lack of control during these events, experience shame or guilt but do not compensate with subsequent bulimia or anorexia and the episodes occur at least 1 day per week for 3 months.[2] The lifetime prevalence of BED in the United States (U.S.) is estimated to be 2.6% and up to 30% in weight-control program patients.[1,3] Lifetime prevalence is more common in women (3.5%) than men (2.0%) but it is not associated with race, marital status or employment.[1,3] The median age of onset is 23 years old and its persists an average of 14 years.[3] BED is commonly (78% of patients) comorbid with at least one other psychiatric diagnosis (e.g. social phobia, major depression, posttraumatic stress disorder or substance abuse).[3] BED patients are at increased risk of chronic pain, diabetes, hypertension and morbid obesity.[1,3]

Binge-eating episodes (BEE) vary greatly in size and duration; they are difficult for patients to objectively distinguish because they are distressed by the loss of control during even small episodes or ashamed to report large episodes.[1] Thus, self-reporting must be verified by clinicians using clear metrics and a structured clinical interview.[1] There are over 20 scales and tools used to diagnose and monitor BED.[1]

BED treatment currently focuses on reducing BEE and improving psychological feelings about eating, weight, body shape and distress[1,4] Comorbid concerns include treatment of coexisting metabolic health issues, depression, anxiety or substance abuse.[1,4] Current approaches include cognitive behavioral therapy, interpersonal psychotherapy, behavioral weight loss treatment or various off-label pharmacotherapies (e.g. second generation antidepressants and topiramate).[1,4] All drugs researched by the Agency for Health Quality Research and some forms of cognitive behavioral therapy are superior to placebo at achieving cessation of and reducing BEE but evidence is limited by few trials, small samples, short durations and heterogeneous outcome measures.[1] In January 2015, lisdexamfetamine became the first drug approved by the U.S. Food and Drug Administration (FDA) for BED treatment under a priority review.[5]

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.

Methods: ClinicalTrials.gov identified 6 completed studies evaluating lisdexamfetamine for BED: NCT02009163 (Phase 3, no results available), NCT01657019 (open-label, safety extension), NCT01718509 (Phase 3),[6] NCT01718483 (Phase 3),[6] NCT01291173 (Phase 2)[7] and NCT01090713 (Phase 3, no results available). An Ovid Medline search including dates from 1946 until Week 2, March 2016 on the exploded terms "lisdexamfetamine dimesylate OR SPD489" AND "Binge-Eating Disorder" identified just 2 published papers but, only one[7] was a randomized controlled trial.

Clinical Efficacy: Clinical efficacy was established in 1 Phase 2 dose-ranging study (n=260)[7] and 2 Phase 3 trials (n=383, n=390).[6] All 3 trials had low risk of bias but were of short duration (12 weeks). The primary endpoint, change in number of BEE days per week at end of treatment, was based on a daily diary maintained by the patient and confirmed by clinician interview. All studies established statistical superiority over placebo for lisdexamfetamine 50-70mg daily on the primary outcome (see Comparative Evidence Table below) but, the clinical importance of the treatment effect is difficult to interpret because of the log-transformed scale used and short duration of the trial. The secondary outcome results in all 3 trials, total cessation of BEE for 4 weeks, was more impressive. Three to 4 patients would need to be treated with lisdexamfetamine 50-70mg daily rather than placebo for 11 weeks to achieve 4 weeks total cessation of BEE. Unfortunately, all trials excluded patients with any history of mental health comorbidity (including anorexia or bulimia) or substance abuse. So, it is difficult to extrapolate these results to a population where 78% of patients have mental health co-morbities. No comparison was made to current psychotherapy treatment or other drug options.

Clinical Safety: No new safety issues were raised in these trials. Cardiovascular effects (hypertension and increased heart rate) and substance abuse potential remain areas of concern.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Binge-Eating Episode Frequency
2) Binge-Eating Cessation Time

Primary Study Endpoint:
1) Change from baseline in binge-eating days per week @ week 12 or early termination using a mixed-effects model for repeated measured – least squares mean on a log-transformed scale

Comparative Evidence Table

Ref./ Study Design	Intervention/ Duration	Patient Population	N	Efficacy Endpoints	RD/NNT	Safety Outcomes	RD/NNH	Risk of Bias / Applicability
1. Study 1 *(NCT01718483)* & Study 2 *(NCT01718509)*[6] Phase 3, R-PCT, PG, DB MC (93 with 85 U.S.) Nov 2012 – Sep 2013	1. LDX 50 - 70mg PO daily @ 0700 x 12 weeks. (wk 1 30mg; wk 2 50mg; wk 3 70mg; wk 4, if 70mg not tolerated, reduced to 50mg) -No other dose adjustments allowed 2. PCB PO daily @ 0700 x 12 weeks -All capsules identical appearance -Follow-up 1 week after week 12 or at early termination -Mean daily dose: Study 1/ 56.9mg Study 2/57.6 mg - mean follow-up Study 1/ ~76 days Study 2/ ~74 days -Patients screened 2-4 weeks.	Demographics: mean age: 37.1-38.7 years female: 82.7% -87.8% white: 71.8% - 78.1% obese: 67.2% -69.2% CGI-S moderately ill: 47.1% - 58.0% Key Inclusion Criteria: - 18-55 years old -BEE ≥ 3 days / wk x 2 consecutive wks AND CGI-S ≥ 4 AND confirmed BED using DSM-IV-TR - BMI ≥18 and ≤ 45 Key Exclusion Criteria: -current anorexia nervosa, bulimia nervosa, psychiatric disorders controlled with prohibited drugs or uncontrolled with any symptom that may confound clinical assessment -current psychotherapy or weight loss support -BED ≤ 3 months -use of stimulants for dieting for BED ≤ 6 months - MADR-S ≥ 18, suicide risk, ideation or previous attempt -lifetime history of psychosis, mania, hypomania, dementia, attention-deficit disorder - history of cardiovascular disease, hypertension, or arrhythmia -lifetime history of substance abuse (except nicotine)	ITT: *Study 1:* LDX: n=192 PCB: n=191 *Study 2:* LDX: n=195 PCB: n=195 mITT (excluded patients who do not take study drug or have <1 baseline assessment): *Study 1:* LDX: n=190 PCB: n=184 *Study 2:* LDX: n=174 PCB: n=176 Attrition (exclusions + loss to follow-up): *Study 1* LDX: 5/192=2.6% PCB: 15/191=7.6% *Study 2 (may include patients from 2 sites that were excluded after randomization)* LDX: 36/195=18.5% PCB : 37/195=19.0% Safety Analysis: *Study 1:* LDX: n=192 PCB: n=187 *Study 2:* LDX: n=181 PCB: n=185	Change from baseline in BEE days / wk @ week 12 or early termination (mixed-effects model for repeated measured – least squares mean) *Study 1:* LDX: -3.87 PCB: -2.51 Mean Difference: -1.35 95%CI (-1.70,-1.01) p < 0.001 *Study 2:* LDX:-3.92 PCB: -2.26 Mean Difference: -1.66 95%CI (-2.04,-1.28) p < 0.001 90% power assumptions met 4-wk binge-cessation @ wk 12 *Study 1:* LDX:76/190 (40.0%) PCB:26/184 (14.1%) *Study 2:* LDX:63/174 (36.2%) PCB:23/176 (13.1%)	NA NA RD: 25.9% 95%CI (17.3, 34.5) p<0.001 NNT=4 RD: 23.1% 95%CI (14.4,31.8) p<0.001 NNT=4	Withdrawal due to ADE: *Study 1:* LDX: 12/192= 6.3% PCB: 5/187= 2.7% *Study 2:* LDX: 7/181= 3.9% PCB: 5/185= 2.7% Serious ADE*: *Study 1:* LDX: 3/192= 1.6% PCB: 2/187= 1.1% *Study 2:* LDX: 1/181= 0.06% PCB: 2/185= 1.1% *anaphylaxis, syncope, cholecystitis, fibula fracture, agitation, anxiety, lumbar fracture	RD = 3.6% 95%CI (-8.2,0.08) NA RD = 1.2% 95%CI (-5.4, 2.8) NA RD= 0.05% 95%CI (-3.5,2.4) NA RD= 0.05% 95%CI (-2.1, 3.3) NA	**Risk of Bias**: **Probably Low despite some unclear reporting.** Selection Bias: Low; unclear sequence generation but interactive voice response system implies computer generated random sequence, good allocation concealment; groups even at baseline Performance Bias: Low; identical intervention Detection Bias: Unclear who outcome assessors were; but assume it was treating clinicians who were blinded. Attrition Bias: Unclear; low reported attrition despite mITT: slightly higher in study 1 placebo; Unclear if Study 2 withdrawal numbers included study site that was excluded; higher rate suggests they were. Reporting Bias: Low; all outcomes reported **Applicability**: Patient: Extensive exclusion of mental health comorbidities limits applicability Intervention: Oral capsule, easily reproducible; adherence monitoring not achievable in practice Comparator: placebo appropriate Outcomes: Subjective, but valid, clinically important outcome that includes patient reporting; authors made reasonable attempt to increase reliability with certified, trained clinician verification using standardized criteria. Outcomes may not be sustainable for longer durations. Setting: not described

2. *NCT01291173*[7] Phase 2, R-PCT, PG, DB MC (28 U.S.) May 2011 – Jan 2012	1. LDX 30mg x 11 wks 2. LDX 50mg (wk 1 30mg; wk 2 50mg x 10 wks) 3. LDX 70mg PO daily (wk 1 30mg; wk 2 50mg; wk 3 70mg x 9 wks) -No other dose adjustments allowed 2. PCB PO daily x 11 weeks -All capsules identical appearance and inert ingredients. -Follow-up 1 week after week 11 or at early termination	Demographics: Age: 38.7 years Female: 81.5% White: 78% Non-Latino: 88.8% Weight: 98.6 kg BMI 34.9 Obese: 58.7% Key Inclusion Criteria: - 18-55 years old - met DSM-IV-TR criteria for BED - BMI ≥ 25 and ≤ 45 Key Exclusion Criteria: - current bulimia/anorexia or another psychiatric disorder - lifetime history of bipolar disorder or psychosis -MADRS of ≥ 18 -weight loss intervention within 3 months -use of psychostimulant within 6 months -personal/family history of cardiovascular disease -history of suspected drug abuse -lifetime history of psychostimulant abuse -recent therapy with any psychoactive drug -nicotine allowed	ITT: PCB: n= 64 (1 did not receive study drug) LDX30: n= 66 LDX50: n= 65 LDX70: n= 65 mITT (excluded patients who do not take study drug or have <1 baseline assessment): PCB: n= 62 LDX30: n= 66 L-50: n= 64 L-70: n= 63 Attrition (exclusions + loss to follow-up): PCB: 6/64 = 9.4% LDX30: 6/66 = 9.1% LDX50: 4/65 = 6.2% LDX70: 4/65 = 6.2% Safety Analysis: PCB: n= 63 LDX30: n= 66 LDX50: n= 65 LDX70: n= 65	Change from baseline in BEE days / wk @ week 12 or early termination (mixed-effects model for repeated measured – least squares mean) on the log-transformed scale (BE days per week) + 1. Log-transformed, least-squared mean BE days (SE): PCB: -1.23 (0.069) LDX30: -1.24 (0.067) LDX50: -1.49 (0.066) LDX70: -1.57 (0.067) Mean difference in BEE days / wk vs. PCB: LDX30: -0.01 p=0.88 LDX 50: -0.26 p=0.008 LDX70: -0.35 p<0.001 4-wk binge-cessation @ wk 12 PCB: 21.3% LDX30: 34.8% LDX50: 42.2% LDX70: 50.0%	NA RD vs PCB: LDX30: 13.5% p=0.09 LDX50: 20.9% p=0.01 NNH=5 LDX70: 28.7% p<0.001 NNH= 3	Withdrawal due to ADE: PCB: 0/64 (0.0%) LDX30: 3/66 (4.5%) LDX50: 1/65 (1.5%) LDX70: 3/65 (4.6%) Serious ADE*: PCB: 0/64 (0.0%) LDX30: 2/66 (3.0%) LDX50: 0/65 (0.0%) LDX70: 1/65 (1.5%) *methamphetamine overdose, acute pancreatitis, appendicitis (all deemed unrelated to study drug)	NA NA	**Risk of Bias**: **Probably Low despite some unclear reporting.** Selection Bias: Low; unclear sequence generation but interactive voice response system implies computer generated random sequence, good allocation concealment; groups even at baseline Performance Bias: Low; identical intervention Detection Bias: Unclear who outcome assessors were; but assume it was treating clinicians who were blinded Attrition Bias: Unclear; low reported attrition despite mITT: Unclear if withdrawal numbers included study site that was excluded Reporting Bias: Low **Applicability**: Patient: Extensive exclusions applies to very narrow population of moderate to severe disease, obese & no mental health comorbidities Intervention: Oral capsule, easily reproducible; adherence monitoring not achievable in practice Comparator: placebo appropriate Outcomes: Subjective, but valid, clinically important outcome; authors attempt to increase reliability with certified, trained clinician verification using standardized criteria. Longer term studies are needed to determine if the treatment effect is sustained beyond 11 weeks. Setting: US, university clinics, psychiatric & research centers; implies a level of care not generalizable to community care and the same treatment effect may not be achieved

Abbreviations [alphabetical order]: ADE: adverse drug event; BED = binge-eating disorder; BEE = binge-eating episodes; BMI- body mass index; CI = confidence interval; CGI-S = Clinical Global Impressions-Severity score; ITT = intention to treat; DB = double-blind; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th ed. ;LDX = lisdexamfetamine; mITT = modified intention to treat; MADR-S = Montgomery-Asberg Depression Rating Scale; ; mITT = modified intention to treat; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PCB = placebo; PG = parallel group; PP = per protocol; RD: risk difference; R-PCT = randomized, placebo-controlled trial; wk = week

References:

1. Berkman N, Brownley K, Peat C, et al. Management and outcomes of binge-eating disorders. Agency for Healthcare Research and Quality. December 2015. http://www.effectivehealthcare.ahrq.gov/ehc/products/563/2157/binge-eating-report-151207.pdf. Accessed March 11, 2016.

2. Cooper R. *Diagnosing the Diagnostic and Statistical Manual of Mental Disorders*. London, GB: Karnac Books; 2014. http://site.ebrary.com/lib/alltitles/docDetail.action?docID=10869982. Accessed March 22, 2016.

3. Forman SF. Eating disorders: Overview of epidemiology, clinical features, and diagnosis. In: *UpToDate [on-line database]*. 2016 ed. United States: Wolters Kluwer Health; Updated January 11, 2016. http://www-uptodate-com.liboff.ohsu.edu/ Accessed March 10, 2016.

4. Sysko R, Devlin M. Binge eating disorder in adults: Overview of treatment. In: *UpToDate [on-line database]*. 2016 ed. United States: Wolters Kluwer Health; Updated September 3, 2015. http://www-uptodate-com.liboff.ohsu.edu/ Accessed March 10, 2016.

5. Summary memo and approval decision for lisdexamfetamine for the treatment of Binge Eating Disorder. United States Food and Drug Administration. January 30, 2015. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/021977Orig1s037.pdf. Accessed March 11, 2016.

6. McElroy SL, Hudson J, Ferreira-Cornwell MC, Radewonuk J, Whitaker T, Gasior M. Lisdexamfetamine dimesylate for adults with moderate to severe Binge eating disorder: results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251-1260. doi:10.1038/npp.2015.275.

7. McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(3):235. doi:10.1001/jamapsychiatry.2014.2162.

8. Vyvanse Label. Shire US, Inc. April 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021977s039lbl.pdf. Accessed March 22, 2016.

Appendix 1: Highlights of Prescribing Information[8]

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VYVANSE® (lisdexamfetamine dimesylate) capsules, for oral use, CII

Initial U.S. Approval: 2007

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants (amphetamines and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	01/2015
Dosage and Administration (2)	01/2015

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

VYVANSE is a central nervous system (CNS) stimulant indicated for the treatment of (1):

- Attention Deficit Hyperactivity Disorder (ADHD)
- Moderate to Severe Binge Eating Disorder (BED)

Limitation of Use: VYVANSE is not indicated for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.

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

Indication	Initial Dose	Titration Schedule	Recommended Dose	Maximum Dose
ADHD (2.2)	30 mg every morning	10 mg or 20 mg weekly	30 mg to 70 mg per day	70 mg per day
BED (2.3)	30 mg every morning	20 mg weekly	50 mg to 70 mg per day	70 mg per day

- Prior to treatment, assess for presence of cardiac disease (2.4)
- Severe renal impairment: Maximum dose is 50 mg/day (2.5)
- End stage renal disease (ESRD): Maximum dose is 30 mg/day (2.5)

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

Capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)

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

- Known hypersensitivity to amphetamine products or other ingredients in VYVANSE (4)
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose (4, 7.2)

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

- *Serious Cardiovascular Reactions:* Sudden death in children and adolescents with serious heart problems, as well as sudden death, stroke, and myocardial infarction in adults reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. (5.4)
- *Suppression of Growth:* Monitor height and weight in pediatric patients during treatment (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with stimulants (5.6)

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

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in children, adolescents, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust VYVANSE dosage accordingly. (2.6, 7.1)

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

- *Pregnancy:* Based on animal data, may cause fetal harm (8.1)
- *Nursing Mothers:* Discontinue drug or nursing taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

Appendix 2: Proposed Prior Authorization Criteria

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

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

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

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		60 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		30 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg

CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg

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

Table 3. Standard Combination Therapy for ADHD

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the treated diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs do not require co-pay and are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5

Approval Criteria		
5. Is the request for an approved FDA indication defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

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

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: patiromer powder for oral suspension

Date of Review: 3/17/16
Generic Name: patiromer
PDL Class: Potassium Exchangers

End Date of Literature Search: 3/17/16
Brand Name (Manufacturer): Veltassa® (Relypsa)
AMCP Dossier Received: Yes

Research Questions:

- Is patiromer more effective than placebo at maintaining normal potassium levels in patients with chronic kidney disease (CKD) and patients with heart failure (HF) who are also on ACEIs, ARBs or spironolactone?
- Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which patiromer is more effective or safe?

Conclusions:

- Patiromer was studied in 1 phase 2 trial, a two-part, single blind, phase 3 trial, and a 52-week, open-label randomized, dose-finding phase 2 trial. Major limitations of the data include a high risk of performance bias and selection bias. Generalizability is limited by relatively few study sites within the U.S., significant exclusion criteria, difficult dosing schedules, and a lack of data comparing patiromer to other measures to reduce potassium. In addition, in the primary efficacy study, only patients who initially responded to treatment with patiromer were randomized to the primary trial period, increasing the risk of bias and potentially the beneficial effect of the drug observed. Lastly, this study was sponsored and designed in collaboration by the pharmaceutical company.
- There is low quality evidence that patiromer can decrease serum potassium levels from 0.35 mEq/L to 1.23mEq/L over 4 weeks of therapy in patients with CKD and hyperkalemia on a renin angiotensin aldosterone system (RAAS) inhibitor. The magnitude of potassium decrease is more pronounced with a higher baseline potassium level.
- There is low quality evidence that in patients with CKD on a RAAS inhibitor with baseline hyperkalemia, patiromer is associated in a reduction in the recurrence of hyperkalemia (60% vs. 15%) through 8 weeks of treatment.
- The trials were short term and not designed to detect differences in any long term complications of chronic hyperkalemia (sudden cardiac death or ventricular arrhythmias).There is insufficient evidence that patiromer prevents long term complications, including arrhythmias.
- The most common adverse effects seen short-term are gastrointestinal (flatulence, diarrhea, constipation, vomiting, nausea), hypomagnesemia, chronic renal failure, and anemia. There is a boxed warning to administer other oral medications at least 6 hours before or 6 hours after patiromer, due to the potential binding of patiromer to other medications.
- Longer studies are needed to assess the safety of long term use and to appropriately define its place in therapy. It remains unclear, if patiromer will allow for the long term administration of RAAS therapy in patients with CKD or HF and hyperkalemia. Consideration of the risk versus benefit of RAAS inhibitor therapy and adjustment or discontinuation of other medications or herbal treatments that may contribute to serum potassium is necessary.
- Due to the slow onset of patiromer, there is currently no place in the acute treatment of hyperkalemia (≥ 6.5 mEq/L).

Recommendations:

- Defer PDL decisions until a review of sodium polystyrene sulfonate and zirconium cyclosilicate (awaiting FDA approval) at an upcoming P&T meeting.
- Recommend clinical PA criteria to prevent use in the emergent setting or in scenarios not supported by the medical literature (Appendix 2).

Background:

Hyperkalemia is common in patients with chronic kidney disease (CKD) or heart failure (HF). Multiple definitions of hyperkalemia exist, including potassium levels over 5.0, 5.5, or 6.0mEq/L.[1] Hyperkalemia is due to altered potassium handling by the kidneys, aldosterone resistance leading to decreased potassium excretion, acidosis or lack of insulin.[2] In HF with reduced ejection fraction, (HFrEF), angiotensin converting enzyme inhibitors (ACEi,), angiotensin II receptor blockers (ARBs), and aldosterone antagonists have been shown to be effective in reducing morbidity and mortality but can also cause hyperkalemia. These medications have also demonstrated the ability to decrease progression of kidney disease in patients with diabetes and CKD. Therefore, the optimization of treatment with these medications is often limited by the development of hyperkalemia.

Hyperkalemia can result in flaccidity of muscles, paralysis, and more seriously can cause life-threatening cardiac arrhythmias and increased mortality.[3] Treatment is indicated in patients with potassium levels over 6mEq/L, or with rapid increases in potassium level.[4, 5] Several medications are used to treat hyperkalemia in the emergent setting (see Table 1). Most of these have a fast onset and work either by shifting potassium intracellularly or by removing potassium from the body. However, there is no data to support the use of these therapies in the setting of chronic hyperkalemia. Although sometimes used chronically in patients, the prolonged use of sodium polystyrene sulfonate (SPS) increases the risk of developing bowel necrosis due to its sorbitol containing formulation. It also has an unpleasant taste, and commonly causes diarrhea. The largest study evaluating SPS involved only 32 patients with either acute or chronic renal disease; however these patients were only treated for up to six days.[6] The only other current option to lower potassium level are loop diuretics. Chronic use of loop diuretics is limited by electrolyte imbalances and they may not be as effective in patients with CKD. Patiromer, a cation exchange polymer, was developed as a potential option for treatment in chronic hyperkalemia. It is not effective for the emergency treatment of life threatening hyperkalemia because of its delayed onset of action.[7] In addition to medications, several other measures may be effective to potentially reduce serum potassium. This includes counselling on a low potassium diet and review of medications that can contribute to an elevated potassium level (NSAID, potassium-sparing diuretic, potassium or herbal supplements). Patiromer is a nonabsorbed polymer that binds potassium in exchange for calcium predominantly in the distal colon, increasing fecal potassium excretion. As it is not absorbed, the amount of calcium absorbed remains small.

Table 1. Acute treatment for hyperkalemia

Shift potassium intracellularly	Remove potassium
Insulin (with glucose)	Diuretics (i.e. loop, thiazide)
Sodium bicarbonate (for metabolic acidosis)	Sodium polystyrene sulfonate
β-2 adrenergic agonists (i.e. albuterol)	

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:

Patiromer was studied in 1 phase II trial, a two-part, single blind, phase III trial, and a 52-week, open-label randomized, dose-finding phase II trial for both the prevention and treatment of hyperkalemia. Patients included in the clinical trials had either chronic kidney disease (CKD) or heart failure (HF).

The PEARL-HF trial was a 4 week phase II trial evaluating patiromer for the prevention of hyperkalemia which is an off-label use in patients treated with standard therapy for HF with serum potassium of 4.3 to 5.1 mEq/L. Over half of the patients included had CKD, and 36% had a history of hyperkalemia (7.5% had both CKD and history of hyperkalemia). Overall more normokalemia patients with HFrEF on standard therapy were able to titrate up to spironolactone 50 mg daily and avoid hyperkalemia than patients on placebo.[8] This trial found that the change in potassium with patiromer use was -0.45mEq/L ($p<0.001$). The clinical significance of this difference in potassium is unclear, as even in the placebo group potassium only increased by 0.22 mEq/l. Fewer patients on patiromer experienced hyperkalemia (serum potassium > 5.5 mEq/L) compared to placebo (7.3% vs. 24.5%). Ninety-one percent of patients in the patiromer group and 74% of patients in the placebo group were successfully increased to the higher spironolactone dose ($p=0.019$). However, it is unclear if this increased spironolactone dose has a higher mortality benefit compared to 25 mg, as the mean spironolactone dose achieved in previous HF trials was 26 mg/day.[9] The patients in this study are a good representation of the HF patients who could clinically benefit from patiromer use, as they had other risks for developing hyperkalemia, such as comorbid CKD and more advanced age. However, this study did not evaluate patiromer for the treatment of hyperkalemia in patients with HF.

The primary phase III trial (OPAL-HK) evaluated the use of patiromer in patients with hyperkalemia and CKD receiving RAAS inhibitors (n=243).[12,13] After an initial dose titration period based on baseline potassium level, only patients who responded to therapy were randomized to 8 weeks of either continued patiromer therapy or withdrawal. The primary outcome was reduction in serum potassium after 4 weeks compared to baseline, and compared to placebo in an 8-week withdrawal phase. During the first phase, 62% of patients had moderate-to-severe hyperkalemia and the remainder had mild (38%), and the mean change in serum potassium levels from baseline to week 4 was -1.01 mmol/L (95% CI -1.07 to -0.95) with a larger change in patients with moderate-to-severe hyperkalemia (-1.23 mmol/L) compared to those with mild (-0.65 mmol/L). Only patients whose potassium level had been well-controlled during the initial phase were included in the second phase, increasing the risk of bias and potentially the beneficial effect of the drug observed. After week 8 in the withdrawal phase, fifteen percent of patients in the patiromer group and 60% of patients in the placebo group had hyperkalemia with potassium $\geq$5.5mEq/L, and 43% of the patiromer patients and 91% of the placebo patients had hyperkalemia with potassium $\geq$5.1mEq/L (both $p<0.001$). In an exploratory analysis, 94% of patients in the patiromer group were still receiving RAAS inhibitors at the end of the study. However, risk of bias in this study is high and generalizability is low because the run-in phase resulted in only responders and those with moderate hyperkalemia to be randomized in the 8 week trial. A poorer response is expected in the real world setting. This study was funded by the pharmaceutical company and was designed in colloaboration with the sponsor.

AMETHYST-DN trial was a multicenter, open-label, dose-ranging, phase 2 trial of 324 patients with type 2 diabetes mellitus (T2DM) and CKD.[10,11] This trial consisted of three phases and a post-treatment follow-up phase: during the 4-week run-in, patients with serum potassium less than 5.0 mEq/L were randomized to continue the current ACEi/ARB therapy or switch to losartan 100mg daily. After 2 weeks, if blood pressure was uncontrolled, spironolactone 25mg daily was initiated; this could be increased to 50mg daily for further blood pressure lowering. During the second phase, patients with baseline potassium of 5.0-6.0 mEq/L were included in a third cohort that skipped the run-in phase; this third cohort made up about three-fourths of the study population. Patients from all three cohorts were again randomized to 8 weeks of treatment with patiromer at various doses (4.2-16.8 g BID) based on baseline potassium level. The primary endpoint was the mean central lab serum potassium level from baseline to week 4 of the second phase. Overall, serum potassium level decreased by 0.35-0.97mEq/L, with a higher change in potassium level in the moderate hyperkalemia group. A significant number of patients were not treated per protocol; therefore the effect of patiromer on potassium lowering may be greater than that observed. On the other hand, given the open label design of this study and high non-adherence, there is an increased risk for bias. This could especially have occurred in patients at higher potassium levels, who may have been more careful to avoid other sources of potassium, such as potassium found in the diet. It is therefore difficult to say if patiromer was the sole cause of the larger

potassium change in the moderate hyperkalemia group. The proportion of patients with potassium levels within target range at each scheduled visit of the maintenance phase through week 52 ranged from 83.1% to 92.7% in patients with mild hyperkalemia (n = 180) and from 77.4% to 95.1% in patients with moderate hyperkalemia (n = 66).

There is low quality evidence from these studies to support the use of patiromer to lower potassium levels for duration of 4 weeks. However, the amount of potassium lowering may differ from that seen in the single-blind trials, AMETHYST-DN and OPAL-HK.

Clinical Safety:

The AMETHYST-DN trial demonstrated that the most common adverse reactions (≥1%) of long-term patiromer use include worsening CKD (9.2%) or hypertension (7.9%), hypomagnesemia (8.6%), constipation (6.3%), diarrhea (5.6%), and hypoglycemia (3.3%). The amount of CKD worsening was not defined, although this adverse effect led to 8 patients discontinuing therapy. Although hypomagnesemia was a common adverse reaction, no patients discontinued therapy due to hypomagnesemia, and no patients developed severe hypomagnesemia (<1.0mg/dL). However, this is a potential concern, as low magnesium levels are also associated with ventricular arrhythmias, and may increase the risk of death when in combination with low potassium levels.[8]

See Table 2 for common adverse effects seen with short-term use of patiromer, as seen in the PEARL-HF and OPAL-HK trials. The most common adverse effect found in both studies was gastrointestinal (GI) effects. In general, this was reported to be mild to moderate, with no patients experiencing serious GI effects. In the PEARL-HF trial, magnesium decreased on an average of -0.22mg/dL. However, the incidence of ventricular arrhythmias was no different than placebo. Similarly, magnesium levels decreased by -0.1 to -0.2mg/dL in the OPAL-HK trial; there seemed to be no correlation to magnesium decrease and patiromer dose. Nine patients required magnesium replacement therapy. Although chronic renal failure was reported in the OPAL-HK trial, there was no significant change in renal function reported in either of these trials. Anemia was not discussed.

Another concern is the stated warning/precaution that patiromer binds to many orally administered medications and all medications should be administered 6 hours before or after patiromer due to the risk of decreased absorption. This does not seem to be addressed in any of the patiromer studies. In previous rat studies, patiromer did not affect drug absorption for most drugs that are commonly used in HF and CKD; however bioavailability of valsartan and rosiglitazone was decreased by 30%.[8]

There is low evidence, provided by AMETHYST-DN, that patiromer is safe and effective for use for 52 weeks. Overall, the complications of hyperkalemia (i.e. muscle weakness, arrhythmias) were uncommon; further studies with a larger patient population would be needed to determine if patiromer is able to prevent these complications. Studies did not report any significant difference or any clinically significant changes in ECG parameters, however patients at risk for arrhythmias were excluded from trials.

Table 2. Incidence of common adverse effects with short-term patiromer use

Adverse Effect	**Patiromer (n=666)**	**Placebo**
Constipation	7.2%	0
Hypomagnesemia	5.3%	NA
Diarrhea	4.8%	0
Nausea	2.3%	0
Abdominal discomfort	2.0%	NA
Flatulence	2.0%	NA

Look-alike/Sound-alike Error Risk Potential: None

Pharmacology and Pharmacokinetic Properties:[14]

Parameter	
Mechanism of Action	Increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract, resulting in a reduction of serum potassium levels.
Absorption	Not systemically absorbed
Distribution and Protein Binding	N/A, not absorbed
Metabolism	N/A, not absorbed
Half-Life	N/A, not absorbed
Elimination	Fecally

Abbreviations: GI=gastrointestinal, N/A=not applicable

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Long term maintenance of normokalemia
2) Complications of hyperkalemia
3) Discontinuations due to adverse events

Primary Study Endpoint:

1) Mean difference of change in serum K from baseline to 28 days (all three studies)
2) Difference between groups in serum K level after 4 weeks of patiromer discontinuation/continuation

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Pitt et al. (PEARL-HF)[8] Multicenter, double-blind, RCT, phase 2 study 4 weeks	1. Patiromer 15g BID + spironolactone 2. Placebo + spironolactone	Demographics: Age: 68 years Men: 61% White: 96.5% NYHA II: 55% NYHA III: 42.5% LVEF: 40±12% DM: 32% CKD: 56.5% History of hyperkalemia: 36% CKD and history of hyperkalemia: 7.5% Baseline K: 4.67	ITT: 1. 60 2. 60 mITT: 1. 55 2. 49 PP: 1. 56 2. 49 Attrition: 1. 5 (8.3%)	Primary Endpoint: Mean change in serum K from baseline to 28 days: 1. -0.22mEq/L 2. +0.25mEq/L Difference between groups -0.45mEq/L, p<0.001 Secondary Endpoint: Proportion of patients increased to spironolactone 50mg/d 1. 50/55 (91%)	N/A ARR 48.6% NNT 2	Outcome: GI disorders 1. 21% 2. 6% Discontinuations due to adverse events: 1. 4 (7%) 2. 3 (6%)	5	**Risk of Bias (moderate)**: Selection Bias: method of randomization and allocation concealment is not specified. Patients in the patiromer group had more ACEi/ARB use and ACEi/ARB plus BB use Performance Bias: double-blind design indicated but blinding not described. Detection Bias: double-

		Key Inclusion Criteria: -Age ≥18 years -History of chronic HF with indication to initiate spironolactone -K 4.3-5.1mEq/L -CKD (eGFR <60mL/min) receiving at least 1 HF therapy, or history of hyperkalemia leading to HF therapy discontinuation in the past 6 months Key Exclusion Criteria: -Severe GI disorders -Major GI surgery -Bowel obstruction -Swallowing disorders -Significant primary valvular disease -Known obstructive/restrictive cardiomyopathy -Unstable or stable arrhythmia -recent UA/ACS/TIA -QTc >500ms, BP > 170/90 mm HG, dialysis, elevated LFTs > 3x ULN	2. 11 (18.3%)	2. 36/49 (74%) p=0.019				blind design indicated but blinding not described. No mention was made regarding blinding of the outcome assessors Attrition Bias: Total attrition rate 13% (low), but differential attrition rate 10% Reporting Bias: all endpoints were reported **Applicability**: Patient: Mainly white patients with HF NYHA II and III (97.5%) and CKD (56.5%). Significant exclusion criteria reduce generalizability of results. Intervention: unclear if separated from other medications according Comparator: No data compared to other measures to manage hyperkalemia Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were

								enrolled from 38 centers in the US, Germany, Czech Republic, Poland, Ukraine, Russia, and Georgia
2. Weir et al. (OPAL-HK)[12] multinational, single-blind, phase 3 study Phase 1. 4 week single-group, single-blind initial treatment Phase 2. 8 week placebo-controlled, single-blind, randomized withdrawal	**Phase 1** 1. K+ 5.1 - <5.5mmol/L Patiromer 4.2g BID* 2. K+ 5.5 - <6.5 mmol/L Patiromer 8.4g BID* **Phase 2^** 1. Continue patiromer dose from Phase 1* 2. Placebo * titrated to effect based on prespecified algorithm and baseline ^ K+ ≥ 5.5 mmol/L @ baseline AND K+ @ end of phase I was 3.8 to <5.1 mmol /L while on patiromer and RAAS inhibitors.	Demographics: Age: 64 years Men: 58% Stage 3 CKD: 46% Stage 4 CKD: 45% T2DM: 57% HF: 42% HTN: 97% K: 5.6mmol/L Key Inclusion Criteria: -Age 18-80 years -Stage 3-4 CKD (eGFR 15 to <60mL/min) -K 5.1 to <6.5mmol/L (Phase 1) and 5.5 to <6.5 mmol/L (Phase 2) -Stable dose of ≥1 RAAS inhibitor for ≥28 days Key Exclusion Criteria: -K-related ECG changes -Severe GI disorders -Uncontrolled arrhythmias - ventricular arrhythmias -Recent cardiac surgery -Renal/heart	**Phase 1** ITT: 1. 92 2. 151 Completers: 1. 85 (89.5%) 2. 134 (88.7%) **Phase 2** ITT: 1. 55 2. 52 Attrition: 1. 0 (0.0%) 2. 1/52 (1.9%)	**Phase 1** Mean change in serum K level to week 4: both groups -1.01 95% CI -1.07 to -0.95 p<0.001 Proportion of patients with K 3.8 to <5.1mmol/L at week 4: 76% (95% CI 70-81%) **Phase 2** Difference in median change in serum K level: 1. 0.72 mmol/L 2. 0 mmol/L Difference 0.72 mmol/L (95% CI 0.46 to 0.99); p<0.0001 Proportion of patients with recurrent hyperkalemia: 1. 8/55 (15%, 95% CI 6-24%) 2. 31/52 (60%, 95% CI 47-74%) p<0.001	N/A ARR 45.2% NNT 3	Outcome: Supraventricular extrasystoles Patiromer: 2 (4%) Discontinuations due to adverse events: N=10 (group not specified)	34	**Risk of Bias (high)**: Selection Bias: Central randomization occurred, only patients who responded to patiromer were included for randomization Performance Bias: single-blinded design Detection Bias: single-blinded design Attrition Bias: 42.3% of patients in the phase 2 placebo group discontinued prematurely, most commonly due to elevated potassium levels meeting prespecified criteria Reporting Bias: all primary and secondary endpoints were reported **Applicability**: Patient: Poor generalizability due to significant exclusion criteria and the run in phase allowed for only responders and those

		transplant -ACS,TIA/stroke, SBP ≥180/<110 mmHg, DBP ≥110/<60 mmHg -T1DM -HF exacerbation in the past 3 months, NYHA stage IV						with moderate hyperkalemia to be included. Intervention: unclear if separated from other medications according Comparator: No data compared to other measures to manage hyperkalemia Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were enrolled from Eastern Europe (24 sites), the European Union (21 sites), and the US (14 sites)
3. Bakris, et al (AMETHYST-DN)[10] Multicenter, open-label, dose-ranging, RCT, phase 2 study	**Treatment phase** *K>5.0-5.5* 1. Patiromer 4.2g BID 2. Patiromer 8.4g BID 3. Patiromer 12.6g BID *K>5.5-6.0* 4. Patiromer 8.4g BID 5. Patiromer	Demographics: Mean Age: 66 years Men: 63.2% White: 100% CKD Stage 3: 64.5% ACEi: 49.3% ARB: 24.3% Mean K: 5.3 Key Inclusion Criteria: -Age 30-80 years -T2DM and CKD (eGFR 15 to <60mL/min), with/out HTN	**Treatment phase** ITT: 1. 74 2. 74 3. 74 4. 26 5. 28 6. 30 PP: 1. 56 2. 51 3. 50	Mean change in central lab serum K level from baseline to week 4 of treatment phase 1. 0.35 (95% CI 0.22-0.48) mEq/L 2. 0.51 (95% CI 0.38-0.63) mEq/L 3. 0.55 (95% CI 0.42-0.68) mEq/L 4. 0.87 (95% CI 0.60-1.14) mEq/L 5. 0.97 (95% CI 0.70-1.23) mEq/L	N/A	Outcome: Worsening CKD: 28 (9.2%) Worsening HTN: 24 (7.9%) Discontinuations due to adverse events: 1. 4 2. 2 3. 7 4. 2	N/A	**Risk of Bias (moderate):** Selection Bias: web-based system used to assign patients to cohorts/starting doses Performance Bias: open-label design Detection Bias: open-label design Attrition Bias: low attrition rate overall (2%), although a significant number of patients were not

	12.6g BID 6. Patiromer 16.8g BID	-Receiving ACEi/ARB/both for ≥28 days prior to screening Key Exclusion Criteria: -Preexisting hyperkalemia with K>5.0, later included pts w/K 5.0 to <6.0 in 3rd cohort	4. 17 5. 21 6. 16 Attrition: 1.1 (1.4%) 2.2 (2.7%) 3.2 (2.7%) 4. 0 5. 1 (3.6%) 6. 0	6. 0.92 (95% CI 0.67-1.17) mEq/L p<0.001 vs. baseline for all changes by hyperkalemia strata and by starting-dose groups within strata Secondary Endpoints: Mean changes in serum K level from baseline to other visits Figure 3		5. 2 6. 2		treated per protocol; the effect of patiromer on K lowering may be greater than observed Reporting Bias: all endpoints were reported **Applicability**: Patient: white patients with CKD (64.5% had stage 3) and T2DM Intervention: unclear if separated from other medications according to package insert. Comparator: Dose-ranging study Outcomes: Primary outcome was a surrogate outcome. Short term study not designed to detect differences in long term complications of hyperkalemia. Setting: Patients were enrolled from 48 sites in 5 European countries.

Abbreviations [alphabetical order]: ACEi = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; BB = beta blocker; BID = twice daily; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; HF = heart failure; HTN = hypertension; ITT = intention to treat; K = potassium; LVEF = left ventricular ejection fraction; mITT = modified intention to treat; N = number of subjects; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; P4.2 = patiromer 4.2mg twice daily; P8.4 = patiromer 8.4mg twice daily; Pat = patiromer; Pla = placebo; PP = per protocol; QTc = corrected QT interval; RAAS = renin angiotensin aldosterone system; RCT = randomized, controlled trial; SBP = systolic blood pressure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal; US = United States. GI disorders: flatulence, diarrhea, constipation, vomiting; Recurrent hyperkalemia: one potassium value of 5.5 mmol/L or higher through week 8

References:

1. Kovesdy CP. Management of hyperkalemia in chronic kidney disease. Nat Rev Nephrol. 2014;10(11):653-662.
2. Ingelfinger JR. A new era for the treatment of hyperkalemia? N Engl J Med. 2015;372:275-277.
3. Segal A. Potassium and Dyskalemias. In: Mount DB, Sayegh MH, Singh AK, eds. Core Concepts in the Disorders of Fluid, Electrolytes and Acid-Base Balance. New York, NY: Springer Science+Business Media; 2012.
4. Hollander-Rodriguez JC, Calvert JF. Hyperkalemia. Am Fam Physician. 2006;73(2):283-290.
5. UK Renal Association. Clinical practice guidelines: Treatment of acute hyperkalemia in adults. 2014. Available at: www.renal.org.
6. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL. Management of hyperkalemia with a cation-exchange resin. N Engl J Med. 1961;264:115-119.
7. Veltassa® [package insert]. Redwood City, CA: Relypsa Inc; 2015.
8. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011;32(7):820-828. doi: 10.1093/eurheartj/ehq502. Epub 2011 Jan 5.
9. 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-e239.
10. Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. JAMA. 2015;314(2):151-161. doi: 10.1001/jama.2015.7446.
11. Supplement to: Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. JAMA. 2015;314(2):151-161. doi: 10.1001/jama.2015.7446.
12. Weir MR, Bakris GL, Bushinsky DA et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-221. doi:10.1056/NEJMoa1410853. Epub 2014 Nov 21.
13. Supplement to: Weir MR, Bakris GL, Bushinsky DA et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-221. doi:10.1056/NEJMoa1410853. Epub 2014 Nov 21.
14. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated Periodically. Accessed March 17, 2016.

Appendix 1: Highlights of Prescribing Information[7]

Black Box Warnings: None

Risk Evaluation Mitigation Strategies: None

Indications: Hyperkalemia
- *Limitations*: Not to be used as an emergency treatment for life-threatening hyperkalemia due to its delayed onset of action

Dosage and Administration: Starting dose 8.4g orally once daily with food
- Adjust dose by 8.4g daily as needed at one-week intervals to obtain desired serum potassium target range
- Doses of patiromer in excess of 50.4g/day have not been tested. Excessive doses of patiromer may result in hyperkalemia. Restore serum potassium if hypokalemia occurs

Formulations: Powder for oral suspension (8.4, 16.8, and 25.2g packets)
- *Active Ingredient*: patiromer sorbitex calcium
- *Inactive Ingredient*: xanthan gum

Contraindications: Known hypersensitivity to patiromer or any of its components

Warnings and Precautions:
- Worsening of gastrointestinal motility; use should be avoided in patients with severe constipation, bowel obstruction or impaction, as patiromer may be ineffective or worsen gastrointenstinal motility.
- Hypomagnesemia,; patiromer binds to magnesium in the colon which could result in hypomagnesmia. This was reported in 5.4% of patients in clinical trials.
- Binding to other oral medications; patiromer binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after patiromer.

Adverse Reactions: Common (incidence $\geq$2%): constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, flatulence

Drug Interactions: Take other orally administered drugs at least 6 hours before or after patiromer

Use in Specific Populations:
- *Pregnancy*: patiromer is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.
- *Lactation*: patiromer is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.
- *Pediatric Use*: safety and efficacy in pediatric patients have not been established

- *Geriatric Use*: of the 666 patients treated with patiromer in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.
- *Renal Impairment*: of the 666 patients treated with patiromer in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

Storage and Stability: Refrigerate. Must be used within 3 months or being taken out of the refrigerator

Patiromer (Valtassa®)

Goals:

- Restrict use of patiromer to patients with persistent or recurrent hyperkalemia not requiring urgent treatment.
- Prevent use in the emergent setting or in scenarios not supported by the medical literature.
- Encourage use to optimize medications with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Patiromer (Valtassa®)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on patiromer)?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have persistent or recurrent serum potassium of ≥ 5.5 mEq/L despite a review for discontinuation of medications that may contribute to hyperkalemia (e.g., potassium supplements, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed or cannot tolerate sodium polystyrene?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have hyperkalemia requiring emergency intervention (serum potassium ≥ 6.5 mEq/L)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Does the patient have hypomagnesemia (serum magnesium < 1.4 mg/dL)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Does the patient have a severe GI disorder (i.e., major GI surgery (e.g., large bowel resection), bowel obstruction/impaction, swallowing disorders, gastroparesis, severe constipation)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve up to 6 months

Renewal Criteria		
1. Is the patient's potassium level < 5.1 mEq/L and has this decreased by at least 0.35 mEq/L from baseline?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Clinical Considerations:

-Monitoring

-Monitor potassium at baseline and at each dose titration (weekly for first 8 weeks, then monthly thereafter).

-Hypomagnesemia was reported in 9% of patients in clinical trials. Monitor serum magnesium every 2 weeks for 2 months, then monthly thereafter. Consider magnesium supplementation or risk vs. benefit of continued treatment with patiromer.

-Administration

-It is recommended to administer other oral medications at least 6 hours before or 6 hours after patiromer, due to the potential binding of patiromer to other orally administered medications.

-Administer patiromer with food. Do not heat or add heated foods/liquids. Do not take patiromer in its dry form

-Prepare each dose immediately prior to administration following the steps below:

-1): Add about 1 ounce (30 mL) of water to an empty glass or cup

-2): Empty the entire contents of the packet(s) into the glass or cup

-3): Stir the mixture thoroughly

-4): Add an additional 2 ounces (60 mL) of water to the glass or cup

-5): Stir the mixture thoroughly; the powder will not dissolve and the mixture will look cloudy

-6): Drink the mixture immediately. If some powder remains in the glass after drinking, add more water, stir, and drink immediately. Repeat as needed to ensure the entire dose is administered

---

P&T / DUR Review: *05/16 (EL/MH)*
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: lesinurad tablet, oral

Date of Review: May 2016
Generic Name: lesinurad
PDL Class: Gout

End Date of Literature Search: April 2016
Brand Name (Manufacturer): Zurampic® (AstraZeneca)
AMCP Dossier Received: Yes

Research Questions:

- What are the differences in efficacy between lesinurad and other anti-gout agents at reducing acute attacks of gout, either when treated alone or concomitantly with another anti-gout agent?
- What are the differences in harms between lesinurad and other anti-gout agents when used to prevent acute attacks of gout?
- Are there any subpopulations based on demographics (age, race, gender, etc.) or comorbid conditions or concomitant drugs that lesinurad has demonstrated greater efficacy/effectiveness or less harm than other anti-gout agents?

Conclusions:

- The U.S. Food and Drug Administration (FDA) approved lesinurad 200 mg daily as an adjunct with a xanthine oxidase inhibitor (allopurinol or febuxostat) for hyperuricemia based on 3 unpublished, multinational, phase 3 clinical trials of unclear risk of bias and uncertain applicability. Though the 400 mg daily dose was studied, the FDA denied approval of the dose based on increased risk for major cardiovascular and renal events compared to placebo.
- There is insufficient comparative evidence that lesinurad is superior to existing anti-gout agents when used in combination with a xanthine oxidase inhibitor.
- There is insufficient evidence that lesinurad in combination with a xanthine oxidase inhibitor demonstrates efficacy in reduction of gout flares, provides symptom relief, results in function improvement, or improves health-related quality of life versus a xanthine oxidase inhibitor alone.
- There is insufficient evidence for use of lesinurad as monotherapy for management of hyperuricemia.
- There is low quality evidence that daily doses of lesinurad 200 mg in combination with allopurinol may result in over half of patients achieving a serum uric acid less than 6 mg/dL over 6 months [54% vs. 28% with placebo, respectively; RR 0.26 (95% CI, 0.17 to 0.36; p<0.0001) and 55% vs. 23%, respectively; RR 0.32 (95% CI, 0.23 to 0.41; p<0.0001)]; similarly, in combination with febuxostat, there is low quality evidence adjunctive use of lesinurad 200 mg daily may result in over half of patient achieving a serum uric acid less than 5 mg/dL over 6 months [57% vs. 47% with placebo; RR 0.10 (95% CI, -0.03 to 0.23; p=0.1298)]. Lesinurad did show statistically significant reductions in serum uric acid levels relative to placebo over 6 months (range -0.79 to -1.08 mg/dL). The clinical significance of these reductions and how it relates to prevention of gouty attacks is unclear.
- There is moderate quality evidence that lesinurad treatment is associated with an increased risk of renal adverse events, including reversible and non-reversible elevations in serum creatinine and acute renal failure.
- There is insufficient evidence that any subgroups based on a particular demographic may benefit from lesinurad more than the general population for which it has been studied. All patients studied were adults, mostly obese white males between 21 to 82 years of age.

Recommendations:

- Due to limited evidence of improvement in clinically relevant outcomes and unknown long term safety risks, maintain Zurampic® (lesinurad) as non-preferred on the PMPDP.

Background:

Gout is an inflammatory arthritic disease initiated by monosodium urate crystal deposition in joints and connective tissue tophi which often lead to significant pain and disability.[1-4] Gout affects 3.9% of the adult U.S. population but is most prevalent in middle-aged men and post-menopausal women.[3] Chronic hyperuricemia, which stems from physiologic disturbances of urate metabolism and clearance, is the most important risk factor for the development of gout.[1-3] Other risk factors for the development of gout in men include obesity, weight gain, hypertension, use of diuretic agents, and alcohol.[1,2,4] Accumulation of excessive serum uric acid may also result in a range of destructive renal complications such as urolithiasis, chronic urate nephropathy, and acute renal failure.[1,2,4] The goals of gout treatment are to alleviate the pain and inflammation of acute gout attacks and to prevent gout flares and and complications from uric acid crystal deposition.[1,2]

The American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) guidelines recommend serum uric acid levels ≤6 mg/dL in patients with gout.[1,2,5,6] Most patients with elevations in uric acid will not develop gout; however, if left untreated, progression towards gout may occur, which generally follows 4 stages: asymptomatic hyperuricemia, acute gout, interval gout, and chronic tophaceous gout. Pharmacologic therapy for gout is typically initiated for acute attack.[7]

Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids have been used to control the symptoms of acute gout. NSAIDs and colchicine are commonly used to relieve associated inflammation and pain but do not affect urate excretion or metabolism.[7-9] Corticosteroids such as oral prednisone may be used as an alternative to NSAIDs or colchicine in patients with renal impairment or risk of hemorrhage. [7-9]

The management of chronic gout for prevention of acute gouty attack is largely based upon effective control of serum uric acid concentrations.[7-9] Elevated serum urate levels (>7 mg/dL in men; >6 mg/dL in women) are related to purine metabolism defects, under-excretion of uric acid, amplified nucleic acid turnover, or hyper-synthesis of purine.[1,2] Three main pharmacologic mechanisms are targeted for gout treatment: management of hyperuricemia through reduction of uric acid production, increased urate secretion through reabsorption inhibition, or by enhanced enzymatic breakdown of uric acid.[7-9] Xanthine oxidase inhibitors (XOIs) such as allopurinol and febuxostat represent the mainstay of chronic gout therapy.[7-9] XOIs are utilized to manage overproduction and/or underexcretion of urate and by the inhibition of xanthine to uric acid conversion.[7-9] Probenecid, a second-line uricosuric agent, inhibits urate transporters in the proximal renal tubules to prevent uric acid reabsorption and accelerate excretion.[9] Other agents such as pegloticase and rasburicase are recombinant enzymatic proteins used to catalyze the oxidation of urate to allantoin.[9,10] These enzymes are typically reserved for individuals unresponsive or intolerant to XOIs or uricosuric therapy.[9,10]

Lesinurad (Zurampic®) is a new uricosuric agent proposed to increase excretion of uric acid through inhibition of URAT1 transport proteins in a mechanism similar to probenecid.[9,10]

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 for lesinurad was based on 3 unpublished, phase 3, double-blind, randomized, placebo-controlled clinical trials of unclear risk of bias and uncertain applicability (Studies 301, 302, and 304)[11] that compared lesinurad as an adjunct to a XOI to placebo with a XOI over 12 months (see study details in the evidence table). Only study 301 was completely conducted within the U.S. The primary endpoint of the studies, defined as the proportion of subjects who had a sUA less than 5.0 (study 304) or 6.0 mg/dL (studies 301, 302) was only reported to 6 months. Study 303 was originally initiated to investigate the efficacy and safety of lesinurad monotherapy but the study was prematurely discontinued by the sponsor for concerns of renal-associated adverse events.[11]

All 3 studies were conducted in adults between 22-82 years with hyperuricemia and gout diagnosis on a stable dose of a XOI. In addition, all patients had the option to receive routine colchicine or NSAIDs of unknown doses with or without a proton pump inhibitor through month 5 for prevention of gouty attack. Patients with significant cardiac disease (unstable angina, myocardial infarction, stroke, DVT, uncontrolled hypertension during screening, etc.) or hepatic disease were excluded. At the conclusion of the 12-month study period for each trial, patients had a 14-day follow-up.[11]

In study 301, patients successfully screened during the initial 28-day period were randomized 1:1:1 by renal function (60 mL/min cutoff) and presence of tophi to one of the following 3 arms (each arm received ≥300 mg per day of allopurinol except 200 mg per day for moderate renal dysfunction): placebo; lesinurad 200 mg daily; or lesinurad 400 mg per day. A greater proportion of patients on lesinurad 200 mg and 400 mg daily demonstrated a modest statistically significant response to therapy compared to placebo (54% and 59%, respectively vs. placebo (28%)). No dose response was evident between the daily 200 mg and 400 mg doses. The mean change in serum uric acid from baseline to month 6 was statistically significant for lesinurad 200 mg (-1.00 mg/dL; 95% CI, -1.35 to -0.66; p<0.001) and 400 mg (-1.23 mg/dL; 95% CI -1.58 to -0.89; p<0.001). Other secondary endpoints studied included the proportion of subjects who required treatment for a gout flare month 6 to month 12; the proportion of subjects with more than 1 target tophus at baseline who experienced complete resolution of at least 1 target tophus by month 12; and patient reported outcomes regarding disease activity, pain, and functioning, for which differences from placebo were not found to be statistically significant.[11]

Study 302 was a 12-month, multinational trial (n=610) of unclear risk of bias and uncertain applicability with an identical study design to Study 301.[11] The primary endpoint was statistically significantly higher for both lesinurad doses compared to placebo (55% and 67%, respectively vs. placebo (23%)). A dose-response was observed between the 200 mg and 400 mg doses. The mean change in serum acid (mg/dL) from baseline to month 6 was statistically significant for the 200 mg (-1.08 mg/dL; 95% CI, -1.41 to -0.75; p<0.001) and 400 mg doses (-1.36 mg/dL; 95% CI, -1.69 to -1.03; p<0.001) compared to placebo. Secondary endpoints were similar to study 301. The difference in the proportion of subjects who required treatment for a gout flare from month 6 to month 12 compared to placebo was not statistically significant for either lesinurad dose. Secondary patient reported outcome assessments were also not considered statistically significant due to the hierarchical testing method used for multiple endpoints.[11]

Study 304 was designed similarly to studies 301 and 302 except lesinurad was used as an adjunct to feboxostat 80 mg daily instead of allopurinol. It was a 12-month multinational study (n=324) of adults with tophaceous gout with or without continued hyperuricemia on allopurinol or febuxostat.[11] Successfully screened patients were randomized into one of 3 groups: placebo; lesinurad 200 mg daily; or lesinurad 400 mg daily. The primary endpoint was the proportion of patients with serum uric acid less than 5 mg/dL by month 6. The primary endpoint for the lesinurad 200 mg daily dose (57%) was not statistically significant from placebo (47%), but was statistically significant for the 400 mg dose (76%). The mean change in serum uric acid from baseline to month 6 was statistically significant for the 200 mg dose (-0.79 mg/dL; 95% CI, -1.28 to -0.30, p=0.002) and 400 mg dose (-1.88 mg/dL; 95% CI, -2.36 to -1.40, p<0.001). Secondary efficacy variables were generally not supportive of a beneficial response of lesinurad due to the hierarchical testing used for multiple endpoints and inappropriate use of unadjusted p-values.[11]

Clinical Safety:

The safety population evaluated all subjects who received at least one dose of the randomized study medication.[11] The safety review for lesinurad plus XOI noted concerns of higher rates of death, major adverse cardiac events (MACE) rates, serious adverse events, and rates of serious and non-serious renal adverse events.[11] Overall, adverse events leading to discontinuation occurred in 9.4%, 6.3%, and 5.4% in the lesinurad 400 mg, lesinurad 200 mg, and placebo arms, respectively.[11] Overlapping confidence intervals and the presence of underlying concomitant medical conditions presented a challenge to establish safety conclusions for lesinurad, however, exposure-adjusted combined incidence of death rates for lesinurad arms appeared low overall (0 for placebo; 5 for lesinurad (<1%). The incidence of MACE were comparably low in the lesinurad 200 mg arm, but almost doubled in the lesinurad 400 mg arm with the majority of increased events attributed to nonfatal MI (see Table 1).[11] Blood pressure, cholesterol, and ECG findings appeared to be unaffected by lesinurad.[11] Again, the studies were not designed to assess long-term safety data and to what extent lesinurad contributes to MACE.[11]

Table 1: Incidence of Adjudicated MACE Events (Studies 301, 302, and 304).[11]

	Lesinurad 400 mg + XOI (n=510)	Lesinurad 200 mg + XOI (n=511)	Placebo + XOI (n=516)
Number patients with adjudicated CV events	15	18	17
MACE	8	4	3
CV Death	2	2	0
Nonfatal MI	7	2	1
Nonfatal stroke	0	0	3

Abbreviations: CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction.

The increased risk of adverse renal events was highest with lesinurad 400 mg while lesinurad 200 mg appeared to be more similar to placebo.[11] Increased blood creatinine was the most common adverse event leading to discontinuation in 1.8%, 0.8%, and 0.8% of the lesinurad 400 mg, lesinurad 200 mg, and placebo groups, respectively[11] A black box warning identifies risk of acute renal failure with lesinurad.[12] A summary of renal events are listed in Table 2.

Table 2: Incidence of Renal-related Adverse Events in Studies 301, 302, and 304.[11]

	Lesinurad 400 mg + XOI (n=510)	Lesinurad 200 mg + XOI (n=511)	Placebo + XOI (n=516)
Increased SCr	11.8%	5.7%	4.5%
Increased BUN	7.8%	4.3%	2.3%
Renal failure	1.2%	0.8%	1.2%
Renal failure, acute	0.8%	0.0%	0.4%
Nephrolithiasis	2.2%	0.6%	1.7%

Abbreviations: BUN = blood urea nitrogen; SCr = serum creatinine

Other common adverse events were upper respiratory tract infection, hypertension, headache, and influenza.[11]

Table 3: Common Adverse Events in Studies 301, 302, and 304.[12]

Preferred Term	Placebo + XOI (n=516)	Lesinurad 400 mg + XOI (n=510)	Lesinurad 200 mg + XOI (n=511)	Total Lesinurad + XOI (n=1021)
Upper respiratory tract infection	44 (8.5%)	57 (11.2%)	46 (9.0%)	103 (10.1%)
Hypertension	25 (4.8%)	35 (6.9%)	31 (6.1%)	66 (6.5%)
Headache	21 (4.1%)	30 (5.9%)	27 (5.3%)	57 (5.6%)
Influenza	14 (2.7%)	16 (3.1%)	26 (5.1%)	42 (4.1%)

Look-alike / Sound-alike Error Risk Potential: None identified.

Pharmacology and Pharmacokinetic Properties:[12]

Parameter	
Mechanism of Action	Selective uric acid reabsorption inhibitor that reduces the function of the URAT1 and OAT4 transporter proteins involved in renal urate reabsorption
Absorption	Rapid, almost 100 % bioavailability; maximum plasma concentrations (Cmax) attained within 1 to 4 hours.
Distribution and Protein Binding	Vd is 20 L; >98% is bound to albumin
Metabolism	Oxidative metabolism mainly via CYP2C9
Half-Life	Approximately 5 hours
Elimination	Total clearance is approximately 6 L/hr. Urine (63%; roughly 30% as unchanged drug); feces (32%).

Abbreviations: Cmax = maximum serum drug concentration; L = liters; URAT = urate transporter 1; OAT = organic anion transporter; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Incidence of gout flares
2) Symptom relief
3) Function improvement
4) Health-related quality of life

Primary Study Endpoints:
1. Proportion of patients achieving a target serum uric acid level <6.0 mg/dL at 6 months (studies 301 & 302) or <5 mg/dL at 6 months (study 304)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
Study 301 R,DB,PC,MC Phase 3 Unpublished	1. lesinurad 200 mg + allopurinol once daily 2. lesinurad 400 mg + allopurinol once daily 3. Placebo + allopurinol once daily 12 months	Demographics: Mean Age: 52 (22-81) yr Males: 94% White: 76% Mean BMI: 35 mg/m^2 Mean baseline sUA: 6.94 mg/dL (±1.27) Mean gout flares ≤1 y: 5 (±3.6) Est CrCl ≥60 mL/min: 79% Key Inclusion Criteria: ▪Adults 18-85 y ▪Gout dx ▪Allopurinol mono tx ▪Able to take colchicine or an NSAID ▪sUA level > 6.5 mg/dL ▪≥2 gout flares ≤1 y Key Exclusion Criteria: ▪Unresolved acute gout flare at least 7 d prior to baseline visit ▪>14 drinks of alcohol consumed per week ▪ NYHA class III/IV HF ▪ h/o MI, CVA, DVT ≤1 y; ▪ Anticoagulants ▪ Uncontrolled HTN ▪Est CrCl <30 mL/min	ITT: 1. 201 2. 201 3. 201 Attrition: 1. 61 (30%) 2. 60 (30%) 3. 52 (26%)	Primary Endpoint: sUA level <6.0 mg/dL at month 6: 1. 54% 2. 59% 3. 28% Treatment difference: 1 vs 3: RR 0.26 (95% CI, 0.17 to 0.36), p<0.0001 2 vs 3: RR 0.31 (95% CI, 0.22 to 0.41), p<0.0001 Key Secondary Endpoints: Mean rate of gout flares requiring tx months 6-12: **mean rates NR** 1 vs 3: RR 0.99 (95% CI, 0.61 to 1.61), p=0.98 2 vs 3: RR 0.88 (95% CI, 0.54 to 1.43), p=0.61 Mean change in serum acid from baseline to month 6: 1 vs 3: -1.00 mg/dL (95% CI -1.35 to -0.66), p<0.001 2 vs 3: -1.23 mg/dL (95% CI -1.58 to -0.89), p<0.001	26/4 31/4 NS NS NA NA	Deaths: (Combined Studies 301, 302, 304): 1. 2 (<1%) 2. 3 (1%) 3. 0 S-TEAE (Combined Studies 301, 302, 304): 1. 24 (5%) 2. 44 (9%) 3. 29 (6%) MACE: CV death, non-fatal MI, non-fatal stroke (pooled data from studies 301 and 302): 1. 2 2. 6 3. 2 p-value not given Serum Creatinine Elevation (> 1.5x baseline) 1. 15 (4%) 2. 32 (8%) 3. 9 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) No details on randomization procedure or attempts to conceal allocation methods; similar baseline demographics Performance Bias: (unclear) Extensive screening with a run-in period; no details on methods to maintain blinding Detection Bias: (unclear) No details provided on outcome assessment blinding; imputation of missing data unknown Attrition Bias: (high) high attrition rates Reporting Bias: (unclear) unpublished study; funded by drug sponsor **Applicability**: Patient: Extensive inclusion and exclusion criteria; disproportionate participation of obese white males Intervention: Only tested in combination with allopurinol Comparator: Active comparator needed for comparative evidence; more patients on PBO took >300 mg/day of allopurinol compared to lesinurad groups () Outcomes: Primary endpoint of little significance; addition of lesinurad to allopurinol does not prevent gouty flares vs. allopurinol alone; unclear dose-response; more lesinurad patients took thiazide diuretics which may have affected the urinary excretion of UA Setting: Conducted only in sites in U.S.

Study 302 R, DB, PC, MC Phase 3 Unpublished	1. lesinurad 200 mg + allopurinol once daily 2. lesinurad 400 mg + allopurinol once daily 3. Placebo + allopurinol once daily 12 months	Demographics: Mean age: 51 y Males: 96% White: 79% Mean BMI: 34 mg/m^2 Mean baseline sUA: 6.94 mg/dL (±1.27) Mean gout flares ≤1 y: 5 (±3.6) Est CrCl ≥60 mL/min: 84% Key Inclusion/Exclusion Criteria: See trial 301	ITT: 1. 204 2. 200 3. 206 Attrition: 1. 42 (21%) 2. 55 (28%) 3. 52 (25%)	Primary Endpoint: sUA level <6.0 mg/dL at month 6: 1. 55% 2. 67% 3. 23% 1 vs 3: RR 0.32 (95% CI, 0.23 to 0.41), p<0.0001 2 vs 3: RR 0.43 (95% CI, 0.34 to 0.52), p<0.001 Secondary Endpoints: Mean rate of gout flares requiring tx months 6-12: **mean rates NR** 1 vs 3: RR 0.88 (95% CI, 0.57 to 1.37), p=0.57 2 vs 3: RR 0.93 (95% CI, 0.60 to 1.45), p=0.75 Mean change in serum acid from baseline to month 6: 1 vs 3: -1.08 mg/dL (95% CI -1.41 to -0.75), p<0.001 2 vs 3: -1.36 mg/dL (95% CI -1.69 to -1.03), p<0.001	 32/4 43/3 NS NS NA NA	(Pooled safety data – see study 301)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) See study 301 Performance Bias: (unclear) See study 301 Detection Bias: (unclear) See study 301 Attrition Bias: (high) See study 301 Reporting Bias: (unclear) See study 301 **Applicability**: Patient: See study 301 Intervention: See study 301 Comparator: Active comparator needed for comparative evidence; more patients with kidney stones in placebo arm than lesinurad arms (14% vs. 9-11% respectively) Outcomes: See study 301 Setting: US (51%), Canada, Europe, Australia, New Zealand, South Africa

Study 304 R, DB, PC, MC Phase 3 Unpublished	1. lesinurad 200 mg + febuxostat 80 mg once daily 2. lesinurad 400 mg + febuxostat 80 mg once daily 3. Placebo + febuxostat once daily 12 months	Demographics: Mean age: 54 y Males: 95% White 80% Mean BMI: 32 mg/m^2 Mean baseline sUA: 5.27 mg/dL (±1.63) Mean gout flares ≤1 y: 7 (±8) Est CrCl >60 mL/min: 77% EstCrCl <60: 23% Key Inclusion/Exclusion Criteria: Same key criteria as trial 301 with the additional inclusion criteria: ▪sUA ≥8 mg/dL if not on ULT or ≥6 mg/dL if on ULT ▪ ≥1 tophus on the hands/wrists and/or feet/ankles 5-20 mm in diameter	ITT: 1. 106 2. 109 3. 109 Attrition: 1. 30 (28%) 2. 33 (30%) 3. 26 (24%)	Primary Endpoint: sUA level <5.0 mg/dL at month 6: 1. 57% 2. 76% 3. 47% 1 vs 3: RR 0.10 (95% CI, -0.03 to 0.23), p=0.1298 2 vs 3: RR 0.29 (95% CI, 0.17 to 0.42), p<0.0001 Secondary Endpoints: Frequency of gout flares: 1 vs 3: RR 1.2 (95% CI, 0.7 to 2.1), p=0.05493 2 vs 3: RR 0.5 (95% CI, 0.3 to 1.0), p=0.0401 Mean change in serum acid from baseline to month 6: 1 vs 3: -0.79 mg/dL (95% CI -1.28 to -0.30), p=0.002 2 vs 3: -1.88 mg/dL (95% CI -2.36 to -1.40), p<0.001	 NS 29/4 NS NS NA NA	MACE: (CV death, non-fatal MI, non-fatal stroke) 1. 2 2. 2 3. 1 p-value NR Serum Creatinine Elevation (>1.5x baseline) 1. 7 (7%) 2. 8 (8%) 3. 3 (3%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) See study 301 Performance Bias: (unclear) See study 301 Detection Bias: (unclear) See study 301 Attrition Bias: (high) See study 301 Reporting Bias: (unclear) See study 301 **Applicability:** Patient: See study 301 Intervention: See study 301 Comparator: Active comparator needed for comparative evidence Outcomes: See study 301 Setting: US (75%), Canada, Europe, Australia, New Zealand

Abbreviations: AE=adverse event; ARR = absolute risk reduction; CI = confidence interval; CVA = cerebral vascular accident; DB=double blind; DVT = deep vein thrombosis; Est CrCl = estimated Creatinine Clearance; ITT = intention to treat; MC=multicenter; MI = myocardial infarction; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NSAID=non-steroidal anti-inflammatory drug; NYHA=New York Heart Association; PBO=placebo; PC=placebo controlled; PP = per protocol; R=randomized; S-TEAE = Serious treatment emergent adverse event; sUA = serum uric acid; ULT=Urate lowering therapy

References:

1. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care & Research. 2012;64(10):1431-1446. doi:10.1002/acr.21772.
2. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care & Research. 2012;64(10):1447-1461. doi:10.1002/acr.21773.
3. Diagnosis of Gout - Research Review - Final | AHRQ Effective Health Care Program. https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2188. Accessed April 7, 2016.
4. Diagnosis, Treatment, and Prevention of Gout - American Family Physician. http://www.aafp.org.liboff.ohsu.edu/afp/2014/1215/p831.html. Accessed April 7, 2016.
5. Zhang W. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). Annals of the Rheumatic Diseases. 2006;65(10):1301-1311. doi:10.1136/ard.2006.055251.
6. Zhang W. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT). Annals of the Rheumatic Diseases. 2006;65(10):1312-1324. doi:10.1136/ard.2006.055269.
7. Management of Gout - Research Review - Final | AHRQ Effective Health Care Program. https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2195. Accessed April 7, 2016.
8. Sivera F, Andrés M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis. 2014;73(2):328-335. doi:10.1136/annrheumdis-2013-203325.
9. Diaz-Torne C, Perez-Herrero N, Perez-Ruiz F. New medications in development for the treatment of hyperuricemia of gout. [Review]. Current Opinion in Rheumatology. 2015;27(2):164-169. doi:10.1097/BOR.0000000000000146.
10. Crittenden DB, Pillinger MH. New Therapies for Gout. Annual Review of Medicine. 2013;64(1):325-337. doi:10.1146/annurev-med-080911-105830.
11. Lesinurad Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207988Orig1s000SumR.pdf. Accessed April 7, 2016.
12. Zurampic (lesinurad) [prescribing information] Wilmington, DE: AstraZeneca Pharmaceuticals LP, 2015.

Appendix 1: Highlights of Prescribing Information

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

ZURAMPIC® (lesinurad) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: RISK OF ACUTE RENAL FAILURE, MORE COMMON WHEN USED WITHOUT A XANTHINE OXIDASE INHIBITOR

See full prescribing information for complete boxed warning.

- **Acute renal failure has occurred with ZURAMPIC and was more common when ZURAMPIC was given alone.**
- **ZURAMPIC should be used in combination with a xanthine oxidase inhibitor. (1.1, 5.1, 6.1)**

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

ZURAMPIC is a URAT1 inhibitor indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone. (1)

Limitations of Use:

- ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia. (1.1)
- ZURAMPIC should not be used as monotherapy. (1.1, 5.1)

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

- ZURAMPIC is recommended at 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat. The maximum daily dose of ZURAMPIC is 200 mg. (2.1)
- Failure to take ZURAMPIC with a xanthine oxidase inhibitor may increase the risk of renal adverse reactions. (2.1, 5.1)
- ZURAMPIC tablets should be taken in the morning with food and water. (2.1)
- Patients should be instructed to stay well hydrated. (2.1)
- Assess renal function before initiating ZURAMPIC. Do not initiate ZURAMPIC if eCLcr is below 45 mL/min. (2.2)
- Discontinue ZURAMPIC if eCLcr persistently falls below 45 mL/min. (2.2)

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

Tablet: 200 mg. (3)

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

- Severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis. (4, 8.6)
- Tumor lysis syndrome or Lesch-Nyhan syndrome. (4)

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

- *Renal events*: Adverse reactions related to renal function have occurred after initiating ZURAMPIC. A higher incidence was observed at the 400 mg dose, with the highest incidence occurring with monotherapy use. Monitor renal function at initiation and during therapy with ZURAMPIC, particularly in patients with eCLcr below 60 mL/min, and evaluate for signs and symptoms of acute uric acid nephropathy. (5.1)
- *Cardiovascular events:* Major adverse cardiovascular events were observed with ZURAMPIC; a causal relationship has not been established. (5.2)

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

Most common adverse reactions in 12-month controlled clinical trials (occurring in greater than or equal to 2% of patients treated with ZURAMPIC in combination with a xanthine oxidase inhibitor and more frequently than on a xanthine oxidase inhibitor alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Moderate Cytochrome P450 2C9 (CYP2C9) Inhibitors: Use with caution. (7.1)
- Sensitive CYP3A Substrates: Monitor for efficacy of the CYP3A substrate. (7.2)

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

- Renal impairment: Not recommended for patients with eCLcr below 45 mL/min. . (2.2, 5.1, 8.6)
- Hepatic impairment: Not recommended for patients with severe hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2015

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: brivaracetam [tablet and solution, oral; solution, intravenous]

Date of Review: July 2016
Generic Name: brivaracetam
PDL Class: Antiepileptic Drugs

End Date of Literature Search: March 2016
Brand Name (Manufacturer): Briviact® (UCB Pharmaceuticals)
AMCP Dossier Received: No

Research Questions:

- What is the evidence for the efficacy of brivaracetam (BRV) in treating adults with uncontrolled focal seizures and how does it compare to other antiepileptic drug (AED) therapy?
- How well is BRV tolerated in patients with uncontrolled epilepsy and does it compare to other AED therapy?
- Based on the evidence available does BRV have a role in therapy for patients with epilepsy?

Conclusions:

- Three short-term, industry-sponsored, multi-national Phase 3 trials of unclear risk of bias and uncertain applicability lasting from 8-12 weeks evaluated the efficacy of oral brivaracetam compared to placebo. [1-3] Intravenous formulations were not studied in clinical trials. All 3 trials were conducted in adults with uncontrolled focal seizures maintained on 1 to 3 antiepileptic medications. Daily BRV doses between 50 and 150 mg statistically significantly reduced seizure frequency in the studied patient population. These trials provide low quality evidence that adjunctive use of BRV may reduce seizures by 7-12% versus placebo. Seizure events were self-reported by patients, which may have introduced some bias into reporting the primary outcome of reduced seizure frequency.
- There is insufficient comparative evidence to evaluate efficacy or harms data of BRV with other AED therapies.
- Tolerability of BRV was similar to placebo. Primary adverse effects included fatigue, somnolence and dizziness.
- There is insufficient evidence to evaluate the efficacy and long-term safety of BRV and what role it might play as an adjunct for management of focal seizures.

Recommendations:

- Maintain BRV as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).

Background: Epilepsy affects about 1% of the United States adult population.[4] The main treatment of epilepsy is antiepileptic drug (AED) therapy. Over 20 AEDs are approved for treatment of seizures.[5] Drug therapy is generally initiated after two or more unprovoked seizures. Approximately one third of patients experience seizures despite pharmacotherapy.[6] Selection of medication therapy is based on type of seizure, adverse effects associated with the medication, and patient specific parameters. Many AEDs are associated with increased risk for impaired psychomotor function resulting in increased fall risk and the possibility

of a fracture. All AEDs carry an FDA "black box" warning regarding the risk of suicidal thinking associated with their use. Some AEDs (e.g., valproate) may cause fetal malformations or neurodevelopment impairment and should be avoided during pregnancy. Drug interactions can occur with certain AEDs due to hepatic enzyme induction or inhibition depending on which medications are concurrently administered. Most of the newer AEDs have been developed in an effort to improve safety and tolerability. The U.K.'s National Institute for Health Care and Excellence (NICE) epilepsy guidelines provide an outline with detailed prescribing considerations for the different AEDs.[7]

Seizures are broadly classified as either generalized or focal. According to the International League Against Epilepsy (ILAE) definition, generalized seizures arise within bilaterally distributed networks while focal seizure originate within a network limited to one hemisphere of the brain.[8] Brivaracetam (BRV) has primarily been evaluated in adult focal seizures. According to the 2012 NICE epilepsy treatment guidelines, first-line agents for treatment of focal seizures include carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and valproate. Second-line agents include clobazam, gabapentin, and topiramate. Other agents that may be effective include lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide. Monotherapy is preferred to reduce adverse effects and enhance quality of life. A 2011 meta-analysis focused on the clinical comparability of AEDs used as adjunctive therapy in patients with refractory focal epilepsy. Sixty-two placebo-controlled and 8 head-to-head RCTs were included in the review. The primary objectives were to evaluate seizure reduction and tolerability rates. The authors found very small differences between AED therapies and concluded that no single AED showed more effectiveness over other agents as add on therapy. Withdrawal rates were higher with oxcarbazepine (OR 1.60; 95% confidence interval [CI], 1.12-2.29) and topiramate (OR 1.68; 95% CI, 1.07-2.63) and lower with gabapentin (OR 0.65; 95% CI, 0.42-1.00) and levetiracetam (OR 0.62; 95% CI, 0.43-0.89).[10] Given the paucity of evidence, general consensus is to choose add-on medications with a different mechanism of action and a different adverse event profile than the first AED on which the patient was started.

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:

Three multi-national phase 3 RCTs with unclear risk of bias and uncertain applicability assessed the short-term efficacy and safety of BRV (see Evidence Table for details below). Brivaracetam, an analog of levetiracetam, is a selective high affinity synaptic vesicle protein 2A ligand. In study N01254, adjunctive BRV was administered in doses ranging from 20 to 150 mg per day in adults with uncontrolled epilepsy during an 8-week dose finding period. An 8-week stable dose maintenance period followed the initial phase. The study population included patients with focal epilepsy (90%) and generalized epilepsy (10%). The primary objective in this study was to confirm safety and tolerability of BRV. The proportion of patients reporting at least 1 concomitant AED was similar in the BRV (66%) and placebo (65.3%) arms. The most commonly reported side effects included headache, somnolence and dizziness. The discontinuation rate due to AE's was similar in both groups (BRV 6.1%, placebo 5%). In the cohort of patients with focal seizures, the absolute percent reduction in seizure frequency from baseline compared to placebo was 7.3% and did not reach statistical significance (p=0.125). Confidence intervals were not reported by the authors. The median percent reduction in seizure frequency was 26.9% for BRV versus 16.7% for placebo (p=0.070). The 50% or greater response rate (defined as ≥50% relative reduction in self-reported seizures from baseline) for BRV (30.3%) was statistically significant (p=0.006) compared to placebo (16.7%). The authors concluded BRV was well tolerated in adults with uncontrolled epilepsy, but further evaluation of efficacy in reducing focal seizures was needed.

Study N01252 was a double-blind, placebo-controlled RCT. Patients were randomized to 3 doses of BRV (20, 50, and 100 mg per day) or placebo in adults with uncontrolled focal seizures despite treatment with 1-2 concomitant AEDs over a 12-week treatment period. The primary outcome evaluated in this study was

the focal seizure frequency per week over the treatment period. Patients reported the occurrence of seizures on daily record cards, which were reviewed with the investigators at each study visit. The study did not meet statistical significance for the primary efficacy endpoint and the authors did not provide a statistical analysis of the primary outcome in their report. The analysis of percent reduction over placebo in focal seizure frequency per week were not significant for the 20 mg per day (6.8%; 95% CI, -4.8-17.1%) or the 50 mg per day (6.5%; 95% CI -5.2-16.9%) arms. However, the 100 mg per day arm did show statistical significance (11.7%; 95% CI 0.7-21.4%).

Study N01253 was also a double-blind, randomized controlled trial in adults with focal epilepsy. In the first 8 weeks, patients were randomized to receive placebo or BRV 5, 20 or 50 mg per day without dose titration. The primary endpoint of median seizure reduction was evaluated during the 12-week treatment period. Significant median percent reduction in seizure frequency over placebo was only noted with BRV 50 mg per day (12.8%; p=0.025). The other 2 dosing regimens did not achieve statistical significance in reducing seizure frequency (BRV 5 mg = -0.9%, p = 0.885 and BRV 20 mg = 4.1%, p = 0.492). Confidence intervals were not reported by the authors. In conclusion, based on the results of these low quality trials, brivaracetam may be an effective adjunct in treating adult patients with uncontrolled focal seizures that have not been effectively managed with other antiepileptic medications

Clinical Safety:
The majority of adverse events observed in short-term phase 3 trials were mild to moderate in severity. Headache, somnolence, dizziness, and fatigue were the most commonly reported adverse events. Adverse events that resulted in premature discontinuation of the studies were relatively similar across all BRV doses and placebo-treated groups in N01252 but early discontinuations were much higher in the BRV-treated groups in N01253. The most commonly reported adverse events that led to premature study discontinuation were psychiatric disorders (i.e., aggression, anxiety, irritability, depression and insomnia).

In N01252, serious adverse events (a life-threatening event, or an event resulting in death, permanent or significant disability, a congenital birth defect, or hospitalization) occurred more often in placebo-treated subjects (6%) than BRV-treated patients (2.3%). There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, vital signs or ECG measurements. In N01253, serious adverse events occurred more often in BRV-treated patients (2.3%) than placebo-treated subjects (0%). In addition, 2 subjects died from the BRV 50 mg per day group. One subject died from cardiorespiratory arrest following a seizure on the first day of the dose taper period immediately following the final 12-week follow-up. The second subject died from a large subarachnoid hemorrhage 2 weeks after discontinuing the study drug. There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, vital signs or ECG measurements. In N01254, serious adverse events occurred in 5.3% of the BRV-treated subjects and 7.4% of the placebo-treated subjects. The most frequently reported SAEs were convulsions (n=10: BRV 2.8%, PBO 0.8%) and status epilepticus (n=3, all occurred in one BRV-treated subject). One death occurred in a BRV-treated subject who drowned after experiencing a convulsion while swimming. There were no clinically significant changes from baseline in laboratory parameters (blood chemistry or urinalysis), body weight, or vital signs. However, there were 3 BRV-treated subjects that experienced ECG abnormalities of sinus bradycardia.

Look-alike / Sound-alike Error Risk Potential: None identified

Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	High affinity ligand for SV2A (similar to LEV). The precise role of the protein in neurotransmission is unclear but SV2A-binding affinity is strongly correlated with anticonvulsant potency in animal models and low levels of SV2A are correlated with seizures in animal models.
Absorption	Rapidly absorbed through GI tract with ~100% bioavailability
Distribution and Protein Binding	Weakly bound to plasma proteins (<20%)
Metabolism	Extensively transformed into 3 major metabolites
Half-Life	7-8 hours
Elimination	>95%urine, <1%feces

Abbreviations: AED = antiepileptic drugs; GI = gastrointestinal; LEV = levetiracetam; SV2A = synaptic vesicle protein 2A.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Seizure reduction (all types)
2) Hospitalizations
3) Adverse events leading to withdrawal from study

Primary Study Endpoint:

1) Median percent reduction in focal seizures from baseline versus placebo

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Ryvlin, et al.[1] MC, DB, PC, PG, RCT Phase 3 N01252	1. BRV 10 mg BID 2. BRV 25 mg BID 3. BRV 50 mg BID 4. PBO BID 1:1:1:1 12 weeks	Demographics: -Mean age: 37.2 y -Male: 57.0% -White: 76.6% -Mean duration of epilepsy: 21.8 y -Focal seizures/week: 1.95 -≥2 concomitant AEDs: 78.9% Key Inclusion Criteria: -Age 16-70 y -Focal epilepsy -Uncontrolled focal seizures (h/o ≥2 focal seizures per month in 3 months) -≥8 focal seizures during 8-week baseline period -1-2 concomitant AED (inc LEV or BZD) before and during study Key Exclusion Criteria: -Nonmotor simple focal seizures -h/o seizures only occurring in clusters -h/o status epilepticus	mITT: 1. 99 2. 99 3. 100 4. 100 Attrition: 1. 6% 2. 11% 3. 6% 4. 8%	Primary Endpoint: Median focal seizure frequency/week over 8 weeks (Q1-Q3 -25-75th percentile) 1. 1.34 (0.70-3.12) 2. 1.49 (0.69-2.78) 3. 1.26 (0.52-2.93) 4. 1.75 (0.76-5.12) Secondary Endpoints: Median % reduction vs. PBO from baseline in self-reported focal seizures/week: 1. 6.8% (95% CI, -4.8 to 17.1%; p=0.239) 2. 6.5% (95% CI, -5.2 to 16.9; p=0.261) 3. 11.7% (95% CI, 0.7 to 21.4%; p=0.037) Median % reduction in self-reported focal seizures/week from baseline: 1. 30.0% (p=0.019 vs. PBO) 2. 26.8% (p=0.092 vs. PBO) 3. 32.5% (p=0.004 vs. PBO) 4. 17.0% ≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 27.3% (p=0.339. vs. PBO) 2. 27.3% (p=0.3720. vs. PBO) 3. 36.0% (p=0.0230. vs. PBO) 4. 20.0% Seizure-free: 1. 2% 2. 0% 3. 4% 4. 0%	NA NA NA NS NS NA NA NS NA NS NS 16%/7 NR NR NR	D/C due to AE: 1. 4.0% 2. 5.1% 3. 5.0% 4. 4.0% p-values NR Drug-related AE: 1. 23.2% 2. 37.4% 3. 42.0% 4. 31.0% p-values NR SAE: 1. 1.0% 2. 4.0% 3. 2.0% 4. 6.0% p-values NR Headache: 1. 14.1% 2. 18.2% 3. 9.0% 4. 9.0% p-values NR Somnolence: 1. 8.1% 2. 6.1% 3. 8.0% 4. 9.0% p-values NR Fatigue: 1. 3.0% 2. 4.0% 3. 8.0% 4. 2.0% p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear. Central randomization by IVRS stratified by geographic region and concomitant LEV use (of which was limited to 20% per group). Performance Bias: unclear. Method of blinding not stated; unclear if double-dummy design. Vagus nerve stimulation, BZD use b/w groups unknown. Assigned dose could be reduced once, which placed patients into a different study arm than originally allocated. Detection Bias: High. Unknown if data assessors blinded. Seizures were self-reported. Statistical tests utilized appropriate. Study powered; assumptions stated but not referenced. Imputation of data unknown. Attrition Bias: Low. mITT performed but all but 1 patient randomized were analyzed. At 12 weeks, attrition rates were low, similar. Reporting Bias: High. Statistical analysis of primary outcome not completed. Funded by UCB Pharma. **Applicability**: Patient: Young or middle-aged adult males and females, mostly white race w/ h/o focal seizures since childhood; experience about 2 focal seizures per week on multiple AEDs (carbamazepine >valproic acid >lamotrigine >oxcarbazepine >LEV). Intervention: Used as an adjunctive agent (3rd or 4th line). Formulation unknown. Doses tapered off at end of study or were enrolled into long-term, open-label study. Comparator: active control more appropriate; concomitant AEDs were relatively equal across all groups. Outcomes: Absolute reduction in seizure frequency/week would be more clear. Safety outcomes observed only until week 16. Setting: 88 sites in Europe and India. No U.S> sites. Subjects evaluated at baseline, week 2, 4, 8 and 12.

2. Biton, et al.[2] MC, DB, PC, PG, RCT Phase 3 N01253	1. BRV 2.5 mg BID 2. BRV 10 mg BID 3. BRV 25 mg BID 4. PBO BID 1:1:1:1 12 weeks	Demographics: -Mean age: 38.2 y -Male: 49.2% -White: 72.2% -Mean duration of epilepsy: 24.0 y -Focal seizures/week: 2.5 -≥2 concomitant AEDs: 85.6% Key Inclusion Criteria: See N01252 Key Exclusion Criteria: - See N01252	mITT: 1. 96 2. 99 3. 101 4. 96 Attrition: 1. 15% 2. 7% 3. 8% 4. 5%	Primary Endpoint: Median % reduction vs. PBO from baseline in self-reported focal seizures/week: 1. -0.9% (95% CI NR; p=0.885) 2. 4.1% (95% CI NR; p=0.492) 3. 12.8% (95% CI NR; p=0.025) Secondary Endpoints: Median % reduction in self-reported focal seizures/week from baseline: 1. 20.0% (p=0.991 vs. PBO) 2. 22.5% (p=0.386 vs. PBO) 3. 30.5% (p=0.003 vs. PBO) 4. 17.8% ≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 21.9% (p=0.353 vs. PBO) 2. 23.2% (p=0.239 vs. PBO) 3. 32.7% (p=0.008 vs. PBO) 4. 16.7% Seizure-free (no reported seizures of any kind) 1. 1.1% 2. 1.0% 3. 4.0% 4. 0%	 NS NS NA NS NS NA NS NS 16%/7 NR NR NR	D/C due to AE: 1. 8.2% 2. 4.0% 3. 5.9% 4. 2.0% p-values NR Drug-related AE: 1. 44.3% 2. 46.0% 3. 55.4% 4. 35.7% p-values NR SAE: 1. 1.0% 2. 2.0% 3. 3.0% 4. 0% p-values NR Headache: 1. 11.3% 2. 6.0% 3. 12.9% 4. 14.3% p-values NR Somnolence: 1. 14.4% 2. 14.0% 3. 16.8% 4. 7.1% p-values NR Dizziness: 1. 12.4% 2. 14.0% 3. 15.8% 4. 9.2% p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear. Central randomization by IVRS stratified by geographic region and concomitant LEV use (of which was limited to 20% per group). Performance Bias: unclear. Described as "matching placebo" with patients and investigators blinded to treatment. Vagus nerve stimulation, BZD use b/w groups unknown. Assigned dose could be reduced once, which placed patients into a different study arm than originally allocated. Detection Bias: unclear. Unknown if data assessors blinded or if seizures were self-reported. Statistical tests utilized appropriate. Study powered; assumptions stated but not referenced. Imputation of data unknown. Attrition Bias: High. mITT performed (≥1 dose received), which excluded 8 patients allocated to groups, including 4 patients due to randomization errors. Reporting Bias: Low. Outcomes reported as prespecified. Funded by UCB Pharma. **Applicability**: Patient: Young or middle-aged adult males and females, diverse racial groups w/ h/o focal seizures since childhood; experience about 2.5 focal seizures per week on multiple AEDs (carbamazepine, > lamotrigine, >LEV, >phenytoin, >valproic acid, >oxcarbazepine). Intervention: Used as an adjunctive agent (3rd or 4th line); doses studied lower than FDA-approved doses. Formulation unknown. Doses tapered off at end of study or were enrolled into open-label long-term study. Comparator: active control more appropriate; concomitant AEDs were relatively equal across all groups. Outcomes: Absolute reduction in seizure frequency/week would be more clear. Safety outcomes limited to treatment period only. Setting: 85 sites in North America, Mexico, Brazil and Australia. Follow-up intervals not specified.

3. Kwan, et al.[3] MC, DB, PC, PG, RCT Phase 3 N01254	1. BRV 10 mg BID, titrated at 2-week intervals to 25 mg, 50 mg or 75 mg BID as tolerated during 8 week dose-finding period 2. PBO BID 3:1 8-week dosing-finding period, followed by 8-week maintenance period	Demographics: -Mean age BRV, PBO: 35.6 y, 36.5 y -Male BRV, PBO: 50.4%, 57.0% -White BRV, PBO: 58.2%, 57.0% -Mean duration of epilepsy BRV, PBO: 21.2 y, 22.0 y Focal seizures: 89.8% ≥2 concomitant AEDs: 82.7% Median focal seizures/week BRV, PBO: 1.42, 1.47 Key Inclusion Criteria: -Age 16-70 y -Uncontrolled seizures (h/o ≥2 focal seizures/month or ≥2 days w/ primary generalized seizures/month -≥4 focal seizures or generalized seizure (any type) days during 4-week baseline period -1-3 concomitant AED (inc LEV or BZD) before and during study Key Exclusion Criteria: -Nonmotor simple focal seizures -h/o seizures only occurring in clusters -h/o status epilepticus	mITT: 1. n=359 2. n=121 Attrition: 1. 10% 2. 8%	Primary Endpoint: Median % reduction vs. PBO from baseline in self-reported focal seizures/week: 1. 7.3% (p=0.125) Secondary Endpoints (reported only in focal seizure mITT population only): Median % reduction in self-reported focal seizures/week from baseline: 1. 26.9% (p=0.070 vs. PBO) 2. 18.9% 95% CI not reported ≥50% responder rate (≥50% reduction from baseline in self-reported focal seizures/week): 1. 30.3% (p=0.006 vs. PBO) 2. 16.7% 95% CI not reported Seizure-free (no reported seizures of any kind) 1. 1.5% (p=0.337 vs. PBO) 2. 0% Exploratory endpoints in the generalized seizure mITT population are not reported.	NS NS 13.6%/8 NS	D/C due to AE: 1. 6.1% 2. 5.0% p-values NR SAE: 1. 5.3% 2. 7.4% p-values NR Headache: 1. 14.2% 2. 19.8% p-values NR Somnolence: 1. 11.1% 2. 4.1% p-values NR Dizziness: 1. 8.6% 2. 5.8% p-values NR Fatigue: 1. 7.8% 2. 4.1% p-values NR Psychiatric AEs: 1. 12.3% 2. 11.6% p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear. Randomization process unclear; performed by permuted blocks; stratified by epilepsy type (focal or generalized), LEV use and geographic region. h/o generalized seizure and LEV use was limited to 20% in each arm. Performance Bias: unclear. Described as "matching placebo" with patients and investigators blinded to treatment. Vagus nerve stimulation, BZD use b/w groups unknown. Detection Bias: unclear. Unknown if data assessors blinded. Seizures were self-reported on daily record cards; missed recordings could not be accounted for. Statistical tests utilized appropriate. Study powered; based on secondary efficacy endpoint; assumptions stated and referenced. Imputation of data unknown. Missing 95% CI. Attrition Bias: High. mITT performed (≥1 dose received) and 63/543 subjects excluded from analysis. Reporting Bias: Low. Multiple subgroup analyses were prespecified. Funded by UCB Pharma. **Applicability**: Patient: Young or middle-aged adult white or Asian males and females w/ h/o focal seizures since childhood; experience about 1.5 focal seizures per week on multiple AEDs (carbamazepine, >valproic acid, >lamotrigine, >topiramate, >LEV). Intervention: 25.1% received 100 mg/d; 51.8% received 150 mg/d. Formulation unknown. Doses tapered off over 1-3 weeks at end of study or were enrolled into open-label long-term study. Comparator: Active control more appropriate; concomitant AEDs were relatively equal across all groups. Outcomes: Study was powered to assess % reduction in focal seizures versus placebo despite claim to assess safety outcomes. Setting: 74 sites in Asia and Europe.

Abbreviations [alphabetical order]: AE = adverse events; AED = antiepileptic drug; ARR = absolute risk reduction; BID = twice daily; BRV = brivaracetam; BZD = benzodiazepine; CI = confidence interval; DB = double blinded; h/o = history of; ITT = intention to treat; IVRS = interactive voice response system; LEV = levetiracetam; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; PC = placebo-controlled; PBO = placebo; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse events (a life-threatening event, or an event resulting in death, permanent or significant disability, a congenital birth defect, or hospitalization)

References:

1. Kwan, P., Trinka, E., Van Paesschen, W., Rektor, I., Johnson, M. E., & Lu, S. (2014). Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. *Epilepsia*, *55*(1), 38–46. http://doi.org/10.1111/epi.12391.

2. Ryvlin, P., Werhahn, K. J., Blaszczyk, B., Johnson, M. E., & Lu, S. (2014). Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: Results from a double-blind, randomized, placebo-controlled trial. *Epilepsia*, *55*(1), 47–56. http://doi.org/10.1111/epi.12432.

3. Biton, V., Berkovic, S. F., Abou-Khalil, B., Sperling, M. R., Johnson, M. E., & Lu, S. (2014). Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: A phase III randomized, double-blind, placebo-controlled trial. *Epilepsia*, *55*(1), 57–66. http://doi.org/10.1111/epi.12433.

4. Centers for Disease Control and Prevention (CDC). (2012). Epilepsy in adults and access to care--United States, 2010. *MMWR. Morbidity and Mortality Weekly Report*, *61*(45), 909–913.

5. Krishnamurthy, K. B. (2016). Epilepsy. *Annals of Internal Medicine*, *164*(3), ITC17–ITC32. http://doi.org/10.7326/AITC201602020.

6. Duncan, J. S., Sander, J. W., Sisodiya, S. M., & Walker, M. C. (2006). Adult epilepsy. *Lancet (London, England)*, *367*(9516), 1087–1100. http://doi.org/10.1016/S0140-6736(06)68477-8.

7. Epilepsies: diagnosis and management | Appendix-E-Pharmacological-treatment | Guidance and guidelines | NICE. (n.d.). Retrieved April 1, 2016, from https://www.nice.org.uk/guidance/CG137/chapter/Appendix-E-Pharmacological-treatment.

8. Moshé, S. L., Perucca, E., Ryvlin, P., & Tomson, T. (2015). Epilepsy: new advances. *Lancet (London, England)*, *385*(9971), 884–898. http://doi.org/10.1016/S0140-6736(14)60456-6

9. Canevini, M. P., De Sarro, G., Galimberti, C. A., Gatti, G., Licchetta, L., Malerba, A., … SOPHIE Study Group. (2010). Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. *Epilepsia*, *51*(5), 797–804. http://doi.org/10.1111/j.1528-1167.2010.02520.

10. Costa, J., Fareleira, F., Ascenção, R., Borges, M., Sampaio, C., & Vaz-Carneiro, A. (2011). Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia*, *52*(7), 1280–1291. http://doi.org/10.1111/j.1528-1167.2011.03047.

Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BRIVIACT® (brivaracetam) tablets, for oral use
BRIVIACT® (brivaracetam) oral solution
BRIVIACT® (brivaracetam) injection, for intravenous use
Initial U.S. Approval: 2016

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

BRIVIACT is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy. (1)

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

- The recommended starting dosage is 50 mg twice daily. Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day). (2.1)
- BRIVIACT injection may be used when oral administration is temporarily not feasible.
- *Hepatic Impairment* For all stages of hepatic impairment, the recommended starting dosage is 25 mg twice daily; maximum dosage is 75 mg twice daily. (2.5, 8.7, 12.3)

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

- Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg (3)
- Oral solution: 10 mg/mL (3)
- Injection: 50 mg/5 mL single-dose vial (3)

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

Hypersensitivity to brivaracetam or any of the inactive ingredients in BRIVIACT. (4)

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

- *Suicidal Behavior and Ideation*: Monitor patients for suicidal behavior and ideation. (5.1)
- *Neurological Adverse Reactions*: Monitor for somnolence and fatigue, and advise patients not to drive or operate machinery until they have gained sufficient experience on BRIVIACT. (5.2)
- *Psychiatric Adverse Reactions*: Behavioral reactions including psychotic symptoms, irritability, depression, aggressive behavior, and anxiety; monitor patients for symptoms. (5.3)
- *Hypersensitivity Bronchospasm and Angioedema*: Advise patients to seek immediate medical care. Discontinue and do not restart BRIVIACT if hypersensitivity occurs. (5.4)
- *Withdrawal of Antiepileptic Drugs*: BRIVIACT should be gradually withdrawn. (5.5)

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

Most common adverse reactions (at least 5% for BRIVIACT and at least 2% more frequently than placebo) are somnolence/sedation, dizziness, fatigue, and nausea/vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-844-599-2273 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- *Rifampin* Because of decreased BRIVIACT concentrations, increasing BRIVIACT dosage in patients on concomitant rifampin is recommended. (2.6, 7.1)
- *Carbamazepine* Because of increased exposure to carbamazepine metabolite, if tolerability issues arise, consider reducing carbamazepine dosage in patients on concomitant BRIVIACT. (7.2)
- *Phenytoin* Because phenytoin concentrations can increase, phenytoin levels should be monitored in patients on concomitant BRIVIACT. (7.3)
- *Levetiracetam* BRIVIACT had no added therapeutic benefit when co-administered with levetiracetam. (7.4)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2016

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

Literature Scan: Erythropoiesis Stimulating Agents

Date of Review: July 2016

Date of Last Review: May 2014
Literature Search: April 2014 – April 2016

Current Status of PDL Class: see **Appendix 1**

Conclusions:

- In controlled trials, patients with chronic kidney disease (CKD) experienced greater risk for death, serious adverse cardiovascular reactions and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. [1–3]
- For patients with CKD, consider ESA treatment when the hemoglobin level is less than 10 g/dL. This recommendation does not define how far below 10 g/dL is appropriate before an ESA is initiated. Individualize dosing and use the lowest effective dose of ESA sufficient to reduce the need for red blood cell transfusions. Adjust dosing as appropriate.[2]
- There is low quality evidence of no difference between ESAs for prevention of blood transfusions or all-cause mortality.[4] All ESA agents increase risk for hypertension equally, though evidence is imprecise.[4] The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis remain uncertain and analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness are not possible at this time.[4]

Recommendations:

- No further review or research needed at this time. No modification to the prior authorization (PA) clinical criteria is needed. Evaluate comparative ESA costs in the executive session.

Previous Conclusions:

- For ESA treatment of CKD anemia, there is no target Hb level that is considered at less risk for death, serious cardiovascular events or stroke. Recommendations are to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- For ESA treatment of chemotherapy induced anemia there is evidence of higher mortality, tumor progression and higher thromboembolic events associated ESA therapy. The majority of these trials targeted Hb targets > 12 g/dl. Both American and European updated treatment guidelines caution that ESA initiation should incorporate patient preferences for risk and benefit. The lowest ESA dose to prevent transfusion should be used. Non-responders should discontinue ESA after 6-8 weeks. There are no differences in efficacy or safety between the epoetin and darbepoetin.

- Peginesatide was removed from the market in February 2013 due to 19 reports of anaphylaxis following first dose (including 3 deaths) in patients receiving dialysis. It is recommended it be removed entirely from the PDL.
- There is no new comparative evidence that changes the previous conclusions.

Previous Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:

A systematic review by the Cochrane Collaboration compared the efficacy and safety between ESAs (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta and biosimilar ESAs), placebo, or no treatment in adults with chronic kidney disease (CKD).[4] Fifty-six eligible studies involving 15,596 adults with CKD were identified. Risks of bias in the included studies was generally high or unclear for more than half of studies. There was moderate to low confidence that epoetin alfa (OR 0.18, 95% CI 0.05 to 0.59), epoetin beta (OR 0.09, 95% CI 0.02 to 0.38), darbepoetin alfa (OR 0.17, 95% CI 0.05 to 0.57), and methoxy polyethylene glycol-epoetin beta (OR 0.15, 95% CI 0.03 to 0.70) prevented blood transfusions compared to placebo.[4] The authors could not determine if all ESAs were similar or different in their effects on preventing blood transfusions. Confidence in the comparative effectiveness of different ESAs was generally very low. The comparative effects of ESAs compared with another ESA, placebo or no treatment on all-cause mortality were imprecise.

All ESAs increased the odds of hypertension compared to placebo (epoetin alfa OR 2.31, 95% CI 1.27 to 4.23; epoetin beta OR 2.57, 95% CI 1.23 to 5.39; darbepoetin alfa OR 1.83, 95% CI 1.05 to 3.21; methoxy polyethylene glycol-epoetin beta OR 1.96, 95% CI 0.98 to 3.92). The authors' confidence in the comparative effects of ESAs on hypertension was low due to imprecision in treatment estimates. The comparative effects of all ESAs on cardiovascular mortality, myocardial infarction (MI), stroke, and vascular access thrombosis were uncertain and analyses for major cardiovascular events, end-stage kidney disease (ESKD), fatigue and breathlessness were not possible.[4]

The reviewers concluded there is insufficient evidence to suggest the superiority of any ESA formulation based on available safety and efficacy data. Direct comparative data for the effectiveness of different ESA formulations based on patient-centered outcomes (such as quality of life, fatigue, and functional status)

are sparse and poorly reported. Comparative treatment effects of different ESA formulations on other patient-important outcomes such as survival, MI, stroke, breathlessness and fatigue are very uncertain.[4]

New Guidelines:
NICE guidelines on anemia management in Chronic Kidney Disease were partially updated in 2015.[5] The sections new or updated in 2015 include:
guideline development group and scope, methodology, diagnostic tests for the prediction of response to iron therapy, concurrent illness, iron therapies and treatment of ESA resistance. All other sections and recommendations from the 2011 guideline remain unchanged. The evidence reviewed by the guideline development group led to the conclusion that there is no difference between darbepoetin and epoetin alfa in terms of efficacy and safety.[5]

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:

1. EPOGEN (Epoetin alfa).[Prescribing Information]. Thousand Oaks, CA: Amgen Inc., March 2016.

2. Research C for DE and. Drug Safety and Availability - FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm. Accessed April 12, 2016.

3. Aranesp (Darbepoetin alfa) [Prescribing Information]. Thousand Oaks, CA: Amgen Inc. July 2015.

4. Palmer SC, Saglimbene V, Mavridis D, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2014;12:CD010590. doi:10.1002/14651858.CD010590.pub2.

5. National Clinical Guideline Centre (UK). *Anaemia Management in Chronic Kidney Disease: Partial Update 2015*. London: Royal College of Physicians (UK); 2015. http://www.ncbi.nlm.nih.gov/books/NBK299242/. Accessed April 11, 2016.

6. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO*. 2010;28(33):4996-5010. doi:10.1200/JCO.2010.29.2201.

7. Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M. Anemia in HIV Infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis*. 2004;38(10):1454-1463. doi:10.1086/383031.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INJECTION	VIAL	PROCRIT	EPOETIN ALFA	Y
INJECTION	SYRINGE	ARANESP	DARBEPOETIN ALFA IN POLYSORBAT	Y
INJECTION	VIAL	ARANESP	DARBEPOETIN ALFA IN POLYSORBAT	Y
INJECTION	VIAL	EPOGEN	EPOETIN ALFA	N

Appendix 2: New Clinical Trials

A total of 21 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Search: ((("Hematinics"[Mesh]) AND "Hematinics" [Pharmacological Action]) AND ("Hematinics/administration and dosage"[Mesh] OR "Hematinics/adverse effects"[Mesh] OR "Hematinics/therapeutic use"[Mesh] OR "Hematinics/toxicity"[Mesh])) AND ("Epoetin Alfa"[Mesh] OR "Erythropoietin"[Mesh]) Filters: Clinical Trial, 5 years; adults; safety: efficacy

Erythropoiesis Stimulating Agents (ESAs)

Goal(s):

- Cover ESAs according to OHP guidelines and current medical literature.
- Cover preferred products when feasible.

Length of Authorization:

- 12 weeks initially, then up to 12 months
- Quantity limit of 30 day per dispense

Requires PA:

- All ESAs require PA for clinical appropriateness.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this continuation therapy?	**Yes:** Go to #12	**No:** Go to #4
4. Is the requested product preferred?	**Yes:** Go to #6	**No:** Go to #5
5. Will the prescriber 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 covered alternatives in class.	**No:** Go to #6

Approval Criteria		
6. Is the diagnosis anemia due to chronic renal failure[2] or chemotherapy[6,4] ?	**Yes:** Go to #7	**No:** Go to #8
7. Is Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% and/or ferritin >100 ng/mL?	**Yes:** Approve for 12 weeks with additional approval based upon adequate response.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the diagnosis anemia due to HIV[7]?	**Yes:** Go to #9	**No:** Go to #10
9. Is the Hgb <10 g/dL or Hct <30% **AND** Transferrin saturation >20% **AND** Endogenous erythropoietin <500 IU/L **AND** If on zidovudine, is dose <4200 mg/week?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the diagnosis anemia due to ribavirin treatment[6]?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the Hgb <10 g/dL or Hct <30% **AND** Is the transferrin saturation >20% and/or ferritin >100 ng/mL **AND** Has the dose of ribavirin been reduced by 200 mg/day and anemia persisted >2 weeks?	**Yes:** Approve up to the length of ribavirin treatment.	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient responded to initial therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:

1. Oregon Health Policy and Research Current Prioritized List of Health Services. Available at: http://cms.oregon.gov/oha/OHPR/pages/herc/current-prioritized-list.aspx Accessed September 12.2012
2. National Kidney Foundation. NKF KDOQI Guidelines. *NKF KDOQI Guidelines* 2006. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm . Accessed May 25, 2012.
3. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hermatology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients With Cancer. *JCO* 2010:28(33):4996-5010. Available at: www.asco.org/institute-quality/asco-ash-clinical-practice-guideline-update-use-epoetin-and-darbepoetin-adult. Accessed May 1, 2012.
4. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*. 2010:116(20):4045-4059.
5. Volberding PA, Levine AM, Dieterich D, et al. Anemia in HIV infection: Clinical Impact and Evidence-Based Management Strategies. *Clin Infect Dis*. 2004:38(10):1454-1463. Available at: http://cid.oxfordjournals.org/content/38/10/1454. Accessed May 8, 2012.
6. Recombinant Erythropoietin Criteria for Use for Hepatitis C Treatment-Related Anemia. VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel. April 2007

P&T Review: *5/16 (DM); 5/14; 11/12; 6/12; 2/12, 9/10*
Implementation: *1/1/13; 9/24/12; 5/14/12*

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

Literature Scan: Antivirals for Herpes Simplex Virus

Date of Review: May 2016

Date of Last Review: January 2014
Literature Search: March 2016

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

Conclusions:

- A scan of the literature identified 3 new high quality systematic reviews and 2 new high quality clinical practice guidelines on antivirals for the treatment of herpes simplex virus (HSV).
- A Cochrane review investigating antiviral efficacy against herpes simplex labialis (HSL) in immunocompetent patients found short-term (5-7 days) oral acyclovir 400 mg twice daily effectively prevents HSL reoccurrence (RR 0.26; 95% CI 0.13 to 0.51); however, treatment with 800 mg twice daily and 200 mg five times daily found no preventative effects.[1] Long-term (> 1 month) oral acyclovir was more effective in preventing HSL compared to placebo (0.85 events/4 months vs. 1.80 events/ 4 months; P=0.009) based on one small trial.[1] Valacyclovir was associated with fewer HSL recurrent infections compared to placebo (0.12 vs. 0.21 episodes per month) in one trial (n=95) lasting 16 weeks.[1] Topical antivirals were not shown to be effective in preventing HSL.[1]
- One systematic review on the preventative effects of oral antivirals on genital herpes in immunocompetent and non-pregnant adults found at least one clinical reoccurrence in 54% of patients treated with valacyclovir compared to 46% of those treated with acyclovir (RR 1.16, 95% CI 1.01 to 1.34; P=0.04).[2] Famciclovir was associated with at least one clinical reoccurrence in 35% of patients compared to 29% in valaciclovir patients (P=0.30).[2] Antivirals (acyclovir, valacyclovir and famciclovir) were found to be superior to placebo for preventing genital herpes reoccurrence.[2]
- Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV recommend episodic or daily antiviral suppressive therapy for treating oral and genital HSV lesions.[3] Antivirals are also recommended for prevention in those with HIV and HSV.[3]
- Guideline recommendations for the treatment of sexually transmitted diseases recommend antivirals for the treatment and prevention of reoccurrence of genital herpes.[4]

Recommendations:

- No further research is needed at this time. Continue current prior authorization (Appendix 2). Costs should be evaluated in executive session.

Previous Conclusions:

- Evidence does not support a difference in effectiveness or harms outcomes between antiviral agents for HSV.

Previous Recommendations:

- No further review or research needed at this time.

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:
Cochrane - Interventions for prevention of herpes simplex labialis (cold sores on the lips)
A Cochrane review looked at the evidence to support treatment of HSL on the lips. Included trials looked at immunocompetent patients, age 12 years and older, in 32 trials of low to moderate quality.[1] For prevention, acyclovir 400 mg twice daily for 1 month or less was found to reduce the recurrence (RR 0.26, 95% CI 0.13 to 0.51) but no effect was found with acyclovir 800 mg twice daily and acyclovir 200 mg five times daily.[1] Evidence to support the use of valaciclovir was uncertain (RR 0.55, 95% CI 0.23 to 1.28).[1] The evidence to support famciclovir use was also uncertain, based on one RCT. HSL recurrence with long term (≥1 month) antiviral agent use was reduced with oral acyclovir (1.80 episodes/4-months vs. 0.85/4-months; P=0.003). Valacyclovir was also shown to decrease occurrence of HSV to 0.09 episodes/month. Short-term (≤ 1 month) use of topical agents was not shown to prevent recurrent HSL and long-term (> 1 month) use was inconclusive. Adverse events with antivirals were similar to placebo. Oral levamisole, lysine and LongoVital® (vitamin and herb supplement) found no significant effect on HSL reoccurrence. No statistical differences between foscarnet, 1, 5-pentanediol or sunscreen compared to placebo were found.[1]

Cochrane – Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients
The role of antivirals (acyclovir, valacyclovir, and famciclovir) in the prevention of genital herpes, HSV-1 and HSV-2, in immunocompetent individuals was the topic of a Cochrane review.[2] Almost 7,000 men and women with a mean age of 35 years and 11 yearly recurrences were treated for 2-12 months in studies of high or uncertain risk of bias.[2] Acyclovir 400-1000 mg (n=2049) daily was shown to decrease recurrence compared to placebo (52% vs. 96%; RR 0.48, 95% CI 0.39 to 0.58; I^2 = 81%). No dose-response was demonstrated. Valacyclovir was superior to placebo in reducing genital herpes in 4 trials of 1,788 patients (46% vs. 79%; RR 0.41, 95% CI 0.24 to 0.69; I^2 = 94%). Recurrences were decreased by 32% with famciclovir 125-750 mg daily compared to placebo (RR 0.57, 95% CI 0.50 to 0.64; I^2 = 0%).[2] In one trial (n= 1345), valacyclovir prevented less recurrences compared to acyclovir (RR 1.16, 95% CI 1.01 to 1.34) and famaciclovir was less effective based on reoccurrence compared to valaciclovir (RR 1.18, 95% CI 0.86 to 1.63).[2] The results were uncertain on which antiviral were most effective in decreasing one clinical recurrence.

Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis
A systematic review and meta-analysis for the treatment of HSV epithelial keratitis (EK) included the following antivirals: trifluridine, acyclovir, ganciclovir, and foscarnet (idoxuridine, vidarabine, brivudine and cidofovir were included but not available in the US).[6] Evidence was analyzed using the GRADE method. Four studies compared acyclovir and found no difference in healing after 14 days (90% vs. 89%; RR 0.99, 95% CI 0.90 to 1.09).[6] Ganciclovir was less effective in healing

at 14 days compared to acyclovir (55% vs. 76%; RR 1.38, 95% CI 1.22 to 1.57); however, there was a high degree of heterogeneity in the 28 included studies. Foscarnet was had similar healing rates to acyclovir, ganciclovir and trifluridine based on evidence involving one study for each comparison.[6] Oral acyclovir had healing rates similar to a topical antiviral (RR 0.92, 95% CI 0.79 to 1.07).[6] The combination of oral acyclovir and a topical antiviral compared to a topical antiviral produced more healing (RR 1.36, 95% CI 0.68 to 2.74); however, wide confidence intervals limits the certainty of the results.[6]

New Guidelines:

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America released an update to their 2010 recommendations for treating opportunistic infections in patients with HIV, including HSV.[3] Evidence was reviewed and assessed based on strength and quality of the evidence for the recommendation (Table 1.).

Table 1. System for Rating Recommendations

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

Suppressive antiviral therapy is not recommended for patients with HSV for prevention of HSV-2 if they are not being treated with ART based on AI evidence.[3] The use of antiviral prophylaxis to prevent primary HSV infection is not recommended (AIII).[3] Episodic or daily suppressive therapy is recommended for treatment of HSV. Acyclovir, valacyclovir and famciclovir treatment for 5 to 10 days is recommended for orolabial lesions (AIII) and the same treatment is recommended for genital lesions (AI).[3] Intravenous acyclovir is recommended for severe mucocutaneous lesions (AIII). For prevention of HSV, all oral antivirals are recommended to reduce recurrence (AI) and should be re-evaluated on a yearly basis but may need to continued indefinitely (BIII).[3] Antiviral therapy may be recommended for individuals with a CD4 cell count <250 cells/mm^3 starting antiretroviral therapy (BI). Acyclovir is most commonly recommended for pregnant patients with HSV and HIV; however, valacyclovir has also been used for adherence reasons.[3]

Centers for Disease Control and Prevention – Sexually Transmitted Diseases Treatment Guideline

In 2015 the CDC updated their guideline for sexually transmitted diseases, including HSV.[4] The GRADE methodology was used to analyze the evidence. They recommend that all individuals with a first clinical episode of HSV be treated with an antiviral due to possibility of extended illness and possible neurologic involvement. Acyclovir, famciclovir and valacyclovir are recommended for first clinical episode, suppressive therapy and recurrent genital herpes.[4]

New FDA Drug Approvals:

No new antivirals for HSV were approved.

New Formulations/Indications:

No formulations or indications were found.

New FDA Safety Alerts:
There were no new FDA safety alerts since the last review.

References:

1. Chi CC, Wang SH, Delamere FM, et al. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev*. 2015. Art. No.: CD010095.
2. Le Cleach L, Trinquart L, Do G, et al. Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients. *Cochrane Database of Systematic Reviews*. 2014. Issue 8. Art. No.: CD009036. DOI: 10.1002/14651858.CD009036.pub2.
3. Wilhemus K. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015. Art. No.: CD002898.
4. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morbidity and Mortality Weekly Report*. 2015; 64:1-137.
5. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed March 24, 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	ACYCLOVIR	ACYCLOVIR	Y
ORAL	CAPSULE	ZOVIRAX	ACYCLOVIR	Y
ORAL	ORAL SUSP	ACYCLOVIR	ACYCLOVIR	Y
ORAL	ORAL SUSP	ZOVIRAX	ACYCLOVIR	Y
ORAL	TABLET	ACYCLOVIR	ACYCLOVIR	Y
ORAL	TABLET	ZOVIRAX	ACYCLOVIR	Y
BUCCAL	MA BUC TAB	SITAVIG	ACYCLOVIR	N
ORAL	TABLET	FAMCICLOVIR	FAMCICLOVIR	N
ORAL	TABLET	FAMVIR	FAMCICLOVIR	N
ORAL	TABLET	VALACYCLOVIR	VALACYCLOVIR HCL	N
ORAL	TABLET	VALTREX	VALACYCLOVIR HCL	N
TOPICAL	CREAM (G)	ABREVA	DOCOSANOL	N
TOPICAL	CREAM (G)	DENAVIR	PENCICLOVIR	N
TOPICAL	CREAM (G)	XERESE	ACYCLOVIR/HYDROCORTISONE	N
TOPICAL	CREAM (G)	ZOVIRAX	ACYCLOVIR	N
TOPICAL	OINT. (G)	ACYCLOVIR	ACYCLOVIR	N
TOPICAL	OINT. (G)	ZOVIRAX	ACYCLOVIR	N
TOPICAL	DROPS	ZIRGAN	GANCYCLOVIR	Y
TOPICAL	DROPS	VIROPTIC	TRIFLURIDINE	N

Appendix 2: New Clinical Trials

A total of 93 citations were manually reviewed from the literature search. After further review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to March Week 3 2016
Search Strategy:

#	Searches	Results
1	Acyclovir/	4567
2	famciclovir.mp.	684
3	ganciclovir.mp. or Ganciclovir/	5817
4	valacyclovir.mp.	1052
5	valganciclovir.mp.	813
6	penciclovir.mp.	314
7	docosanol.mp.	58
8	4 or 5 or 6 or 7	2134
9	limit 8 to (english language and humans and yr="2013 -Current")	317
10	limit 9 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review" or systematic reviews)	93

Antivirals, Oral and Topical - HSV

Goal(s):

- Cover oral and/or topical antivirals only for covered diagnoses.
- HSV infections are covered only when complicated by an immunocompromised host.

Length of Authorization:

- Up to 12 months (criteria specific)

Requires PA:

- Non-preferred drugs
- HIC3 = Q5V

Generic	Brand	Route
Famciclovir	Famvir	Oral
Valacyclovir	Valtrex	Oral
Acyclovir	Zovirax	Topical
Penciclovir	Denavir	Topical
Docosanol	Abreva	Topical

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the diagnosis uncomplicated herpes simplex virus infection (B002; B0089; B001; B009)?	**Yes:** Go to #4	**No:** Go to #7
4. Pass to RPh: Is the patient immunocompromised (document ICD10 code). Examples: • Current (not history of) diagnosis of cancer AND currently undergoing chemotherapy or radiation? Document therapy and length of treatment. • Diagnosis of HIV/AIDS?	**Yes:** Approve for the shorter of expected therapy duration or 12 months (applies to topical or oral antivirals for immunocompromised patients).	**No:** Go to #5

Approval Criteria		
5. Is the patient currently taking an immunosuppressive drug? Document name of drug. If drug not in list below, Pass to RPh for evaluation. Immunosuppressive drugs include, but are not limited to: **Immunosuppressants** Abatacept Adalimumab Anakinra Apremilast Azathioprine Basiliximab Certolizumab pegol Cyclosporine Cyclosporine Etanercept Golimumab Hydroxychloroquine Infliximab Leflunomide Methotrexate Natalizumab Rituximab Secukinumab Sirolimus Tacrolimus Tocilizumab Tofacitinib Ustekinumab Vedolizumab	**Yes:** Approve for the shorter of expected therapy duration or 90 days (applies to topical or oral antivirals for immunocompromised client).	**No:** If patient has diabetes mellitus or sickle cell disease, go to #6. All others go to #7.
6. Does the patient have diabetes mellitus or sickle-cell disease? Note: Diabetes mellitus and sickle-cell disease are not considered as immunocompromising for antivirals as for antifungals.	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Pass to RPh to evaluate for immunosuppression. • If not immunocompromised, deny; not funded by the OHP. • If immunocompromised, approve for up to 12 months.

Approval Criteria		
7. RPH only: All other indications need to be evaluated as to whether they are an OHP-funded condition. • If funded, viral diagnoses may be approved for treatment course with "PRN" renewals. If length of therapy is unknown, approve for 3 months intervals only (this is an exception to above guidelines and should be discussed with lead pharmacist). • If unfunded, deny (not funded by the OHP). • Deny non-viral diagnoses (medical appropriateness). • Deny viral ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).	If funded and clinic provides supporting literature, approve for length of treatment.	If unfunded, deny; not funded by the OHP.

P&T Review: *5/16 (KS); 1/14; 1/12; 9/10 (KS)*
Implementation: *1/1/11*